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Differential Effects of Self-Reported Lifetime Marijuana Use on Interleukin-1 Alpha and Tumor Necrosis Factor in African American Adults

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Abstract

It is unknown how lifetime marijuana use affects different proinflammatory cytokines. The purpose of the current study is to explore potential differential effects of lifetime marijuana use on interleukin-1 alpha (IL-1 α) and tumor necrosis factor (TNF) in a community based sample. Participants included 168 African American adults (51% female, median age= 47 years). Upon study entry, blood was drawn and the participants completed questions regarding illicit drug use history whose answers were used to create three groups: lifetime non-drug users (n= 77), lifetime marijuana only users (n= 46) and lifetime marijuana and other drug users (n= 45). In the presence of demographic and physiological covariates, non-drug users were approximately two times more likely (AOR= 2.73, CI= 1.18, 6.31; p= .03) to have higher TNF levels than marijuana only users. Drug use was not associated with IL-1 α . The influence of marijuana may be selective in nature, potentially localizing around innate immunity and the induction of cellular death.

Keywords

Marijuana; Interleukin-1; Tumor Necrosis Factor; African Americans; Adults; Immune Function

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Conflict of Interest Statement

Authors, Larry Keen II, and Arlener D. Turner, declare that they have no conflicts of interest.

Statement of Human Rights

All procedures involving human participants in this study were performed in accordance with the ethical standards of the Howard University Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, informed consent was obtained from all individual participants prior to inclusion in the study.

INTRODUCTION

Marijuana is the most widely used drug in the United States and the usage prevalence has significantly increased over the past decade (NIDA, 2012). This increase in recent years is also evident given the legalization of recreational marijuana usage in two states and legalized medicinal usage in 23 states. With increases in both medicinal and recreational usage of marijuana in the United States, it is critical to continue examining the healthy and deleterious influence of marijuana use. Marijuana's therapeutic usage has garnered much attention in the clinical and experimental literature over the past decade (Aggarwal et al., 2009; Arevalo-Martin et al., 2003; Friedman & Klein, 1999; Klein, 2005). Specifically, researchers have begun to explore the relationship between marijuana use and immune function (Baldwin et al., 1997; Roth, Baldwin, & Tashkin, 2002). However, the vast majority of this literature focus is at the cellular level, which posits marijuana's immunosuppressive effects on innate immunity (Reiss, 2010; Ribeiro et al., 2012). To date, very few studies have examined the recreational use of marijuana and its relationship with proinflammatory cytokines at the public health or epidemiological level.

Dysregulation of proinflammatory cytokines may lead to increases in peripheral cytokine levels, leading to the condition called inflammation. Inflammation is a public health concern due to its' association with many of the leading causes of death, including heart disease, cancer, stroke, diabetes, and Alzheimer's disease (Glass et al., 2010). Given the anti-inflammatory constituents in marijuana, researchers and clinicians have begun exploring novel anti-inflammatory therapies utilizing marijuana as a mitigating vector of chronic inflammation based conditions (Albayram et al., 2011; Cabral & Griffin-Thomas, 2009; Canvin & el-Gabalawy, 1999; Gorelick, 2010; Jackson et al., 2005; Marchetti & Abbracchio, 2005; Raber et al., 1998). Though the literature examining marijuana use and immunity is still in its infancy, findings suggest that marijuana alters a variety of innate and adaptive immune system responses in both animals and humans (Klein, Friedman, & Specter, 1998; Klein et al., 2003; Matsuda et al., 2005; Ribeiro et al., 2012; Snella, Pross, & Friedman, 1995). Specifically, previous research examining marijuana's influence on immune cells posits that the non-psychoactive component cannabidiol modulates innate immune responses, such as lymphocytes, natural killer cells, and macrophage function (Baldwin et al., 1997; Chang, Lee, & Lin, 2001; Klein, 2005; Klein et al., 1998). Overall, marijuana use inhibits macrophage function, which attenuates proinflammatory cytokine proliferation (Klein et al., 2000). This influence is seen in the reduction production and function of the proinflammatory cytokines interleukin-1 alpha, interleukin-6, and tumor necrosis factor (Cabral & Vasquez, 1992; Klein et al., 2000; Kusher et al., 1994; Shivers et al., 1994; Zurier et al., 2003). However, some reports indicate an increase in these cytokines (Fischer-Stenger, Dove Pettit, & Cabral, 1993; Friedman & Klein, 1999; Klein et al., 2000; Shivers et al., 1994).

Marijuana use activates the cannabinoid system, which has a direct influence on the cytokine network (Klein et al., 2000). However, research examining the influence of chronic marijuana use on cytokine levels is still sparse. In previous work, we have shown that when compared to their non-drug using counterparts, individuals who report using marijuana in their lifetimes have lower interleukin-6 levels (Keen, Pereira, & Latimer, 2014). This was

the first epidemiological study to identify differences in resting levels of any proinflammatory cytokines based on marijuana use. Given that each proinflammatory cytokine is responsible for variety of different functions, it is imperative to identify the differential effects of marijuana use on each proinflammatory cytokine.

Overall, the literature regarding the relationship between chronic marijuana use and proinflammatory cytokine function is still unclear. Further examination of this relationship in various samples, such as African Americans adults, may inform both clinical and non-clinical efforts in the future. African Americans may present a unique sample, as they represent higher prevalence of many inflammatory based conditions. These conditions include obesity, high life stress, and at high risk for vascular conditions with inflammatory properties (Black, 2003; McDade, Hawkey, & Cacioppo, 2006; Mohamed-Ali et al., 1997). The purpose of the current study is to examine the associations between self-reported lifetime marijuana use and interleukin-1 alpha and tumor necrosis factor in a community based sample of middle-aged sample of African Americans. We will examine this association utilizing three groups, those who reported no lifetime drug use, individuals who self-reported using marijuana in their lifetime, and those who reported using marijuana in addition to other drugs. We hypothesize that lifetime marijuana use will be associated with lower levels of interleukin-1 alpha and tumor necrosis factor.

METHODS

Participants

Data were derived from the parent study entitled, “Stress and Psychoneuroimmunological Factors in Renal Health and Disease.” A total of 212 African Americans participated in the parent study. The Minority Organ Tissue Transplant Education Program at Howard University Hospital recruited participants through flyers posted in throughout the hospital and community based health fairs conducted by the Hospital in the Washington, DC metropolitan area. The health fairs were conducted by the Howard University Hospital in order to educate local community in a variety of health concerns, such as heart disease, hypertension, renal health and obesity. Inclusion criteria for the parent study included individuals who were 18 years of age and older with no history of traumatic brain injury or psychiatric diagnosis. The Howard University institutional review board approved this study. For the current study, only those with complete interleukin-1 alpha, tumor necrosis factor, and illicit drug use data (n = 168) were included.

Procedure

Upon entering the Howard University Hospital General Clinical Research Center, researchers obtained informed consent from the participants. After participants gave informed consent, a registered nurse obtained a peripheral venous blood sample of approximately ten milliliters and blood pressure readings. Following these collections, study participants completed a demographic, medical history, behavioral health questionnaire and a psychological battery. Study procedures were conducted in one visit and lasted approximately four hours. Participants were remunerated \$50 for their time.

Assessment of Illicit Drug Use

The demographic questionnaire contained questions regarding illicit drug use during the participants' lifetime. The first question read: "Have you ever used an illicit drug or narcotic?" Participants who responded "yes" then answered a series of follow-up questions that probed for the type of drug(s) used, i.e., "Have you ever used (insert drug type here; e.g. "marijuana")?" Response choices were "yes" or "no". The groups non-drug users, marijuana only users, and marijuana and other drugs were created based on these responses.

Quantitation of Serum Interleukin-1 Alpha and Tumor Necrosis Factor

A venous blood sample of approximately 10 mL was collected from each participant. Samples were centrifuged for 30 minutes, aliquoted into six vials, and stored at -70 degrees Celsius at the Howard University General Clinical Research Center until sent to Quest Diagnostics for analyses. Serum interleukin-1 alpha and tumor necrosis factor concentrations (pg/mL) were quantified using Enzyme-Linked Immunosorbent Assay.

Assessment of Covariates

Age (in years), sex, years of education, and annual income was collected via a demographic questionnaire administered by a trained researcher. Self-reported medication use was obtained by asking the question "Are you currently taking any medication?" Participants were given two options for responses, "yes" or "no". A trained member of the nursing staff in the General Clinical Research Center obtained height, weight, and blood pressure. Body mass index (BMI) was calculated utilizing the following formula: weight in kilograms divided by height in meters squared.

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences, Version 20.0 (SPSS Incorporated). Continuous variables are presented as mean (standard deviation). The outcome variables interleukin-1 alpha and tumor necrosis factor were separated into two groups each at the median with below the median representing "Low" values and above the median representing "High" values. Categorical prevalence are reported as the frequency of the subsample and the within group percentage. Independent T-tests and Chi-square test were used to compare respectively continuous and categorical variables between groups. Logistic regression analyses were performed in order to examine the potential associations between illicit drug use and the cytokines in the presence of the covariates. Demographic and physiological covariates that may confound the relationship between drug use and the cytokines were selected based on previous research.

RESULTS

Unadjusted Group differences

As seen in Table 1, the median age was 47 years of age. The total amount of men (51%) was similar to the total amount of women (49%). However, there was a significant difference between the drug using groups on gender ($X^2 = 16.81$, $p = .01$) with all groups having more men than women. There was also a significant difference between the groups based on years

of education ($F [2,165] = 3.40, p = .04$), with marijuana and other drug users ($M = 13.16, SD = 2.08$) having lower levels than their marijuana only ($M = 14.13, p = 2.41$) and Non-drug user ($M = 14.21, p = 2.26$). On average, the sample was obese with a BMI of 31.12 kg/m^2 ($SD = 8.60 \text{ kg/m}^2$). In addition, there were no significant differences among other demographic and physiological variables, including interleukin-1 alpha and tumor necrosis factor.

Unadjusted Associations between Lifetime Drug Use and Cytokines

There were no significant unadjusted associations between either interleukin-1 alpha or tumor necrosis factor and any demographic or physiological variables. Participants who reported no drug use in their lifetime were 2.14 (95% CI: 1.01, 4.54) times more likely to have higher levels of tumor necrosis factor than their marijuana only using counterparts. Marijuana and other drug users were more likely to have higher tumor necrosis factor levels in comparison to their marijuana using counterparts, though this relationship was not significant ($OR = 1.96, 95\% \text{ CI: } 0.84, 4.55$). There was no association between drug use and interleukin-1 alpha. These results can be found in Table 2 and depictions of these relationships are seen in Figure 1 and Figure 2.

Adjusted Associations between Lifetime Drug Use and Cytokines

As seen in Table 2, in the presence of all demographic and physiological variables, drug use was not significantly associated with interleukin-1 alpha. Non-drug users were 2.73 (95% CI: 1.18, 6.31) times more likely than marijuana only users to have higher tumor necrosis factor.

DISCUSSION

The current study examined the associations between self-reported lifetime drug use, interleukin-1 alpha and tumor necrosis factor. The non-drug users were over two times more likely to have higher tumor necrosis factor levels than their marijuana only using counterparts were. In the presence of physiological and demographic covariates, the relationship between self-reported lifetime drug use and tumor necrosis factor levels slightly increased in strength. No relationship emerged between lifetime drug use and interleukin-1 alpha levels. These results support previous literature, which presented lower levels of proinflammatory cytokine interleukin-6 in marijuana only users in comparison to other subgroups (Keen et al., 2014). In addition, these results are consistent with cellular level research that indicates cannabinoids decrease tumor necrosis factor levels (Cabral & Vasquez, 1992; Klein et al., 2000; Kusher et al., 1994).

Interleukin-6, interleukin-1 alpha, and tumor necrosis factor are three of the primary cytokines involved in the brain-immune system connection through sickness behavior (Holmes et al., 2011; Maier & Watkins, 1998). Interestingly, there was a differentiation in the effects of self-reported lifetime drug use and the cytokines interleukin-1 alpha and tumor necrosis factor in the current study. Specifically, lifetime drug use was associated with tumor necrosis factor, but not interleukin-1 alpha. Given that interleukin-6 also has anti-inflammatory properties, including the ability to down regulate tumor necrosis factor, it is

possible that the current findings align with previous research (Keen et al., 2014) and are based on this specific cytokine network. Though tumor necrosis factor and interleukin-1 alpha are both involved in clotting, connective tissue remodeling or even tissue destruction, the present study presents a differentiation in tumor necrosis factor and interleukin-1 alpha function based on lifetime drug use. Moreover, the biological influences of tumor necrosis factor and interleukin-1 alpha differ mainly in the fact that tumor necrosis factor is a part of the apoptotic domain or cell death, whereas interleukin-1 has no death domain (Feldman et al., 2000). This may be connected to marijuana's immunosuppressive influence.

Overall, the levels of TNF seemed to be within range of other normal or average subsamples reported in the literature. The TNF levels of in the current sample of African Americans were lower than symptomatic HIV-1 positive participants presented by Roux-Lombard and colleagues (1989), but very close to the HIV-1 asymptomatic subsample in the same study. The current sample's median value was well below levels presented in patients with congestive or chronic heart failure (Levine et al., 1990; Testa et al., 1996). However, the "normal" control group in the heart failure study presented by Feldman et al. (2000) had very similar values to the levels presented in this sample. The TNF levels in the current sample were also consistent with a subsample of smokers and lower than a subsample of participants with asthma (Keatings et al., 1995). However, the median values of Interleukin-1 alpha in the current sample were also more than double the levels in the young adult to middle-aged sample of smokers presented by Yang et al. (2014). Additionally, Interleukin-1 alpha levels were higher than those reported in a sample of senile or cognitively impaired Chinese sample (Li et al., 2011).

In the current study, the groups differed significantly based on covariates age and sex. Specifically, the marijuana using group was younger and predominately male. This is consistent with prevalence statistics and previous literature (Degenhardt et al., 2008). Though this is a community-based sample of African Americans, these findings suggest that there may be a sub group of younger males driving the differences among the groups based on their recreational use of marijuana. Historically, previous research has suggested males are more likely to experience substance abuse based on national trends (Brady and Randall, 1999). However, there is also a sex difference suggested based in proinflammatory markers (Sperry et al., 2008). Moreover, there is potential age-related changes in proinflammatory markers that may cause potential variations in the results (O'Mahony et al., 1998; Stowe et al., 2010). Specifically, older individuals experience increases in proinflammatory markers, such as IL-6, IL-1 receptor agonists, and C-reactive protein (Ferrucci et al., 2005). Taken together, further research is necessary to elucidate the relationship between marijuana use and proinflammatory markers. Age and sex may have orthogonal influence upon the relationship between recreational marijuana use, but a priori design and analyses are necessary to continue exploring the this issue. Identifying differential effects based on age and sex will further the knowledge base and allow researchers to tailor interventions or research methodology for subgroups within the African American communities.

Our findings are subject to limitations. First, the subjects in the current study were non-fasting at time of blood draw and the time of blood draw was between 9am and 6pm. In addition, patients reported taking medications, but other than our exclusion criteria

(psychological disorders and brain trauma), we do not know what the intended use or names of these medications. Lastly, the parent study did not measure frequency of illicit drug use, thus leaving the current study unable to examine the association between frequencies of illicit drug use and resting cytokine levels and limiting generalizability to cannabis and illicit drug users.

The current findings support the growing literature positing the immunosuppressive influence of marijuana use. This preliminary study also presents a potential differentiation in marijuana's influence on the immune system, as non-drug users were more likely to have higher tumor necrosis factor but not interleukin-1 alpha than marijuana use only counterparts were. Future research should further identify other proinflammatory or immune agents that are influenced by marijuana use in various diseased and healthy sample types. Further exploration will allow for extrapolation to both frequent and moderate marijuana users. This is especially important given the legalization efforts and prevalence of marijuana use in the United States.

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REFERENCES

- Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer HD. Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future. *Journal of Opioid Management*. 2009; 5(3):153–168.
- Albayram O, Alferink J, Pitsch J, Piyanova A, Neitzert K, Poppensieker K, Bilkei-Gorzo A. Role of CB1 cannabinoid receptors on GABAergic neurons in brain aging. *Proceedings of the National Academy of Sciences of the United States of America*. 2011; 108(27):11256–11261. doi: 10.1073/pnas.1016442108. [PubMed: 21690345]
- Arevalo-Martin A, Vela JM, Molina-Holgado E, Borrell J, Guaza C. Therapeutic Action of Cannabinoids in a Murine Model of Multiple Sclerosis. *The Journal of Neuroscience*. 2003; 23(7):2511–2516. [PubMed: 12684434]
- Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine*. 1997; 156(5):1606–1613. doi: 10.1164/ajrccm.156.5.9704146. [PubMed: 9372683]
- Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain, Behavior, and Immunity*. 2003; 17(5):350–364.
- Brady KT, Randall CL. Gender Differences in Substance Use Disorders. *The Psychiatric Clinics of North America*. 1999; 22(2):241–252. [PubMed: 10385931]
- Cabral GA, Griffin-Thomas L. Cannabinoids as therapeutic agents for ablating neuroinflammatory disease. *Endocrine, Metabolic & Immune Disorders Drug Targets*. 2008; 8(3):159–172.
- Cabral GA, Griffin-Thomas L. Emerging role of the cannabinoid receptor CB2 in immune regulation: therapeutic prospects for neuroinflammation. *Expert Reviews in Molecular Medicine*. 2009; 11:e3. doi: 10.1017/S1462399409000957. [PubMed: 19152719]
- Cabral GA, Vasquez R. Delta-9-Tetrahydrocannabinol Suppresses Macrophage Extrinsic Antiherpesvirus Activity. *Proceedings of the Society for Experimental Biology and Medicine*. 1992; 199(2):255–263. [PubMed: 1311105]

- Campbell VA, Gowran A. Alzheimer's disease; taking the edge off with cannabinoids? *British Journal of Pharmacology*. 2007; 152(5):655–662. doi: 10.1038/sj.bjp.0707446. [PubMed: 17828287]
- Canvin JM, el-Gabalawy HS. Anti-inflammatory therapy. *Physical Medicine and Rehabilitation Clinics of North America*. 1999; 10(2):301–317. [PubMed: 10370933]
- Chang YH, Lee ST, Lin WW. Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: involvement of eicosanoids. *Journal of Cellular Biochemistry*. 2001; 81(4):715–723. [PubMed: 11329626]
- Degenhardt L, Chiu W, Sampson N, Keslar RC, Anthony JC, Angemeyer M, Buffaerts R, de Girolamo G, Gureje O, Huang Y, Karam A, Kostyuchenko S, Lepine JP, Mora MEM, Neumark Y, Ormel JH, Pinto-Mesa A, Posada-Villa J, Stein DJ, Takeshima T, Wells JE. Toward a Global View of Alcohol, Tobacco, Cannabis, and Cocaine Use: Findings from the WHO World Mental Health Surveys. *PLOS Medicine*. 2008; 5(7):1054–1067.
- England H, Summersgill HR, Edye ME, Rothwell NJ, Brough D. Release of interleukin-1alpha or interleukin-1beta depends on mechanism of cell death. *Journal of Biological Chemistry*. 2014; 289(23):15942–15950. doi: 10.1074/jbc.M114.557561. [PubMed: 24790078]
- Feldman AM, Combs A, Wagner D, Kadakomi T, Kubota T, Li YY, McTiernan C. The Role of Tumor Necrosis Factor in the Pathophysiology of Heart Failure. *Journal of the American College of Cardiology*. 2000; 35(3):537–544. [PubMed: 10716453]
- Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub Dennis, Guralnik JM, Longo DL. The origins of age-related proinflammatory state. *Blood*. 2005; 105(6):2294–2299. [PubMed: 15572589]
- Fischer-Stenger K, Dove Pettit DA, Cabral GA. Delta 9-tetrahydrocannabinol inhibition of tumor necrosis factor-alpha: suppression of post-translational events. *Journal of Pharmacology and Experimental Therapeutics*. 1993; 267(3):1558–1565. [PubMed: 8263818]
- Friedman H, Klein TW. Marijuana and Immunity. *Science & Medicine*. 1999; 6(2):12–21.
- Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell*. 2010; 140(6):918–934. doi: 10.1016/j.cell.2010.02.016. [PubMed: 20303880]
- Gorelick PB. Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. *Annals of the New York Academy of Sciences*. 2010; 1207:155–162. doi: 10.1111/j.1749-6632.2010.05726.x. [PubMed: 20955439]
- Gowran A, Noonan J, Campbell VA. The multiplicity of action of cannabinoids: implications for treating neurodegeneration. *CNS Neuroscience & Therapeutics*. 2011; 17(6):637–644. doi: 10.1111/j.1755-5949.2010.00195.x. [PubMed: 20875047]
- Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, Investigators, C. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 2011; 70(4):576–582. doi: 10.1136/ard.2010.129916. [PubMed: 21109516]
- Grivnenkov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Annals of the Rheumatic Diseases*. 2011; 70(Suppl 1):i104–108. doi: 10.1136/ard.2010.140145. [PubMed: 21339211]
- Hazekamp A, Franjo G. Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids*. 2010; 5(Special Issue):1–21.
- Holmes C, Cunningham C, Zotova E, Culliford D, Perry VH. Proinflammatory cytokines, sickness behavior, and Alzheimer disease. *Neurology*. 2011; 77
- Jackson SJ, Diemel LT, Pryce G, Baker D. Cannabinoids and neuroprotection in CNS inflammatory disease. *Journal of the Neurological Sciences*. 2005; 233(1-2):21–25. doi: 10.1016/j.jns.2005.03.002. [PubMed: 15894331]
- Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in Interleukin-8 and Tumor Necrosis Factor- α in Induced Sputum from Patients with Chronic Obstructive Pulmonary Disease or Asthma. *American Journal of Respiratory and Critical Care Medicine*. 1995; 153:530–534. [PubMed: 8564092]

- Keen L 2nd, Pereira D, Latimer W. Self-reported lifetime marijuana use and interleukin-6 levels in middle-aged African Americans. *Drug and Alcohol Dependence*. 2014 doi: 10.1016/j.drugalcdep.2014.04.011.
- Killestein J, Uitdehaag BM, Polman CH. Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs*. 2004; 64(1):1–11. [PubMed: 14723555]
- Klein TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nature Reviews: Immunology*. 2005; 5(5):400–411. doi: 10.1038/nri1602.
- Klein TW, Friedman H, Specter S. Marijuana, immunity and infection. *Journal of Neuroimmunology*. 1998; 83(1-2):102–115. [PubMed: 9610678]
- Klein TW, Lane B, Newton CA, Friedman H. The Cannabinoid System and Cytokine Network. *Proceedings of the Society for Experimental Biology and Medicine*. 2000; 225:1–8. [PubMed: 10998193]
- Klein TW, Newton C, Larsen K, Lu L, Perkins I, Nong L, Friedman H. The cannabinoid system and immune modulation. *Journal of Leukocyte Biology*. 2003; 74(4):486–496. doi: 10.1189/jlb.0303101. [PubMed: 12960289]
- Kusher DI, Dawson LO, Taylor AC, Djeu JY. Effect of the Psychoactive Metabolite of Marijuana, Delta-9-Tetrahydrocannabinol (THC), on the Synthesis of Tumor Necrosis Factor by Human Large Granular Lymphocytes. *Cellular Immunology*. 1994; 154:99–108. [PubMed: 8118892]
- Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated Circulating Levels of Tumor Necrosis Factor in Sever Chronic Heart Failure. *New England Journal of Medicine*. 1990; 323(4):236–241. [PubMed: 2195340]
- Li G, Wang LY, Shofer JB, Thompson ML, Peskind ER, McCormick W, Larson EB. Temporal relationship between depression and dementia: findings from a large community-based 15-year follow-up study. *Archives of General Psychiatry*. 2011; 68(9):970–977. doi: 10.1001/archgenpsychiatry.2011.86. [PubMed: 21893662]
- Licastro F, Pedrini S, Caputo L, Annoni G, Davis LJ, Ferri C, Grimaldi LME. Increased plasma levels of interleukin-1, interleukin-6 and a-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain? *Journal of Neuroimmunology*. 2000; 103:97–102. [PubMed: 10674995]
- Maier SF, Watkins LR. Cytokines for Psychologists: Implications of Bidirectional Immune-to-Brain Communication for Understanding Behavior, Mood, and Cognition. *Psychological Review*. 1998; 105(1):83–107. [PubMed: 9450372]
- Marchalant Y, Brothers HM, Wenk GL. Inflammation and aging: can endocannabinoids help? *Biomedicine and Pharmacotherapy*. 2008; 62(4):212–217. doi: 10.1016/j.biopha.2008.02.004. [PubMed: 18400455]
- Marchetti B, Abbracchio MP. To be or not to be (inflamed)--is that the question in anti-inflammatory drug therapy of neurodegenerative disorders? *Trends in Pharmacological Sciences*. 2005; 26(10):517–525. doi: 10.1016/j.tips.2005.08.007. [PubMed: 16126283]
- Matsuda K, Mikami Y, Takeda K, Fukuyama S, Egawa S, Sunamura M, Matsuno S. The cannabinoid 1 receptor antagonist, AM251, prolongs the survival of rats with severe acute pancreatitis. *Tohoku Journal of Experimental Medicine*. 2005; 207(2):99–107. [PubMed: 16141678]
- McDade TW, Hawkey LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. *Psychosomatic Medicine*. 2006; 68(3):376–381. doi: 10.1097/01.psy.0000221371.43607.64. [PubMed: 16738067]
- Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *Journal of Clinical Endocrinology and Metabolism*. 1997; 82(12):4196–4200. doi: 10.1210/jcem.82.12.4450. [PubMed: 9398739]
- NIDA. Research Report Series: Marijuana. 2012. <http://www.drugabuse.gov/publications/research-reports/marijuana/letter-director>
- O'Mahony L, Holland J, Jackson J, Feighery C, Hennessy TPJ, Mealy K. Quantitative intracellular cytokine measurement: age-related changes in proinflammatory cytokine production. *Clinical & Experimental Immunology*. 1998; 113:213–219. [PubMed: 9717970]

- Prenninx BWH, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, Pahor M. Inflammatory MARKers and Depressed Mood in Older Persons: Results from the Health, Aging and Body Composition Study. *Biological Psychiatry*. 2003; 54:566–572. doi: 10.1016/S0006-3223(02)01811-5. [PubMed: 12946885]
- Raber J, Sorg O, Horn TF, Yu N, Koob GF, Campbell IL, Bloom FE. Inflammatory cytokines: putative regulators of neuronal and neuro-endocrine function. *Brain Research: Brain Research Reviews*. 1998; 26(2-3):320–326. [PubMed: 9651548]
- Reiss CS. Cannabinoids and Viral Infections. *Pharmaceuticals (Basel, Switzerland)*. 2010; 3(6):1873–1886. doi: 10.3390/ph3061873.
- Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, Vitoretto LB, Mariano-Souza DP, Quinteiro-Filho WM, Palermo-Neto J. Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. *European Journal of Pharmacology*. 2012; 678(1-3):78–85. doi: 10.1016/j.ejphar.2011.12.043. [PubMed: 22265864]
- Roth MD, Baldwin GC, Tashkin DP. Effects of delta-9-tetrahydrocannabinol on human immune function and host defense. *Chemistry and Physics of Lipids*. 2002; 121:229–239. [PubMed: 12505703]
- Roux-Lombard P, Modoux C, Cruchaud A, Dayer J. Purified Blood Monocytes from HIV 1-Infected Patients Produce High Levels of TNF α and IL-1. *Clinical Immunology and Immunopathology*. 1989; 50:374–384. [PubMed: 2492910]
- Shivers SC, Newton C, Friedman H, Klein TW. Delta-9-Tetrahydrocannabinol (THC) Modulates IL-1 Bioactivity in Human Monocyte/Macrophage Cell Lines. *Life Sciences*. 1994; 54(17):1281–1289. [PubMed: 8164509]
- Singh T, Newman AB. Inflammatory markers in population studies of aging. *Ageing Res Rev*. 2011; 10(3):319–329. doi: 10.1016/j.arr.2010.11.002. [PubMed: 21145432]
- Snella E, Pross S, Friedman H. Relationship of Aging and Cytokines to the Immunomodulation by Delta-9-Tetrahydrocannabinol on Murine Lymphoid Cells. *International Society for Immunopharmacology*. 1995; 17(12):1045–1054.
- Sperry JL, Friese RS, Frankel HL, West MA, Cuschieri J, Moore EE, Harbrecht BG, Peitzman AB, Billiar TR, Maier RV, Remick DG, Minei JP. Male Gender is Associated with Excessive IL-6 Expression Following Severe Injury. *Journal of Trauma*. 2008; 64(3):572–578.
- Stowe RP, Peek MK, Cutchin MP, Goodwin JS. Plasma Cytokine Levels in a Population-Based Study: Relation to Age and Ethnicity. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2010; 65A(4):429–433.
- Testa M, Yeh M, Lee P, Fanelli R, Loperfido F, Berman JW, LeJemmetel TH. Circulating Levels of Cytokines and Their Endogenous Modulators in Patients with Mild to Severe Congestive Heart Failure Due to Coronary Artery Disease or Hypertension. *Journal of the American College of Cardiology*. 1996; 28(4):964–971. [PubMed: 8837575]
- Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Newman AB. The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline. *Journal of the American Medical Association*. 2004; 292(18):2237–2242. [PubMed: 15536110]
- Yang YS, Lim HK, Hong KK, Shin MK, Lee JW, Lee SW, Kim NI. Cigarette smoke-induced interleukin-1 α may be involved in the pathogenesis of adult acne. *Ann Dermatol*. 2014; 26(1):11–16. doi: 10.5021/ad.2014.26.1.11. [PubMed: 24648681]
- Zurier RB, Rossetti RG, Burstein SH, Bidinger B. Suppression of human monocyte interleukin-1 β production by ajulemic acid, a nonpsychoactive cannabinoid. *Biochemical Pharmacology*. 2003; 65:649–655. [PubMed: 12566094]

Figure 1.
Dot plots of the Interleukin-1 alpha blood levels of each participant separated by drug use sub groups

Figure 2.
Dot plots of the Tumor Necrosis blood levels of each participant separated by drug use sub groups

Table 1

Participant Characteristics.

	Total N = 168	No Drugs n = 77	Marijuana n = 46	Marijuana+ n = 45		
	$\bar{X}$ (SD/%)	$\bar{X}$ (SD/%)	$\bar{X}$ (SD/%)	$\bar{X}$ (SD/%)	F/X ²	p
Age (yrs)					4.25	.12
< 47	89 (53%)	39 (51%)	30 (65%)	20 (44%)		
> 47	79 (47%)	38 (49%)	16 (35%)	25 (56%)		
Ed (yrs)	13.90 (2.29)	14.21 (2.26)	14.13 (2.41)	13.16 (2.08)	3.40	.04
Sex					16.81	.01
Female	85 (51%)	52 (68%)	15 (33%)	18 (40%)		
Male	83 (49%)	25 (32%)	31 (67%)	27 (60%)		
Income					7.90	.09
< \$20K	64 (38%)	25 (33%)	15 (33%)	24 (53%)		
\$20K-\$39K	57 (34%)	26 (34%)	20 (44%)	11 (24%)		
\$40K-\$85K	47 (28%)	26 (34%)	11 (24%)	10 (22%)		
Medication					0.91	.63
No	96 (57%)	42 (55%)	29 (63%)	25 (56%)		
Yes	72 (43%)	35 (45%)	17 (37%)	20 (44%)		
SBP (mm hg)	133.14 (18.61)	134.23 (16.96)	130.22 (18.57)	134.24 (21.29)	0.77	.46
DBP (mm hg)	79.48 (13.97)	80.96 (12.96)	76.43 (13.03)	80.04 (16.22)	1.57	.21
BMI (kg/m²)	31.12 (8.60)	31.18 (8.96)	30.89 (9.30)	31.26 (7.32)	0.02	.98
TNF (pg/mL)					4.24	.12
< 1.70 (pg/mL)	88 (52%)	36 (47%)	30 (65%)	22 (49%)		
> 1.70 (pg/mL)	80 (48%)	41 (53%)	16 (35%)	23 (51%)		
IL-1α (pg/mL)					0.14	.93
< 42 (pg/mL)	88 (52%)	41 (53%)	23 (50%)	24 (53%)		
> 42 (pg/mL)	80 (48%)	36 (47%)	23 (50%)	21 (47%)		

Note: Ed = Years of Education; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; IL-1 α = Interleukin 1 Alpha; TNF = Tumor Necrosis Factor; Marijuana = Lifetime Marijuana use only; Marijuana+ = Lifetime Marijuana and Other Drug Use

*
<.05

**
>.01

Table 2

Associations between illicit drug use and the cytokines in the presence of the covariates

	Tumor Necrosis Factor		Interleukin-1 Alpha	
	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)	Unadjusted OR (CI 95%)	Adjusted OR (CI 95%)
Age				
<47	1	1	1	1
>47	1.14 (0.62, 2.09)	1.22 (0.62, 2.42)	1.26 (0.68, 2.31)	1.12 (0.57, 2.21)
Ed	0.94 (.82, 1.07)	0.99 (.84, 1.17)	0.87 (.76, 1.00)	0.90 (.76, 1.06)
Sex				
Female	1	1	1	1
Male	1.27 (0.69, 2.32)	2.01 (0.95, 4.29)	1.27 (0.69, 2.32)	1.01 (0.48, 2.12)
Income				
< \$20K	1	1	1	1
\$20K-\$39K	0.69 (0.34, 1.41)	0.64 (0.29, 1.43)	1.11 (0.54, 2.27)	1.29 (0.58, 2.87)
\$40K-\$85K	0.71 (0.34, 1.52)	0.81 (0.33, 1.43)	0.62 (0.29, 1.34)	0.76 (0.31, 1.87)
Medication				
No	1	1	1	1
Yes	1.75 (0.94, 3.24)	1.96 (0.97, 4.00)	.97 (0.53, 1.79)	.87 (0.43, 1.75)
SBP (mm hg)	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)	1.01 (0.99, 1.03)	.99 (0.96, 1.02)
DBP (mm hg)	1.01 (0.99, 1.03)	1.00 (0.97, 1.04)	1.02 (1.00, 1.05)	1.03 (0.99, 1.07)
BMI (kg/m2)	1.03 (0.99, 1.07)	1.03 (0.99, 1.07)	0.99 (0.95, 1.03)	0.98 (0.94, 1.02)
Drug Use				
Marijuana	1	1	1	1
Marijuana+	1.96 (0.84, 4.55)	1.95 (0.79, 4.81)	0.88 (0.38, 1.99)	0.67 (0.28, 1.65)
No Drugs	2.14 (1.01, 4.54)*	2.73 (1.18, 6.31)*	0.88 (0.42, 1.82)	0.77 (0.34, 1.74)

Note: Edu = Years of Education; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; Marijuana= Lifetime Marijuana use only; Marijuana+ = Lifetime Marijuana and Other Drug Use

*
<.05