J Behav Med (2019) 42:1073–1081
https://doi.org/10.1007/s10865-019-00038-z

Cardiovascular disease risk factors are elevated among a cohort of young sexual and gender minorities in Chicago

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Received: November 13, 2018 / Accepted: March 30, 2019 / Published online: April 9, 2019

Abstract To date, little research has examined cardiovascular (CVD) risk among young sexual and gender minorities, a population which behavioral research has suggested may be at unique risk of poor CVD outcomes. We assessed behavioral risk factors and biomarkers of CVD risk among young sexual and gender minorities (YSGM) aged 16–29 in Chicago who are participants in the RADAR cohort (analytic N = 936). Multiplex cytokine and inflammatory biomarker assays were run on plasma from all HIV+ participants and demographically-matched HIV- participants (n = 237). Geographic data were used to assess mean C-reactive protein (CRP) level per community area of residence in Chicago. YSGM in this cohort exhibited lower rates of obesity (19.2% in RADAR vs. 35.7% in earlier studies of heterosexual youth) and comparable rates of past 30-day tobacco use (37.9 vs. 38.1%). Conversely, higher rates were observed among several other risk factors including C-reactive protein (mean = 6.9 mg/L vs. 2.1 mg/L), marijuana use (72.5 vs. 45.3%), perceived stress (mean = 15.5 vs. 14.2), and HIV (20.0 vs. < 1% nationally). Finally, we observed geographic heterogeneity in mean CRP values by community area across the Chicago region with the highest and lowest values both found in neighborhoods on the North side of the city. In sum, these analyses demonstrate that YSGM may be at increased risk of CVD beginning from an early age. Future research should assess whether sexual minority-related stressors increase long-term CVD risk and should also longitudinally study the role of multiple risk factors on CVD morbidity and mortality among YSGM.

Keywords Cardiovascular disease · HIV · MSM · Inflammation

Introduction

Past research using data from the National Longitudinal Study for Adolescent Health (Add Health) describes a high burden of cardiovascular disease (CVD) risk factors among young adults, suggesting interventions are needed among this population (Clark et al. 2014). Further work building on these findings used data from the Framingham Offspring Study and demonstrated that exposure to CVD risk factors in early adulthood translates to increased risk later in life, even after adjusting for late-in-life risk factors (Pletcher et al. 2016). Additional work using Add Health data found sexual orientation disparities in CVD risk with young gay and bisexual men experiencing significantly higher levels of C-reactive protein (CRP), diastolic blood pressure, and pulse rate compared with their heterosexual peers (Hatzenbuehler et al. 2013). One contributing factor may be that, as compared with heterosexual youth, young men

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10865-019-00038-z) contains supplementary material, which is available to authorized users.

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who have sex with men (aged 18–29) report increased rates of substance use (Corliss et al. 2010; Newcomb et al. 2014; Hatzenbuehler et al. 2008; Marshal et al. 2009) which have previously been associated with increased risk of cardiovascular disease (Qureshi et al. 2001; Mittleman et al. 2018; American Heart Association 2015). Chronic exposure to various types of stress and stigma, both of which are commonly perceived by sexual and gender minorities (YSGM), has also been associated with increased risk of cardiovascular disease (Dimsdale 2008; Hatzenbuehler et al. 2014). Compounding these issues, young men who have sex with men currently account for nearly 70% of all new HIV diagnoses among adolescents and young adults in the U.S. (CDC 2018) with HIV infection being associated with an increased risk of cardiovascular events (Fisher and Lipshultz 2001). Taken together, these findings suggest that YSGM in the U.S. may be at uniquely increased risk for cardiovascular disease from an early age. Given the rising incidence of HIV diagnoses as well as the co-occurring rates of exposure to chronic stress and stigma among this population, research is needed to understand exposure to cardiovascular disease risk factors among YSGM.

Beyond individual risk factors, community level and geographic factors may also contribute to cardiovascular risk (Pickle and Gillum 1999). Using estimates from the American Community Survey, demographic characteristics can be seen to vary widely across Chicago's 77 community areas, (Census Bureau 2015) the site for the RADAR cohort study among YSGM. For example, community areas located on the North side of Chicago are composed primarily of white residents, which can exceed 80% of the population in some areas, although others have a diverse population of black, white, and Hispanic individuals. Comparatively, the community areas on the South side of the city are composed primarily of black residents with at least 80% of the population in most of these neighborhoods being black. Finally, on the West side of the city, the community areas vary between being majority black and majority Hispanic residents with few areas exceeding 80% of any one racial or ethnic population (Census Bureau 2015). For reference, the community areas on the South and West sides have the highest concentrations of households living below the federal poverty level as well as the lowest per capita income (City of Chicago 2017). During the period 2011–2015, trends in coronary heart disease-related deaths have been on the decline in Chicago, although the highest rates continue to be observed on the South side of the city (Chicago Department of Public Health, Chicago Health Atlas 2018). Further, past research has observed the highest rates of stroke mortality to be concentrated largely on South side of the city (Hunt et al. 2014).

Limited research has focused on cardiovascular disease risk factors among young sexual and gender minorities to date. Developing a better understanding of how cardiovascular risk factors vary among YSGM, particularly in the context of high systemic inflammation among this population (Hatzenbuehler et al. 2013; Everett et al. 2014), is a critical first step towards averting poor health outcomes later in life. To assess this, we analyzed data from large cohort of young sexual and gender minorities in order to: (1) assess cardiovascular disease risk factors among this population; (2) explore proinflammatory cytokines previously associated with cardiovascular disease (C-reactive protein [CRP], interleukin (IL)-1β, IL-6, and IL-15); (3) examine the association between proinflammatory cytokines, demographic characteristics, and health behaviors; and (4) explore whether CRP may vary by community area of residence. Across these analyses we hypothesize that, compared to national cohorts, our sample of YSGM will have a higher prevalence of CVD risk factors and will have higher levels of CVD-associated pro-inflammatory cytokines. Finally, we also hypothesize that the highest levels of CRP will be observed on the South side of the city.

Methods

Study design and recruitment

Data were collected as part of RADAR, an ongoing longitudinal cohort study of Chicago metropolitan area YSGM assigned a male sex at birth. The primary objective of this cohort study is to apply a multilevel perspective (Johnson et al. 2010) to a syndemic of health issues associated with HIV among YSGM (Mustanski et al. 2007). Diverse methods for participant recruitment were used in order to achieve the multiple cohort, accelerated longitudinal design (Miyazaki and Raudenbush 2000). First, a subset of participants from two cohorts, Project Q2 and Crew 450, who were first recruited in 2007 and 2010, respectively, enrolled in RADAR. In 2015, a third cohort of YSGM was recruited. At the time of enrollment into their original respective cohorts, all participants were between 16 and 20 years of age, assigned male at birth, spoke English, and had a sexual encounter with a man in the previous year or identified as gay, bisexual or transgender. Next, the RADAR cohort was expanded through an iterative process where serious romantic partners were recruited at each visit, thereby creating a dynamic, dyadic network. All serious romantic partners who were assigned male at birth and 16–29 years of age were eligible for enrollment into the cohort regardless of current gender identity or sexual orientation. Romantic partners who were assigned female at birth or were older than 29 completed a study visit but

were not enrolled in the cohort. Lastly, cohort members were allowed to refer a maximum of three YSGM peers for enrollment into the study as long as they were between 16 and 29 years of age. All cohort members complete follow-up visits at six-month intervals.

Measures

Demographics

Participants were asked to provide demographic information including age, race/ethnicity, sex assigned at birth, gender identity and sexual orientation at each visit. Participants reporting a Hispanic/Latino ethnicity were coded as such, regardless of their racial identity.

Health measures

Body mass index (BMI) was collected and calculated objectively based on CDC recommendations (CDC 2017). Depressive symptoms were measured by the PROMIS Depression Scale (reported as T-scores: 0–55 "normal", 55.1–59.9 "mild", 60–64.25 "moderate", and > 64.26 "severe") (Choi et al. 2014). Cohen's Perceived Stress Scale was used to measure perception of stress (0–13 indicates low stress, 14–26 indicates moderate stress, and 27–40 indicates high stress) (Roberti et al. 2006). Other health-related factors were also assessed by asking participants to provide information on their use of cigarettes in the past 6 months, their history of chronic health conditions, and whether they currently had healthcare insurance. Marijuana use was self-reported and was operationalized as any use in the past 6 months and no use in the past 6 months. Due to the low rate of use among this population, the use of any other drugs was combined into a single variable and operationalized as any use in the past 6 months versus no other drug use in the past 6 months (Morgan et al. 2016a; b, 2018). The analytic sample included only those individuals who had answered the health-related survey questions (N = 936); data were utilized from the earliest available visit where all health-related survey questions were assessed.

HIV testing

Fingerstick blood samples were collected as part of each participant's visit every six months. Each participant's HIV infection status was determined using the Alere™ Determine™ HIV1/2 Ab/Ag Combo 4th generation point-of-care (POC) test. Those who tested positive on the POC HIV tests received confirmatory HIV antigen and antibody immunoassay testing following current CDC HIV testing guidelines (DiNenno et al. 2017).

Multiplex biomarker analyses

Biomarker data were obtained on a subset of patients and included CRP, IL-1β, IL-6, and IL-15. Each of these were tested among all HIV-infected participants (n = 148). CRP was also assayed on demographically matched (based on age, race, and gender) HIV-negative participants (n = 147). One subject was found to have been enrolled twice, thus duplicated data was deleted in subsequent analyses. For IL-1β, IL-6, and IL-15, a smaller subset of HIV-negative participants was randomly selected from among those with available CRP data (n = 89). Subjects from whom cytokines were assayed were selected from only those who self-reported any sexual activity in prior 6 months. No significant group differences (age, race, and gender) existed between the HIV-negative participants selected versus those not selected for either CRP or cytokine analyses. Final analyses included CRP data on 148 HIV-infected and 147 HIV-negative participants and IL-1β, IL-6, and IL-15 data on 148 HIV-infected and 89 HIV-negative participants.

Multiplexed assays were conducted using the MESO QuickPlex SQ 120 electrochemiluminescence immunoassay platform (Meso Scale Discovery, MSD). IL-1β, IL-6, and IL-15 were measured in participant plasmas using the MSD V-PLEX Custom Proinflammatory Panel 1 (human) kit (IL-1β dynamic range 0.05–375 pg/mL; IL-6 dynamic range 0.06–488 pg/mL; IL-15 dynamic range 0.17–525 pg/mL). Plasma samples were tested for CRP using the MSD V-PLEX Plus Human CRP kit (dynamic range 0.001–49.6 mg/L). CRP results were validated using a second methodology among a small sample (n = 10), a particle enhanced immunoturbidimetric high-sensitivity (hs) CRP assay performed on a Roche/Hitachi cobas c 311 instrument (dynamic range 0.15–20.0 mg/L) at North Shore Laboratory Services. Values between the two platforms were highly correlated (r = 0.99).

Geographic analyses

Using community area of residence at the time of interview, mean CRP level per area was calculated by averaging across all values for individuals living in that area. Community areas were then ordered based on clinically relevant CRP values: ≤ 3.0 mg/L, 3.0 to 9.9 mg/L, and ≥ 10.0 mg/L.

Statistical analyses

Participant characteristics were described using means, standard deviations, and proportions. ANOVA and Pearson's correlation coefficients were used to assess the relationship between risk factors and biomarkers of

inflammation. All analyses were performed in RStudio v1.1353 (RStudio Team 2017).

Results

As shown in Table 1, the mean age of participants was 23.3 years [Standard Deviation (SD) = 3.7]. Among all participants, 320 (34.2%) identified as black, 230 (24.6%) identified as white, 286 (30.6%) identified as Hispanic/Latinx, 23 (2.5%) identified as Asian and 77 (8.2%) identified as a different or mixed race. All participants were assigned male at birth with 648 (69.2%) identifying as gay, 155 (16.6%) identified as bisexual, and 133 (14.2%) identified as other. Mean BMI was 25.5 kg/m^2 (SD 6.3) with 22.5% (n = 205) classified as overweight (BMI $\geq$ 25 kg/m^2 and $<$ 30 kg/m^2) and 19.2% (n = 175) classified as obese (BMI $\geq$ 30 kg/m^2). There were 187 (20.0%) participants who were HIV-positive. Less than one-fifth of participants (18.2%) reported lacking health insurance at the time of interview. Mean perceived stress score was 15.5 (SD 6.7; range 0–35) indicating moderate stress. Mean depression T-score score was 49.3 (SD 9.9; range 38.2–81.3) indicating normal levels of depression. Nearly half of participants reported cigarette use in the past 6 months (n = 445, 47.5%) and 37.9% (n = 355) reported use in the past 30 days. One-third of participants also reported having a history of chronic health conditions other than HIV (n = 297, 31.7%). Finally, 679 (72.5%) participants reported marijuana use in the past 6 months while 324 (34.6%) reported use of any illicit drug other than marijuana.

Table 1 Demographic and health characteristics of participants in the analytic sample, RADAR, Chicago (N = 936)

Characteristic	N	%
Race		
Black	320	34.2
White	230	24.6
Hispanic/Latinx	286	30.6
Asian	23	2.5
Other	77	8.2
Sexual orientation		
Gay	648	69.2
Bisexual	155	16.6
Other	133	14.2
Chronic health conditions other than HIV	297	31.7
HIV-positive	187	20.0
Health insurance	766	81.8
Substance use[a]		
Cigarette use	445	47.5
Marijuana	679	72.5
Any other drugs	324	34.6

Characteristic	Mean	SD
Age	23.3	3.7
BMI	25.5	6.3
Mental health		
Perceived stress score[b]	15.5	6.7
Depression, raw score[c]	13.9	7.0
Depression, T-score	49.3	9.9
Biomarkers[d]		
Raw CRP	6.9	13.6
Log CRP	1.1	1.3
IL-1β	1.3	2.8
IL-6	0.6	0.6
IL-15	1.8	0.5

SD standard deviation, *BMI* body mass index, *CRP* C-reactive protein, *IL* interleukin

[a]In the past 6 months

[b]Measured via Cohen's Perceived Stress Scale, possible range 0-40

[c]Measured via the PROMIS Depression Scale, possible range 8-40

[d]Assessed among HIV+ and demographically matched HIV- participants, (n = 237)

In terms of biologic data, the following means were observed: raw CRP was 6.9 mg/L (SD 13.6), log CRP was 1.1 (SD 1.3), IL-1β was 1.3 pg/mL (SD 2.8), IL-6 was 0.6 pg/mL (SD 0.6), IL-15 was 1.8 pg/mL (SD 0.5). Among all participants with data available (n = 237), raw CRP values ranged from 0.03 to 172.4 with a median value of 3.08. Half of (121; 50.8%) participants had values $\geq$ 3 mg/L and 44 (18.5%) participants had values $\geq$ 10 mg/L. Significant associations (Fig. 1) were observed between raw CRP and BMI (r = 0.13, p = 0.048), raw depression score (r = 0.13, p = 0.046), IL-6 (r = 0.65, $p < 0.001$), and IL-15 (r = 0.21, p = 0.003). IL-1β was significantly associated with HIV-status (F(1) = 22.1, $p < 0.001$), cigarette use in the past six months (F(1) = 9.38, p = 0.002), and IL-15 (r = − 0.29, $p < 0.001$). IL-6 was significantly associated with marijuana use (F(1) = 6.69, p = 0.01), BMI (r = 0.16, p = 0.02), perceived stress score (r = 0.16, p = 0.02), raw depression score (r = 0.14, p = 0.04), raw CRP (r = 0.65, $p < 0.001$), and IL-15 (r = 0.31, $p < 0.001$). Finally, IL-15 was associated with race/ethnicity (F(3) = 3.48, p = 0.02), HIV-status (F(1) = 48.00, $p < 0.001$), health insurance status (F(1) = 8.00, p = 0.005), marijuana use (F(1) = 7.28, p = 0.008), raw CRP (r = 0.21, p = 0.003), IL-1β (r = − 0.29, $p < 0.001$), and IL-6 (r = 0.31, $p < 0.001$). Full results for all associations can be found in supplementary materials, Table S1 and Table S2.

Examining geographic distribution of mean CRP values (Fig. 2), participants reported residing in 52 (67.5%) of 77 Chicago community areas. There was no clear pattern to

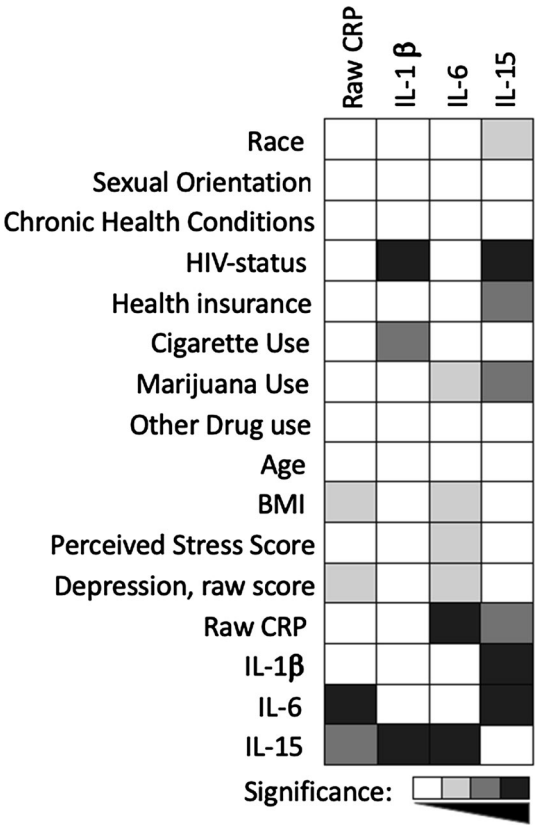

Fig. 1 Associations between demographic and health characteristics among those participants with available biomarker data (n = 237; significance levels include: not significant, $p < 0.05$, $p < 0.01$, and $p < 0.001$)

the distribution of CRP values across community areas although both the highest and lowest CRP values occurred on the North side of the city.

Discussion

In this analysis, we assessed cardiovascular risk factors in a diverse sample of YSGM in Chicago. Our hypotheses were partially supported by the data presented in this report. We observed that, compared to studies conducted on heterosexual adults, YSGM in this sample had a lower prevalence of obesity suggesting they may be less susceptible to obesity-related CVD outcomes. On the other hand, YSGM were observed to have higher levels of CRP, higher rates of marijuana use, perceived stress, and HIV. Geographic analyses, meanwhile, did not support our hypothesis. We observed considerable variation across the city with both the highest and lowest values of CRP on the North side of the city. Further research is needed to assess whether YSGM experience greater levels of stigma in these community areas.

At least three studies serve as crude comparators of these risk factors in non-SGM samples in the same and different age ranges, although direct comparison and statistical evaluation are not possible these studies still serve to provide context for our findings. Compared to other young adults, our sample had lower rates of weight-related CVD risk factors. One past study among U.S. adults (aged 20–39) noted the prevalence of obesity to be 35.7% with the highest rates among black and Hispanic individuals (Hales et al. 2017). Another population-based study among young adult men more comparable to those in this analysis found mean BMI to range from 25.9 to 26.8 kg/m^2, varying based on number of hours of sleep per night (Meyer et al. 2012). Compared to these studies, we observed a lower percent of obese individuals (19.2%) and a similar mean BMI of 25.5 kg/m^2. When considering cigarette use, rates vary considerably based on the age group and year of data collection. Two recent studies assessing current use of cigarettes observed rates of 12.7% (Kann et al. 2018) and 14.7% (Jamal et al. 2018) among grade 12 boys in Illinois and U.S. young adult men (aged 18–24), respectively. Meanwhile, another report assessing past 30-day cigarette use from the National Survey on Drug Use and Health (NSDUH) in 2012 found a tobacco use rate of 38.1% among young men aged 18–25 (U.S. Department of Health and Human Services 2012). Depending on the data source, the rates of cigarette use observed in this study are either three times higher or are comparable. These findings suggest that YSGM may be at a relatively lower weight-related and risk of cardiovascular events in their lifetimes and either comparable or higher risk of tobacco-related CVD events. Longitudinal analyses are needed to better understand how variation in these factors over time, particularly tobacco use, may influence CVD risk among this population.

In contrast, the current results raise the hypothesis that YSGM experience much higher rates for several other risk factors related to cardiovascular disease. For example, we observed high CRP values with mean CRP levels of 6.9 mg/L and over 50% of the sample above 3 mg/L. CRP values > 3 mg/L are associated with a three-fold increased risk of cardiovascular disease, (Ridker et al. 1997) suggesting the risk of cardiovascular disease may be high among this population. However, research on this among young men who have sex with men is limited (Everett et al. 2014; Hatzenbuehler et al. 2013) despite associations of elevated systemic inflammation in young adulthood with poorer health outcomes in middle age (Hancox et al. 2007; Kalhan et al. 2010). In addition to elevated CRP levels, we also observed much higher rates of marijuana use in our sample compared to past national samples (Zhang and Wu 2017) of young adults (72.5 vs. 45.3%). Here, our survey assessed past 6-month use while the national sample

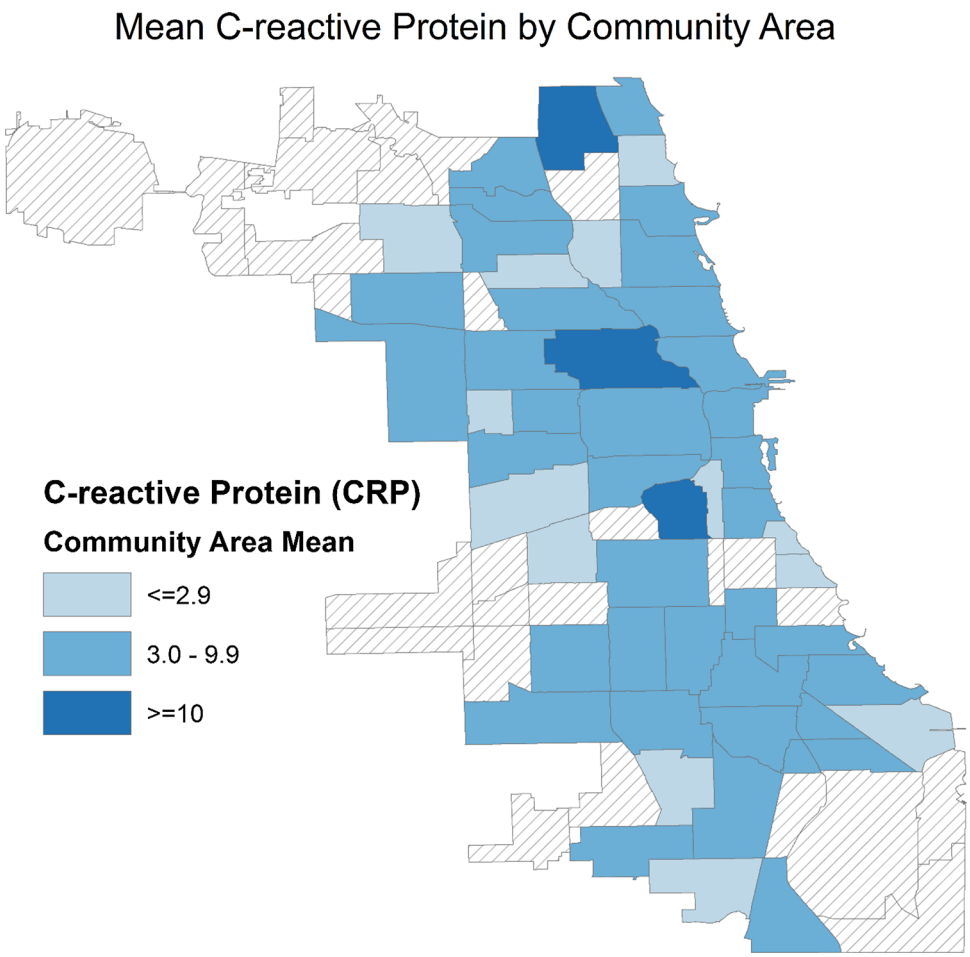

Fig. 2 Distribution of mean C-reactive protein level by community area in Chicago, RADAR, 2015–2017

assessed use over the past 12-month period, however, our values are still comparable given our observed value of 71.3% represents the minimum use in the past 12 months. Findings such as these are key given that past research found that the risk of myocardial infarction increases nearly five-fold during periods immediately following marijuana use (Franz and Frishman 2016) and annually from 1.5 to 3.0% per year (Mittleman et al. 2018). Further, YSGM have a high prevalence of HIV infection which has previously been associated with greater risk of cardiovascular events as the virus progresses later in life even with suppressive ART (Freiberg et al. 2013). Finally, we observed no variation in biomarkers of inflammation by sexual orientation and little variation according to race/ethnicity, only with regards to IL-15. Taken together, these results suggest that YSGM as a population may be at uniquely high risk for CVD beginning at an early age and that the mechanisms leading to CVD risk may be unique. Further longitudinal studies should be conducted to better assess long-term exposure to CVD-related risk factors and CVD outcomes among this population, particularly given the association between CVD risk in young adulthood and risk later in life (Clark et al. 2014; Pletcher et al. 2016).

Causal hypotheses to explain the observed elevated inflammation also require further evaluation. Unique stressors are experienced among young men who have sex with men that may activate several candidate biological pathways. These include stigma, sexually transmitted infections, and substance use that may impact the sympathetic nervous system and/or the hypothalamic–pituitary–adrenal (HPA) axis (Stephens and Wand 2012). Sexual and gender minorities, including those in this analysis, have been shown to experience disproportionately high rates of stress and stigma related to their sexual and gender minority status, (Meyer 2003) potentially increasing the risk of both cardiometabolic events (Hatzenbuehler et al. 2014; Hare et al. 2014) and other adverse health outcomes (Mirowski and Ross 1989; Pearlin 1989; Dohrenwend et al. 1992; Meyer 1995). Illicit substances (Siegel et al. 2002; Reingold et al. 2008) have also been associated with increased inflammation (Mirowski and Ross 1989; Pearlin 1989; Dohrenwend et al. 1992; Meyer 1995) and are used at higher rates among young men who have sex with men compared to young gay women and heterosexuals (Meyer 2003). Given the prevalence of each of these stressors among young men who have sex with men, future research

should also aim to develop a better understanding of whether, and how, these factors may contribute to variability in inflammation among young men who have sex with men.

We observed geographic heterogeneity with respect to mean CRP levels across the Chicago metropolitan region with both the highest and lowest values found in neighborhoods on the North side. The observed distribution of CRP values were not clustered in neighborhoods with the highest violence, the highest percent of minorities, nor the areas with the lowest rates of poverty. One explanation may be that these neighborhoods have the lowest measures of socioeconomic status although, in Chicago, those are found on the West and South sides of the city and thus our findings unlikely able to be attributed to differences in socioeconomic status. Another potential explanation may be that YSGM experience greater stigma in those neighborhoods with the lowest proportion of other YSGM individuals which may be the same community areas observed in this study. Future studies should aim to develop a better understanding of factors associated with the geographic distribution of CRP in order to better develop and target interventions aimed at lowering this CVD-related biomarker.

While we found several important factors associated with cardiovascular disease risk among YSGM, our findings should be considered in the context of their limitations. First, these analyses are limited by not having an available comparison sample of young heterosexual men. Second, several of the comparison studies did not report sexual and gender minority status and thus we cannot be sure they are not included. Next, this sample was a community sample rather than a probability sample and, as such, findings may not generalize to the larger population of YSGM. Finally, we have yet to measure several risk factors (e.g. blood pressure, cholesterol, family history of CVD, sleep quality, etc.) related to CVD risk which would aid in developing a better quantitation of the risk of CVD faced by this group.

Even in the context of these limitations, we have shown that YSGM have a unique profile of risk factors for cardiovascular disease from a young age. We demonstrated that our sample, compared to other young heterosexuals, had lower rates of obesity and comparable rates of tobacco use while simultaneously having elevated C-reactive protein, higher levels of perceived stress, and a high prevalence of HIV. We also observed geographic heterogeneity in the distribution of mean CRP across community areas in Chicago which we hypothesized may be attributable to greater stigma experienced by YSGM individuals in these neighborhoods. Together, these findings suggest that YSGM individuals may require uniquely tailored CVD-prevention interventions. Future research should aim to better understand and prevent these CVD risk factors among this population and measure long-term CV morbidity and mortality as well as their association with these factors among sexual and gender minorities.

Acknowledgements The authors would like to thank the entire RADAR research team, particularly Dr. Thomas Remble and Antonia Clifford for overseeing the project and Daniel T. Ryan for data management. We also thank the RADAR participants for sharing their experiences with us. Services were provided by the Third Coast Center for AIDS Research Viral Pathgogenesis Core.

Funding This study was funded by Grants from the National Institute on Drug Abuse at the National Institutes of Health (F32DA046313, PI: Morgan; U01DA036939, PI: Mustanski; P30AI117943, PI: D'Aquila). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health. The sponsor had no involvement in the conduct of the research or the preparation of the article.

Compliance with ethical standards

Conflict of interest Ethan Morgan, Richard D'Aquila, Mercedes R. Carnethon, and Brian Mustanski declare they have no conflicts of interest.

Human and animal rights and Informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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