Published in final edited form as:

Curr Psychiatry Rep. ; 20(9): 75. doi:10.1007/s11920-018-0946-3.

The Intersection of Sex Differences, Tobacco Use, and Inflammation: Implications for Psychiatric Disorders

Rebecca L. Ashare¹, Reagan R. Wetherill¹

¹Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, 3535 Market Street, Suite 4100, Philadelphia, PA 19104, USA

Abstract

Purpose of Review—Tobacco use, sex differences, and psychiatric disorders are associated with altered immune function. There are also sex differences in tobacco use and psychiatric disorders. This review summarizes findings from the small, but growing literature examining sex differences in the effects of tobacco use on inflammation and the implications for psychiatric disorders.

Recent Findings—We identified four studies that tested the interaction between sex and tobacco/nicotine on inflammation. Although males and females generally exhibited differential tobacco-induced immune responses, the pattern varied depending on the sample (rodents vs. humans) and the method to evaluate inflammation.

Summary—Evidence suggests that sex modulates the effects of tobacco smoke on inflammation. Many inflammation markers associated with sex differences and tobacco use are related to psychiatric disorders. We propose a model in which sex, tobacco use, and inflammation interact to increase risk for psychiatric disorders. Future studies are needed to examine the mechanisms that explain this relationship.

Keywords

Sex differences; Nicotine; Tobacco; Inflammation; Immune function; Psychiatric disorders

Introduction

As one of the leading causes of morbidity and mortality, it is well-known that tobacco smoking contributes to increased risk of cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and cancer [1]. CVD, COPD, and cancer are all characterized by elevated levels of inflammation [2-4]. Thus, a shared mechanism by which tobacco smoking may contribute to these medical conditions may be through tobacco's effects on inflammation [5, 6]. Indeed, tobacco smoking induces inflammatory markers including C-

Rebecca L. Ashare, rlashare@pennmedicine.upenn.edu.

Conflict of Interest Rebecca L. Ashare and Reagan R. Wetherill declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

This article is part of the Topical Collection on *Reproductive Psychiatry and Women's Health*

reactive protein (CRP), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and activated macrophages [7-11]. Numerous studies have also observed sex differences in inflammatory response and immune function [12, 13] as well as in the effects of and ability to quit tobacco smoking [14••]. Therefore, it is plausible that observed sex differences in the prevalence and severity of COPD, CVD, and cancer may be partly attributed to the interaction between sex, tobacco use, and inflammation.

Elevated inflammation and immune dysregulation have been associated with several psychiatric disorders including depression, schizophrenia, and bipolar disorder [15-17]. There is also evidence for sex differences in psychiatric disorders, with the strongest support for a difference in the prevalence of depression, with females having a higher prevalence than males [18••]. Notably, the smoking rate among adults with psychiatric disorders, such as schizophrenia spectrum, bipolar, and recurring depressive disorders, ranges from 45 to 85%, which is 3 to 4 times the rate of the general population [19-21]. Therefore, it is possible that inflammation represents a common mechanism that may partially explain the relationship between tobacco smoking and psychiatric disorders and how sex may modulate this relationship. In this review, we discuss the evidence for sex differences in immune responses, tobacco smoking, and psychiatric disorders and how this information might be used to develop more targeted strategies for treating both tobacco dependence and psychiatric disorders (Fig. 1). We also discuss the potential paradoxical effects of nicotine (vs. tobacco smoking) on inflammation, as well as the implications for emerging tobacco products, such as electronic cigarettes.

Effects of Tobacco Use and Nicotine on Inflammation

Numerous studies have demonstrated that smokers exhibit elevated levels of inflammation across a variety of markers, relative to non-smokers. Tobacco-induced inflammation is believed to be one of the primary pathways by which tobacco smoking contributes to acute and chronic inflammatory diseases, including CVD, COPD, acute respiratory distress syndrome, and lung cancer [6]. Although this topic has been reviewed in depth elsewhere [8, 22, 23], CRP, cytokines (e.g., IL-6), markers of oxidative stress (nitric oxide), cell adhesion molecules (e.g., ICAM), and markers associated with vascular inflammation (e.g., MMP-9) have all demonstrated sensitivity to smoking status [7, 24-27]. Tobacco smoke may also downregulate expression of genes involved with regulation of immune function [9]. Although there is some evidence that smoking burden (e.g., number of cigarettes smoked per day and/or number of years smoked) is positively associated with inflammation [24, 28, 29], others have found no relationship [27]. Importantly, former smokers exhibit lower levels of inflammation relative to current smokers [27] and reductions in inflammation following smoking cessation have been observed, particularly markers reflecting oxidative stress [28, 30]. While the precise duration for decreased inflammation following cessation remains an important research question, several studies have shown a relationship between time since cessation and reductions in inflammation, with times ranging from 4 months to 20 years [27, 30, 31]. Therefore, the adverse effects of tobacco smoking on inflammation may be reversible.

Despite the adverse effects of tobacco use on inflammation, nicotine alone, the main psychoactive ingredient in cigarettes, may have opposite effects. Nicotine attenuates pro-inflammatory cytokines interleukin-1 β (IL)-1 β , IL-6, tumor necrosis factor alpha (TNF)- α [32] and inhibits nuclear factor kappa (NFkB) signaling [33]. Many of nicotine's anti-inflammatory properties are attributed to its activation of the α 7 nicotinic acetylcholine receptors (nAChRs) [32, 34, 35]. For instance, activation of α 7 nAChRs suppresses abnormal activation of microglia and expression of CD14, ICAM-1, CD40, and TNF- α [36-38], and the α 7 nAChR antagonist mecamylamine reverses these effects [36]. In addition, nicotine may alter expression of genes involved with immune function, upregulating some genes (e.g., TGF- β 1, IL-4, CCR2, CXCR6, IL-1 α) and downregulating others (e.g., TNF- α , CCL2, IL-8, IL-10, CXCR4, IRF4) [39, 40].

The differential effects of nicotine alone compared to combustible tobacco may have important implications for emerging tobacco products. For instance, the use of electronic nicotine delivery systems, or ENDS (e.g., e-cigarettes, vape pens), has dramatically increased, particularly among youth and young adults [41]. ENDS deliver nicotine via a liquid that is heated to form a vapor, and thus, deliver nicotine without combusting tobacco. Because ENDS do not burn tobacco, ENDS are typically perceived as less harmful than conventional cigarettes. Short-term studies have shown that switching to ENDS (from combustible tobacco) may yield reductions in inflammation [42]; however, emerging data show that ENDS may cause inflammation similar to, yet distinct from, smoking combustible cigarettes [43, 44]. In general, the magnitude of the effects of ENDS on toxicant exposure is smaller than combustible tobacco, but ENDS still induce inflammation. Interestingly, ENDS aerosol exposure increases cytokine levels, with or without nicotine, suggesting that the chemicals in the aerosol are sufficient to produce pro-inflammatory effects (for a review, see [42]). Other parameters may be important to the inflammatory effects of ENDS including the temperature at which the aerosol is heated, the ingredients used to flavor the aerosol, and the base constituents of e-liquids which are not contained in combustible tobacco (e.g., propylene glycol and vegetable glycerin). When heated, propylene glycol and vegetable glycerin produce carbonyls, including acrolein, formaldehyde, and acetaldehyde, which have adverse effects on lung and cardiovascular function [42, 45]. Moreover, diacetyl, which is used in flavors such as caramel and butterscotch, and benzaldehyde, which is used in fruit flavorings, have been associated with respiratory disease and cytotoxicity [42]. To date, there is a paucity of human data on the long-term effects of ENDS use or the effects of ENDS use among never smokers. Consequently, rigorous research designed to identify the effects of ENDS use is needed.

Sex Differences in Tobacco Use and the Effects of Nicotine

Sex differences exist across all phases of tobacco use. Men initiate nicotine use at a younger age and report greater nicotine use than women [46], yet women escalate use and progress to nicotine use disorder faster than men [47]. Women also have greater difficulty with smoking cessation than men [14]. During acute withdrawal, women report more negative affect [48, 49] and more intense cue-induced craving than men [49, 50]. Women also have a higher risk of developing tobacco-related morbidity and mortality [51, 52], including increased

incidence of lung cancer-related deaths [53], increased risk for heart attack [54], and increased risk for COPD [55].

A large body of literature suggests that sex differences in the effects of nicotine may contribute to the sex differences described above (for recent reviews, see [56-58]). In this section, we provide a brief overview of sex differences in the effects of nicotine. In general, sex differences are first established during early fetal development when sexual differentiation of the brain occurs. If the SRY gene is present on the Y chromosome, testes development and fetal masculinization occurs with a surge of androgen; whereas, in the absence of the SRY gene, there is an excess of estrogen (i.e., estradiol) leading to feminization of the brain [59]. In addition to mediating sexual differentiation of the brain, gonadal hormones (i.e., testosterone, estrogen, progesterone) influence neurotransmission and modulate a variety of behaviors throughout the lifespan [60•]. Thus, sex differences in the effects of nicotine are likely a result of sexual dimorphisms in biology and the influence of gonadal hormones. For example, males and females differ in biological parameters that influence the pharmacokinetics and metabolism of nicotine. Indeed, clinical studies indicate that women metabolize nicotine at a higher rate than men, and ovarian hormones, specifically estrogen, seem to accelerate nicotine metabolism [61, 62]. However, animal studies do not support these findings [63, 64]. Specifically, animal studies have found comparable rates of nicotine metabolism in males and females [63] or faster nicotine metabolism in males compared to females [64]. Species differences, such as social and cultural factors, likely contribute to the inconsistency between human and animal research.

Sex differences and the influence of gonadal hormones are also evident in subjective, cognitive, and physiological responses to nicotine. DeVito and colleagues (2014) assessed the influence of sex and menstrual cycle phase, a common proxy for ovarian hormones, on several measures of nicotine effects, including subjective drug effects, cognition, physiological responses, and symptoms of withdrawal, craving, and affect using an intravenous nicotine paradigm and overnight abstinence in male and female smokers and found that female smokers had diminished subjective effects, but greater physiological responses, to nicotine [65]. Findings also revealed that luteal-phase female smokers (i.e., higher levels of progesterone relative to estrogen) reported diminished subjective nicotine effects and better cognition compared to follicular-phase (i.e., high estrogen, low progesterone) female smokers. These findings are consistent with a series of studies conducted by Perkins demonstrating greater subjective nicotine sensitivity in male smokers [56]. The Perkins studies also showed that female smokers are more sensitive to the non-nicotine conditioned stimuli (or cues) associated with cigarette smoking [56]. Although these are just a few examples of sex differences in nicotine's effects and the potential influence of gonadal hormones, these findings provide insight into the mechanisms underlying sex differences in tobacco use, which, in turn, could have significant effects on smoking-induced inflammation.

Sex Differences in Inflammatory Responses/Immune Regulation

Several studies have demonstrated sex differences in inflammation and immune function [66-69]. Although this topic has been reviewed in detail elsewhere [70], we will provide a

brief overview here. In response to infection, estrogen tends to increase the immune response whereas testosterone decreases it. However, the type of microbe causing the infection (e.g., viruses vs. bacteria) may influence sex-specific susceptibility to the infection [70]. For example, while males tend to be more susceptible to bacterial infection, females may exhibit greater inflammatory response to viral infection [70]. One of the most consistent findings is that females have higher levels of CRP compared to males [66, 67, 71], whereas, in response to bacterial infection, males may express higher levels of IL-6 compared to females [72]. Moreover, there may be stronger associations between inflammation, physical activity, and obesity on subjective outcomes (e.g., fatigue) among females compared to males [68]. Stress-induced inflammatory responses also differ between males and females, which may be due in part to the differential effects of testosterone and estrogen on the hypothalamic-pituitary-adrenal (HPA) axis as well as interactions between glucocorticoid receptors and gonadal hormones. In general, females exhibit greater increases in cytokines following acute stress and tend to show decreased immunity in response to chronic stress [73••].

Despite the wealth of evidence supporting differential immune responses between males and females, research examining the mechanisms for this effect is still emerging. A number of factors may play a role, including hormonal effects, differences in cell responses that are male or female—even prior to the production of sex hormones, and chronic stress [74, 75]. For instance, the X chromosome contains the highest concentration of genes related to immune function and this is believed to play a role in elevated rates of autoimmune disorders among females compared to males [76]. Preclinical studies have also demonstrated important interactions between sex hormones and inflammatory signaling during fetal development [77•]. Moreover, microglia, which are the primary immune cells of the CNS, are sensitive to external factors and have the potential to substantially impact neurodevelopment (for a review, see [78•]). Interestingly, the number of microglia vary by sex and age such that during fetal development male rats have more microglia than female rats, but the reverse pattern has been observed in adults [79]. Estrogen receptors also play an important role as they are expressed on various immune cells including B cells, CD4 and CD8 T cells, monocytes, and natural killer (NK) cells [80]. In large epidemiological samples, the use of sex hormones (i.e., estrogen) is associated with elevated CRP levels [67, 71]. As noted above, estrogen interacts with nicotine to alter activity of several cytochrome P450 (CYP) enzymes, which may ultimately result in making female lungs more susceptible to tobacco smoke-induced inflammation [81].

The Intersection of Sex Differences, Tobacco Use, and Inflammation

This is a growing area of research and the few studies that have been conducted have been preclinical (i.e., rodents) or cross-sectional (Table 1). Nevertheless, there is evidence to suggest that sex differences may play a role in the interaction between nicotine/tobacco use and inflammation. For example, using the spontaneously hypertensive (SH) rat as a model of COPD, Shen and colleagues found that male SH rats exhibited greater inflammatory responses following prolonged exposure to tobacco smoke [85•]. Specifically, male SH rats demonstrated elevated IL-6, TNF- α , and heme oxygenase-1 (HO-1) following tobacco smoke exposure, whereas female SH rats showed no increase. TNF- α can increase the

inflammatory response by activating cytokines (including IL-6), suggesting that male SH rats may be more susceptible to tobacco smoke-induced inflammation. HO-1 is a marker of oxidative stress and is expressed as a mechanism to attenuate inflammation. Therefore, it is possible that the elevated HO-1 observed in SH male rats may reflect a more adaptive response to the increased inflammation in response to exposure to tobacco smoke, relative to female rats [85•].

As noted above, the $\alpha 7$ nAChRs are thought to play an important role in the cholinergic anti-inflammatory pathway, suggesting that a deficiency in $\alpha 7$ nAChRs might exacerbate inflammation [86]. Using a mouse model of colitis, Al Sharari and colleagues tested this hypothesis by treating male and female $\alpha 7$ KO mice and wild-type (WT) mice with dextran sodium sulfate (DSS) to induce colitis symptoms and inflammation [82]. In addition, this study evaluated whether pharmacological approaches to enhancing cholinergic function ($\alpha 7$ nAChR agonist, choline, a positive allosteric modulator of $\alpha 7$ nAChR) would attenuate symptoms of colitis and inflammation. An increase in colitis symptoms and TNF- α was observed among male $\alpha 7$ KO mice, but not among female mice. Rather, the female KO mice showed similar disease severity as the female WT mice. However, while the pharmacological interventions attenuated colitis symptoms, there was no effect on TNF- α levels in male or female mice [82].

In a study comparing patients with COPD, smokers and non-smokers, Faner et al. (2014) tested the effects of smoking on inflammatory markers and changes in expression of genes related to immune function [83]. The authors measured biomarkers of inflammation at baseline and 180 min after smokers smoked two cigarettes following 8 h of abstinence. Although there was no change in any inflammatory marker following smoking or any sex differences before or after smoking, there were sex differences in the leukocyte transcriptome profile. Importantly, the differential expression of genes between baseline and following smoking varied between males and females. Among females, 61 genes were differentially expressed following smoking compared to only 19 genes among males. Of these 61 genes, several related to the immune response (IL18RAP), apoptosis, and cell death (MMP9, ADRB2, TNFSF14) [83].

There may also be sex differences across populations that impact the effect of tobacco smoke on inflammation. For example, Moscovis and colleagues evaluated peripheral blood mononuclear cells (PBMCs) from a sample of Indigenous Australians to compare those with a genetic profile indicating high risk for inflammatory responses versus those with low risk [84]. In addition, they evaluated whether these differences varied between males and females. To induce inflammation, PBMCs were treated with one of seven conditions: lipopolysaccharide (LPS), IFN- γ , cigarette smoke extract (CSE), LPS + IFN- γ , LPS + CSE, IFN- γ + CSE, or LPS + IFN- γ + CSE. Although there were no overall differences between the high-and low-risk genetic profile, there were interactions with sex. When all three inflammation conditions were combined (LPS + IFN- γ + CSE), males tended to show a reduction in cytokine response (IL-6, TNF- α , IL-1 β) relative to females, irrespective of genetic profile. However, among females, those in the high-risk group showed a reduced anti-inflammatory (IL-10) response compared to those in the low-risk group [84]. Although this effect was only observed when CSE was combined with LPS and IFN- γ , low IL-10 is

often associated with elevated levels of pro-inflammatory cytokines which may ultimately increase overall immune dysregulation [87].

Although the studies described above suggest that there may be important interactions between sex and the effects of tobacco smoke on inflammation, some have found that sex does not modulate the effect of tobacco use on inflammation [25] or changes in inflammation following cessation [29]. It is also difficult to determine the association between sex, inflammation, and tobacco use because many studies do not report whether inflammatory markers differed by sex [25, 28, 31] or sample sizes are too small to evaluate this question [30]. Moreover, there is very little evidence regarding the mechanism by which this interaction occurs. Only one study that we know of evaluated the association between testosterone and cigarette smoke-induced inflammation as a function of sex [84]. No correlations were observed among males, but among females, testosterone was positively correlated with IL-1 β , IL-6, IL-8, and TNF- α . However, as previously described, there may be important interactions between sex hormones (particularly estrogen) and nicotine.

What Is the Role of Sex Differences, Tobacco Use, and Inflammation in Psychiatric Disorders?

In the preceding sections, we reviewed evidence for sex differences in tobacco use and in inflammation/immune responses as well as the effects of tobacco use on inflammation/immune responses (pathways a, b, and c in Fig. 1). In this section, we will review some of the recent literature supporting the notion that the interactions among these three factors (shaded box in Fig. 1) play a role in the incidence and treatment of psychiatric disorders. For example, numerous studies have documented higher rates of major depressive disorder (MDD) among females, compared to males—an effect that is observed across cultures [88, 89]. There is also some evidence that bipolar disorder may be more common among females than males, though this may vary by type (bipolar type 1 vs. type 2) [90] and has not been found in all studies [91]. The manifestation and clinical course of the disorder may exhibit more important sex differences than prevalence alone (e.g., females may exhibit more depressive features than males) [92]. Lastly, sex differences have been observed in schizophrenia, with a higher prevalence among males at younger ages, whereas the prevalence may be higher among females at older ages [93]. However, a recent study of global prevalence found no sex difference in the prevalence of schizophrenia at any age [94].

Importantly, rates of tobacco use are higher among individuals with psychiatric disorders. Nearly 43% of persons with MDD are smokers [95, 96], and those with serious mental illness (SMI), such as schizophrenia spectrum, bipolar, and recurring depressive disorders smoke at rates 3 to 4 times those of the general population [19-21]. Smoking increases risk of first incidence, severity, and recurrence of MDD [97-100] and heavier smokers are at higher risk of depression [95, 101]. In addition, tobacco use is associated with first-episode psychosis [102] and those with a psychotic disorder are more nicotine dependent [103]. Moreover, higher levels of inflammation and/or immune dysregulation have been observed in MDD, bipolar disorder, and schizophrenia [15, 104]. Specifically, IL-6, CRP, TNF- α , and MCP-1/CCl2 have been proposed as biomarkers of depression [15, 105, 106]; IL-6, TNF- α ,

IL-1 β , and IL-1RA may represent immune-related biomarkers in schizophrenia [107]; and IL-6, TNF- α , IL-2, and IL-8/CXCL8 have been identified as potential biomarkers of bipolar disorder. As shown in Table 2, there is substantial overlap in the markers of inflammation that have been associated with sex differences, tobacco use, and psychiatric disorders. Despite this connection, few studies have explicitly examined this interaction. However, depressed smokers exhibit elevated levels of IL-6, CRP, and TNF- α compared to non-depressed smokers [108] and recent reviews have proposed inflammation as a potential mechanism to explain the relationship between tobacco use and depression [109, 110]. Based on evidence for sex differences in immune response, we suggest that this is an important factor to consider and should be the focus of future research.

Conclusions and Future Directions

Taken together, the relationship between sex, tobacco use, inflammation, and psychiatric disorders are complex. Nicotine and tobacco use have paradoxical effects, with tobacco smoking leading to an immunosuppressant state [8, 22] and nicotine having anti-inflammatory effects [32, 33]. Sex differences in tobacco use and the effects of nicotine may also influence these effects, as male smokers typically smoke more than female smokers. However, female smokers seem to metabolize nicotine faster [61, 62], have more difficulty with smoking cessation [14••], and have greater risk for smoking-related diseases than male smokers [51, 52]. In general, women have higher levels of inflammation and higher rates of autoimmune diseases [12, 13], which could contribute to the finding that women have higher rates of smoking-related inflammatory disease, including CVD, COPD, and lung cancer. Interestingly, research indicates that estrogen has anti-inflammatory effects; however, sex differences seem to supersede the effects of hormones alone in vivo. When sex, smoking, and inflammation are examined together, the limited number of studies indicates that there could be differential effects, but findings differ across studies.

These interactions may also identify novel treatment targets. For instance, pharmacological treatments to attenuate inflammation have been proposed as potential treatments for depression [111]. While these therapeutics may not have direct effects on smoking behavior, it is plausible that they may ultimately reduce smoking behavior by ameliorating depressive symptoms, which are well-known risk factors for smoking relapse [112]. Based on the evidence presented above, it may also be possible that individuals who are more susceptible to immune dysregulation and depression (i.e., females) may be more likely to benefit from anti-inflammatory medications for smoking cessation. Future studies examining the relationship between sex, smoking, and inflammation are needed, especially given that there seems to be a link between smoking, inflammation, and psychiatric disorders with women showing higher rates of MDD and bipolar disorder, higher levels inflammation, and higher risk of developing smoking-related morbidity and mortality.

Acknowledgments

Funding This research was supported by the National Institute on Drug Abuse grants (R01 DA044906 and R01 DA042682) and National Institute on Alcohol Abuse and Alcoholism grant (K23 AA023894).

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress A report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health 2014.
2. Libby P, Hansson GK. Inflammation and immunity in diseases of the arterial tree: players and layers. *Circ Res.* 2015;116(2):307–11. [PubMed: 25593275]
3. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(26):2645–53. [PubMed: 15215480]
4. Orozco-Morales M, Soca-Chafre G, Barrios-Bernal P, Hernandez-Pedro N, Arrieta O. Interplay between cellular and molecular inflammatory mediators in lung cancer. *Mediat Inflamm.* 2016;2016:3494608.
5. U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.
6. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol.* 2004;43(10):1731–7. [PubMed: 15145091]
7. Sopori M Effects of cigarette smoke on the immune system. *Nat Rev Immunol.* 2002;2(5):372–7. [PubMed: 12033743]
8. Stampfli MR, Anderson GP. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. *Nat Rev Immunol.* 2009;9(5):377–84. [PubMed: 19330016]
9. Spira A, Beane J, Shah V, Liu G, Schembri F, Yang X, et al. Effects of cigarette smoke on the human airway epithelial cell transcriptome. *Proc Natl Acad Sci U S A.* 2004;101(27):10143–8. [PubMed: 15210990]
10. D'Hulst AI, Vermaelen KY, Brusselle GG, Joos GF, Pauwels RA. Time course of cigarette smoke-induced pulmonary inflammation in mice. *Eur Respir J.* 2005;26(2):204–13. [PubMed: 16055867]
11. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J.* 2005;26(17): 1765–73. [PubMed: 15817606]
12. Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. *J Autoimmun.* 2012;38(2–3):J109–19. [PubMed: 22079680]
13. Yang Y, Kozloski M. Sex differences in age trajectories of physiological dysregulation: inflammation, metabolic syndrome, and allostatic load. *J Gerontol A Biol Sci Med Sci.* 2011;66(5):493–500. [PubMed: 21350248]
- 14••. Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: a review. *Prev Med.* 2016;92:135–40. [PubMed: 27471021] Smith and colleagues provide a comprehensive review on sex differences in smoking cessation.
15. Herron JW, Nerurkar L, Cavanagh J. Neuroimmune biomarkers in mental illness. *Curr Top Behav Neurosci.* 2018; 10.1007/7854_2018_45.
16. Leza JC, Garcia-Bueno B, Bioque M, Arango C, Parellada M, Do K, et al. Inflammation in schizophrenia: a question of balance. *Neurosci Biobehav Rev.* 2015;55:612–26. [PubMed: 26092265]

17. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;53:23–34. [PubMed: 24468642]
- 18••. Gobinath AR, Choleris E, Galea LA. Sex, hormones, and genotype interact to influence psychiatric disease, treatment, and behavioral research. *J Neurosci Res*. 2017;95(1–2):50–64. [PubMed: 27870452] This mini-review highlights the importance of studying sex differences, discusses statistical and methodological consideration in evaluating sex differences and how genes interact with sex to influence disease risk and treatment.
19. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA*. 2000;284(20):2606–10. [PubMed: 11086367]
20. Forman-Hoffman VL, Hedden SL, Glasheen C, Davies C, Colpe LJ. The role of mental illness on cigarette dependence and successful quitting in a nationally representative, household-based sample of U.S. adults. *Ann Epidemiol*. 2016;26(7):447–54. [PubMed: 27247163]
21. Centers for Disease Control and Prevention. Vital signs: current cigarette smoking among adults aged ≥18 years with mental illness—United States, 2009–2011. *MMWR Morb Mortal Wkly Rep*. 2013;62(5):81–7. [PubMed: 23388551]
22. Gonçalves RB, Coletta RD, Silvério KG, Benevides L, Casati MZ, da Silva JS, et al. Impact of smoking on inflammation: overview of molecular mechanisms. *Inflamm Res*. 2011;60(5):409–24. [PubMed: 21298317]
23. Arnsen Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun*. 2010;34(3):J258–J65. [PubMed: 20042314]
24. Kianoush S, Bittencourt MS, Lotufo PA, Bensenor IM, Jones SR, DeFilippis AP, et al. Association between smoking and serum GlycA and high-sensitivity C-reactive protein levels: the Multi-Ethnic Study of Atherosclerosis (MESA) and Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *J Am Heart Assoc*. 2017;6(8):e006545. [PubMed: 28838917]
25. Tibuakuu M, Kamimura D, Kianoush S, DeFilippis AP, Al Rifai M, Reynolds LM, et al. The association between cigarette smoking and inflammation: the Genetic Epidemiology Network of Arteriopathy (GENOA) study. *PLoS One*. 2017;12(9): e0184914. [PubMed: 28922371]
26. McEvoy JW, Nasir K, DeFilippis AP, Lima JA, Bluemke DA, Hundley WG, et al. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35(4):1002–10. [PubMed: 25745060]
27. Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, et al. Cigarette smoking and variations in systemic immune and inflammation markers. *J Natl Cancer Inst*. 2014;106(11)
28. King CC, Piper ME, Gepner AD, Fiore MC, Baker TB, Stein JH. Longitudinal impact of smoking and smoking cessation on inflammatory markers of cardiovascular disease risk. *Arterioscler Thromb Vasc Biol*. 2017;37(2):374–9. [PubMed: 27932354]
29. Asthana A, Johnson HM, Piper ME, Fiore MC, Baker TB, Stein JH. Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. *Am Heart J*. 2010;160(3):458–63. [PubMed: 20826253]
30. Van Keulen HV, Gomes AS, Toffolo MC, Oliveira EE, Silva LC, Alves CC, et al. Serum levels of nitric oxide and cytokines in smokers at the beginning and after 4 months of treatment for smoking cessation. *Int J Cardiol*. 2017;230:327–31. [PubMed: 28040275]
31. Peres FS, Barreto SM, Camelo LV, Ribeiro ALP, Vidigal PG, Duncan BB, et al. Time from smoking cessation and inflammatory markers: new evidence from a cross-sectional analysis of ELSA-Brasil. *Nicotine Tob Res*. 2017;19(7):852–8. [PubMed: 28164227]
32. Wei P, Liu Q, Li D, Zheng Q, Zhou J, Li J. Acute nicotine treatment attenuates lipopolysaccharide-induced cognitive dysfunction by increasing BDNF expression and inhibiting neuroinflammation in the rat hippocampus. *Neurosci Lett*. 2015;604:161–6. [PubMed: 26259694]
33. Sugano N, Shimada K, Ito K, Murai S. Nicotine inhibits the production of inflammatory mediators in U937 cells through modulation of nuclear factor-kappaB activation. *Biochem Biophys Res Commun*. 1998;252(1):25–8. [PubMed: 9813140]

34. Wittebole X, Hahm S, Coyle SM, Kumar A, Calvano SE, Lowry SF. Nicotine exposure alters in vivo human responses to endotoxin. *Clin Exp Immunol.* 2007;147(1):28–34. [PubMed: 17177960]
35. Baez-Pagan CA, Delgado-Velez M, Lasalde-Dominicci JA. Activation of the macrophage $\alpha 7$ nicotinic acetylcholine receptor and control of inflammation. *J NeuroImmune Pharmacol* 2015;10(3):468–476. [PubMed: 25870122] This paper reviews the role of $\alpha 7$ nicotinic acetylcholine receptors in controlling inflammation and how activation of the macrophage $\alpha 7$ selectively inhibits production of pro-inflammatory cytokines while leaving anti-inflammatory cytokines undisturbed.
36. Hamano R, Takahashi HK, Iwagaki H, Yoshino T, Nishibori M, Tanaka N. Stimulation of $\alpha 7$ nicotinic acetylcholine receptor inhibits CD14 and the toll-like receptor 4 expression in human monocytes. *Shock (Augusta, Ga).* 2006;26(4):358–64.
37. Suzuki T, Hide I, Matsubara A, Hama C, Harada K, Miyano K, et al. Microglial $\alpha 7$ nicotinic acetylcholine receptors drive a phospholipase C/IP3 pathway and modulate the cell activation toward a neuroprotective role. *J Neurosci Res.* 2006;83(8):1461–70. [PubMed: 16652343]
38. De Simone R, Ajmone-Cat MA, Carnevale D, Minghetti L. Activation of $\alpha 7$ nicotinic acetylcholine receptor by nicotine selectively up-regulates cyclooxygenase-2 and prostaglandin E2 in rat microglial cultures. *J Neuroinflammation.* 2005;2(1):4. [PubMed: 15670336]
39. Rock RB, Gekker G, Aravalli RN, Hu S, Sheng WS, Peterson PK. Potentiation of HIV-1 expression in microglial cells by nicotine: involvement of transforming growth factor-beta 1. *J NeuroImmune Pharmacol.* 2008;3(3):143–9. [PubMed: 18060582]
40. Yang Z, Nesil T, Connaghan KP, Li MD, Chang SL. Modulation effect of HIV-1 viral proteins and nicotine on expression of the immune-related genes in brain of the HIV-1 transgenic rats. *J NeuroImmune Pharmacol.* 2016;11(3):562–71. [PubMed: 27147085]
41. Singh TAR, Corey CG, Husten CG, Neff LJ, Homa DM, King BA. Tobacco use among middle and high school students— United States, 2011–2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:361–7. [PubMed: 27077789]
42. Shields PG, Berman M, Brasky TM, Freudenheim JL, Mathe E, McElroy JP, et al. A review of pulmonary toxicity of electronic cigarettes in the context of smoking: a focus on inflammation. *Cancer Epidemiol Biomark Prev.* 2017;26(8):1175–91. This review provides an overview of the effects of electronic cigarette use on inflammation
43. Ogunwale MA, Li M, Ramakrishnam Raju MV, Chen Y, Nantz MH, Conklin DJ, et al. Aldehyde detection in electronic cigarette aerosols. *ACS Omega.* 2017;2(3):1207–14. [PubMed: 28393137]
44. Hom S, Chen L, Wang T, Ghebrehwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets.* 2016;27(7):694–702. [PubMed: 27096416]
45. Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of electronic cigarettes on the cardiovascular system. *J Am Heart Assoc.* 2017;6(9):e006353. [PubMed: 28855171]
46. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration Retrieved from <https://www.samhsa.gov/data/2017>.
47. DiFranza JR, Savageau JA, Rigotti NA, Fletcher K, Ockene JK, McNeill AD, et al. Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. *Tob Control.* 2002;11(3):228–35. [PubMed: 12198274]
48. Xu J, Azizian A, Monterosso J, Domier CP, Brody AL, Fong TW, et al. Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. *Nicotine Tob Res.* 2008;10(11):1653–61. [PubMed: 18988078]
49. Doran N Sex differences in smoking cue reactivity: craving, negative affect, and preference for immediate smoking. *Am J Addict.* 2014;23(3):211–7. [PubMed: 24724877]
50. Field M, Duka T. Cue reactivity in smokers: the effects of perceived cigarette availability and gender. *Pharmacol Biochem Behav.* 2004;78(3):647–52. [PubMed: 15251274]
51. Kiyohara C, Ohno Y. Sex differences in lung cancer susceptibility: a review. *Gend Med.* 2010;7(5):381–401. [PubMed: 21056866]

52. Allen AM, Oncken C, Hatsukami D. Women and smoking: the effect of gender on the epidemiology, health effects, and cessation of smoking. *Curr Addict Rep*. 2014;1(1):53–60. [PubMed: 27213132]
53. Patel JD, Bach PB, Kris MG. Lung cancer in US women: a contemporary epidemic. *JAMA*. 2004;291(14):1763–8. [PubMed: 15082704]
54. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998;316(7137):1043–7. [PubMed: 9552903]
55. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respir Med*. 2006;100(6):1110–6. [PubMed: 16236491]
56. Perkins KA. Sex differences in nicotine reinforcement and reward: influences on the persistence of tobacco smoking. *Neb Symp Motiv*. 2009;55:143–69.
57. Pogun S, Yararbas G. Sex differences in nicotine action. *Handb Exp Pharmacol*. 2009;192:261–91.
58. Pauly JR. Gender differences in tobacco smoking dynamics and the neuropharmacological actions of nicotine. *Front Biosci*. 2008;13:505–16. [PubMed: 17981564]
59. Konkle AT, McCarthy MM. Developmental time course of estradiol, testosterone, and dihydrotestosterone levels in discrete regions of male and female rat brain. *Endocrinology*. 2011;152(1): 223–35. [PubMed: 21068160]
60. Cross SJ, Linker KE, Leslie FM. Sex-dependent effects of nicotine on the developing brain. *J Neurosci Res*. 2017;95(1–2):422–36. [PubMed: 27870426] Cross and colleagues review the literature on the sex-dependent effect of nicotine across the lifespan with a focus on exposure to nicotine during crucial developmental periods.
61. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther*. 2006;79(5):480–8. [PubMed: 16678549]
62. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. *Pharmacol Biochem Behav*. 2009;92(1):6–11. [PubMed: 19000709]
63. Hatchell PC, Collins AC. The influence of genotype and sex on behavioral sensitivity to nicotine in mice. *Psychopharmacology*. 1980;71(1):45–9. [PubMed: 6779324]
64. Kyerematen GA, Owens GF, Chattopadhyay B, deBethizy JD, Vesell ES. Sexual dimorphism of nicotine metabolism and distribution in the rat. *Studies in vivo and in vitro. Drug Metab Dispos*. 1988;16(6):823–8. [PubMed: 2907460]
65. DeVito EE, Herman AI, Waters AJ, Valentine GW, Sofuoglu M. Subjective, physiological, and cognitive responses to intravenous nicotine: effects of sex and menstrual cycle phase. *Neuropsychopharmacology*. 2014;39(6):1431–40. [PubMed: 24345818]
66. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol*. 2005;46(3):464–9. [PubMed: 16053959]
67. Lakoski SG, Cushman M, Criqui M, Rundek T, Blumenthal RS, D'Agostino RB Jr, et al. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *Am Heart J*. 2006;152(3):593–8. [PubMed: 16923436]
68. Valentine RJ, McAuley E, Vieira VJ, Baynard T, Hu L, Evans EM, et al. Sex differences in the relationship between obesity, C-reactive protein, physical activity, depression, sleep quality and fatigue in older adults. *Brain Behav Immun*. 2009;23(5):643–8. [PubMed: 19133324]
69. Casimir GJ, Duchateau J. Gender differences in inflammatory processes could explain poorer prognosis for males. *J Clin Microbiol*. 2011;49(1):478; author reply –9–9. [PubMed: 21193776]
70. McClelland EE, Smith JM. Gender specific differences in the immune response to infection. *Arch Immunol Ther Exp*. 2011;59(3):203–13.
71. Ishii S, Karlamangla AS, Bote M, Irwin MR, Jacobs DR Jr, Cho HJ, et al. Gender, obesity and repeated elevation of C-reactive protein: data from the CARDIA cohort. *PLoS One*. 2012;7(4): e36062. [PubMed: 22558327]

72. Everhardt Queen A, Moerdyk-Schauwecker M, McKee LM, Leamy LJ, Huet YM. Differential expression of inflammatory cytokines and stress genes in male and female mice in response to a lipopolysaccharide challenge. *PLoS One*. 2016;11(4): e0152289. [PubMed: 27120355]
- 73••. Bekhbat M, Neigh GN. Sex differences in the neuro-immune consequences of stress: focus on depression and anxiety. *Brain Behav Immun*. 2018;67:1–12. [PubMed: 28216088] Bekhbat and Neigh review the literature on sex differences in the neuro-immune consequences of stress, the physiological factors underlying sex differences in the neuro-immune consequences of stress, and discuss the extent to which sex differences in stress-related neuroinflammation account for female bias in stress-linked psychiatric disorders.
74. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. *Neurosci Biobehav Rev*. 2000;24(6):627–38. [PubMed: 10940438]
75. Everett BG, Rosario M, McLaughlin KA, Austin SB. Sexual orientation and gender differences in markers of inflammation and immune functioning. *Ann Behav Med*. 2014;47(1):57–70. [PubMed: 24347405]
76. Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. *J Autoimmun*. 2012;38(2–3): J187–92. [PubMed: 22178198]
- 77•. McCarthy MM, Nugent BM, Lenz KM. Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain. *Nat Rev Neurosci*. 2017;18(8):471–84. [PubMed: 28638119] This review describes the research on the role of immune cells and inflammatory mediators in brain masculinization and epigenetic suppression in brain feminization.
- 78•. Hanamsagar R, Bilbo SD. Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. *The J Steroid Biochem Mol Biol*. 2016;160:127–33. [PubMed: 26435451] Hanamsagar and Bilbo provide an overview of the role of microglia in the onset of modulation of inflammation and sex differences in neurological disorders.
79. Schwarz JM, Sholar PW, Bilbo SD. Sex differences in microglial colonization of the developing rat brain. *J Neurochem*. 2012;120(6):948–63. [PubMed: 22182318]
80. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. *Cell Immunol*. 2015;294(2):63–9. [PubMed: 25682174]
81. Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SF, Sin DD. The role of female hormones on lung function in chronic lung diseases. *BMC Womens Health*. 2011;11:24. [PubMed: 21639909]
82. AlSharari SD, Bagdas D, Akbarali HI, Lichtman PA, Raborn ES, Cabral GA, et al. Sex differences and drug dose influence the role of the alpha7 nicotinic acetylcholine receptor in the mouse dextran sodium sulfate-induced colitis model. *Nicotine Tob Res*. 2017;19(4):460–8. [PubMed: 27639096]
83. Faner R, Gonzalez N, Cruz T, Kalko SG, Agusti A. Systemic inflammatory response to smoking in chronic obstructive pulmonary disease: evidence of a gender effect. *PLoS One*. 2014;9(5): e97491. [PubMed: 24830457]
84. Moscovis SM, Cox A, Hall ST, Burns CJ, Scott RJ, Blackwell CC. Effects of gender, cytokine gene polymorphisms and environmental factors on inflammatory responses. *Innate Immun*. 2015;21(5): 523–30. [PubMed: 25432967]
- 85•. Shen YH, Pham AK, Davis B, Smiley-Jewell S, Wang L, Kodavanti UP, et al. Sex and strain-based inflammatory response to repeated tobacco smoke exposure in spontaneously hypertensive and Wistar Kyoto rats. *Inhal Toxicol*. 2016;28(14):677–85. [PubMed: 27829308] This study examined rat strain and sex differences and the effect of extended tobacco smoke exposure on lung injury and lung inflammation and found that male spontaneously hypertensive rats showed an enhanced, persistent inflammatory response to tobacco smoke exposure.
86. Ghia JE, Blennerhassett P, Deng Y, Verdu EF, Khan WI, Collins SM. Reactivation of inflammatory bowel disease in a mouse model of depression. *Gastroenterology*. 2009;136(7):2280–2288.e4. [PubMed: 19272381]
87. Saxena A, Khosraviani S, Noel S, Mohan D, Donner T, Hamad AR. Interleukin-10 paradox: a potent immunoregulatory cytokine that has been difficult to harness for immunotherapy. *Cytokine*. 2015;74(1):27–34. [PubMed: 25481648]

88. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 2011;9:90. [PubMed: 21791035]
89. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. *J Affect Disord.* 2014;156:156–63. [PubMed: 24388685]
90. Difflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. *Int Rev Psychiatry.* 2010;22(5):437–52. [PubMed: 21047158]
91. Wozniak J, Biederman J, Martelon MK, Hernandez M, Woodworth KY, Faraone SV. Does sex moderate the clinical correlates of pediatric bipolar-I disorder? Results from a large controlled family-genetic study. *J Affect Disord.* 2013;149(1–3):269–76. [PubMed: 23485112]
92. Azorin JM, Belzeaux R, Kaladjian A, Adida M, Hantouche E, Lancrenon S, et al. Risks associated with gender differences in bipolar I disorder. *J Affect Disord.* 2013;151(3):1033–40. [PubMed: 24060589]
93. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. *Int Rev Psychiatry.* 2010;22(5):417–28. [PubMed: 21047156]
94. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull.* 2018; 10.1093/schbul/sby058.
95. Pratt LA, Brody DJ. Depression and smoking in the U.S. household population aged 20 and over, 2005-2008. *NCHS Data Brief* 2010(34):1–8.
96. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA.* 2000;284(20):2606–10. [PubMed: 11086367]
97. Leventhal AM, Kahler CW, Ray LA, Zimmerman M. Refining the depression-nicotine dependence link: patterns of depressive symptoms in psychiatric outpatients with current, past, and no history of nicotine dependence. *Addict Behav.* 2009;34(3):297–303. [PubMed: 19062199]
98. Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression. New evidence from a prospective investigation. *Arch Gen Psychiatry.* 1993;50(1):31–5. [PubMed: 8422219]
99. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. *Arch Gen Psychiatry.* 1998;55(2):161–6. [PubMed: 9477930]
100. Breslau N, Novak SP, Kessler RC. Daily smoking and the subsequent onset of psychiatric disorders. *Psychol Med.* 2004;34(2): 323–33. [PubMed: 14982138]
101. Colman I, Naicker K, Zeng Y, Ataullahjan A, Senthilselvan A, Patten SB. Predictors of long-term prognosis of depression. *CMAJ.* 2011;183(17):1969–76. [PubMed: 22025655]
102. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *J Clin Psychiatry.* 2012;73(4):468–75. [PubMed: 22579146]
103. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res.* 2005;76(2–3):135–57. [PubMed: 15949648]
104. Reus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience.* 2015;300:141–54. [PubMed: 25981208]
105. Eyre HA, Air T, Pradhan A, Johnston J, Lavretsky H, Stuart MJ, et al. A meta-analysis of chemokines in major depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016;68:1–8. [PubMed: 26903140]
106. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M. Cumulative meta-analysis of interleukins 6 and 1 beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun.* 2015;49:206–15. [PubMed: 26065825]
107. Uptegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis. *Schizophr Res.* 2014;155(1–3):101–8. [PubMed: 24704219]

108. Nunes SO, Vargas HO, Brum J, Prado E, Vargas MM, de Castro MR, et al. A comparison of inflammatory markers in depressed and nondepressed smokers. *Nicotine Tob Res.* 2012;14(5): 540–6. [PubMed: 22180575]
109. Walker AJ, Kim Y, Price JB, Kale RP, McGillivray JA, Berk M, et al. Stress, inflammation, and cellular vulnerability during early stages of affective disorders: biomarker strategies and opportunities for prevention and intervention. *Front Psychiatry.* 2014;5:34. [PubMed: 24782789]
110. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med.* 2013;11:200 10.1186/1741-7015-11-200. [PubMed: 24228900]
111. Mathew AR, Hogarth L, Leventhal AM, Cook JW, Hitsman B. Cigarette smoking and depression comorbidity: systematic review and proposed theoretical model. *Addiction.* 2017;112(3):401–12. [PubMed: 27628300]
112. Schmidt FM, Kirkby KC, Lichtblau N. Inflammation and immune regulation as potential drug targets in antidepressant treatment. *Curr Neuropharmacol.* 2016;14(7):674–87. [PubMed: 26769225]

Fig. 1.

Hypothetical model for the interaction between sex, tobacco use, and inflammation. In this review, we propose that the sex differences observed in inflammation (path b) and in tobacco use (path a) may interact to modulate the effect of tobacco use on inflammation. This interaction (shaded box) may have important effects on comorbid conditions associated with inflammation, including psychiatric disorders

Studies investigating sex differences in the effects of nicotine/tobacco on inflammation and immune function

Study	Sample	Methods	Outcomes/results	Conclusions and caveats
A.I. Sharari (2017) [82]	Male and female C57BL/6J (wild-type (WT)) and $\alpha 7$ nicotine receptor (nAChR) knockout (KO) mice	Dextran sodium sulfate (DSS) was administered to induce colonic inflammation Male mice were pretreated with one of three drugs to increase nAChR activations: two $\alpha 7$ nAChR agonists and a positive allosteric modulator of $\alpha 7$ (PHA-543613, choline, and PNU-120596, respectively) Female mice were only pretreated with choline	Males $\alpha 7$ KO mice showed increased colonic histological damage and elevated TNF- α vs. WT All three drugs reduced severity of disease, but none of the drugs reduced TNF- α in DSS-treated mice Females DSS-treated $\alpha 7$ KO mice showed similar disease activity to WT female mice Choline treatment did not reduce colitis symptoms in female mice	The $\alpha 7$ nAChR may play an important role in mediating intestinal inflammation, but the effect was specific to male mice. Only TNF- α was examined as a marker of inflammation. Other cytokines (e.g., IL-6) may be important
Faner (2014) [83]	N = 30 subjects - 9 with COPD (4 female) - 11 smokers without COPD (5 female) - 10 non-smokers without COPD (5 female)	Measured spirometry, inflammatory markers (IL-6, IL-8, CRP), leukocyte mRNA, and real time q-PCR Blood samples collected before (T0) and 180 min (T180) after smoking 2 cigarettes (smokers only)	No sex differences in any biomarkers and no changes following smoking in neutrophils, CD3+, CD4+, CD8+, CD19, B cells or NK, CRP, or IL-6 At T0, sex differences in the leukocyte transcriptome were observed There were also sex differences in changes in expression from T0 to T180 Males The COPD-related signature included upregulation of genes associated with immune function and cellular locomotion; few genes were associated with smoking specifically Females Smoking-related signature included downregulation of many of the genes identified in the male COPD signature	Authors suggest that the differences in leukocyte transcriptomics between males and females indicated a "tighter control of the inflammatory response to smoking in females" Consistent with evidence that small sample size that requires replication
Moscovis (2015) [84]	Isolated peripheral blood mononuclear cell (PBMCs) from a sample of 28 Indigenous Australians (14 females) Only non-smokers (i.e., samples with no detectable cotinine) included in the analysis	Evaluated in vitro cytokine response (IL-1 β , IL-6, TNF- α , IFN- γ , IL-8, and IL-10) to LPS, IFN- γ , and cigarette smoke extract (CSE) alone and in combination (7 conditions in total) Characterized samples according high and low risk for pro-inflammatory response based on genes related to immune function Evaluated correlations between cytokines and testosterone	Males Across all males, combination of LPS, IFN- γ , and CSE showed reduced IL-6, TNF- α , and IL-8 Low-risk genetic profile: males had lower IL-10 responses Females Compared to the low risk profile, those with high-risk profile showed lower IL-10 and IL-6 when exposed to LPS, IFN- γ , and CSE combined No gender differences for CSE alone	Lower levels of the anti-inflammatory cytokine, IL-10, among females with the high-risk profile suggest greater dysregulation of immune responses Small sample size in from homogeneous population warrants replication in larger and more heterogeneous samples
Shen (2016) [85]	12-week-old male and female spontaneously hypertensive (SH) and male Wistar Kyoto (WKY) rats 12 animals per experimental group and time point (48 animals total)	Rats were exposed to filtered air (FA) or tobacco smoke (TS) 3 days/week for 4 or 12 weeks; bronchoalveolar lavage fluid (BALF) was collected. Main outcomes: inflammatory cell differentials (leukocytes, macrophages, neutrophils), cytokine protein and gene expression (TNF- α , IL-1 β , IL-6, IL-10), and oxidative stress (HO-1; assessed in males only)	Males Increased leukocytes, macrophages, and neutrophils at 4 weeks (only neutrophils at 12 weeks) Following TS exposure in male SH rats, higher TNF- α at 4 weeks, greater HO-1 expression at 4 and 12 weeks, and greater IL-6 mRNA expression at 12 weeks Females Showed no changes following TS exposure (except an increase in neutrophils at 4 weeks)	Male SH rat has more robust inflammatory response compared to female SH and WKY rats The increased HO-1 expression following TS, suggests a compensatory response to attenuate inflammation

Table 2

Sex differences, rates of tobacco/nicotine use, and markers of inflammation and immune function in psychiatric disorders

Psychiatric disorder	Sex differences in prevalence and/or treatment response?	Smoking rates compared to general population?	Representative inflammation markers associated with disorder
Major depressive disorder	Higher prevalence in females	Smoking rate is significantly higher	IL-6 ^{a,b} CRP ^{a,b} TNF-α ^{a,b} MCP-1/CCL2 ^{a,b}
Schizophrenia	Higher prevalence among males particularly at younger ages; may be higher prevalence among females at older ages	Smoking rate is significantly higher	IL-6 ^{a,b} TNF-α ^{a,b} IL-1β ^{a,b} IL-1RA ^a
Bipolar disorder	Some evidence for higher prevalence among females; clinical course may differ (e.g., depressive feature may be predominant symptoms in females)	Smoking rate is significantly higher	IL-6 ^{a,b} TNF-α ^{a,b} IL-2 ^a IL-4 ^{a,b} IL-8/CXCL8 ^a CRP ^{a,b}

^aMarker associated with tobacco smoking [8, 22, 23]^bMarker associated with sex differences [70, 80]