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Koushalya Chandrakumar Date

The Association between IPV and Innate, Cellular, and Humoral Immune Responses: A Systematic Review of the Literature

By

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[Degree to be Awarded: MPH]

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By

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MBBS Sri Ramachandra Medical College and Research Institute, 2017

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Abstract

The Association between IPV and Innate, Cellular, and Humoral Immune Responses: A Systematic Review of the Literature

By Koushalya Chandrakumar

Background

Intimate partner violence (IPV) remains a serious public health problem both nationally and globally, given its high prevalence and association with poor mental and physical health. To date, most of the available research focuses on examination of the effect of IPV experience on risk of development of chronic, non-communicable diseases, sexually transmitted infections including HIV, and mental health disorders. Given the well-established link between IPV and various communicable diseases, there is a need to understand whether and how IPV may affect innate, cellular and humoral immunity. The goal of this review is to analyze the breadth of literature available on the topic, assess the gaps in knowledge among what has been studied (i.e. by population, by disease outcome, study design) and to explore trends across studies in association between IPV and innate, cellular and humoral immunity.

Methods

A systematic review of peer-reviewed literature was conducted using three search engines to identify articles that examined the relationship between IPV and immune response in both individuals who have experienced IPV as well as perpetrated IPV. Article titles and abstract were first examined for relevancy and thereafter, if potentially relevant, the full text was reviewed to determine whether the study was eligible for inclusion. Next, data regarding study design, population, predictors, outcomes, and findings was extracted. Lastly, the quality of the included studies was assessed. All findings were descriptively synthesized and examined to ascertain the strengths and gaps in available studies and summarize findings to date.

Results

The search yielded 17 articles. The studies were mostly cross-sectional in design and focused on women who experienced IPV in the United States and Spain. Among the immune outcomes examined across articles, the most highly studied areas included cytokine response (specifically IL-6 and IL-10), CRP levels, T-cell numbers, differentiation, and functionality (especially in the context of HIV), and HSV-specific antibody responses. Several studies examined the association between IPV experience and IL-6, but with discrepant results. Only two studies examined the association between IPV perpetration and immune outcomes, both examining the link between aggression and sIgA levels among perpetrators.

Conclusions

There exists a large gap in the literature examining the impact of IPV experience and perpetration on immune responses, which could be of critical importance given the causal link between IPV and infectious diseases and should be addressed by future research.

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Introduction

Background and Significance

Intimate partner violence, defined by the Centers for Disease Control (CDC) as "physical violence, sexual violence, stalking and psychological aggression (including coercive tactics) by a current or former intimate partner (i.e., spouse, boyfriend/girlfriend, dating partner, or ongoing sexual partner)," remains a serious public health problem both nationally and globally (Breiding, Basile, Smith, Black, & Mahendra, 2015).

According to the 2011 National Intimate Partner and Sexual Violence Survey (NISVS), in the US, over 10 million women and men in the United States experience some form of intimate partner violence each year by a current or former intimate partner (Breiding *et al*., 2015). Additionally, "over 1 in 5 women (22.3%) and nearly 1 in 7 men (14.0%) have experienced severe physical violence by an intimate partner at some point in their lifetime, translating to nearly 29 million U.S. women and nearly 16 million U.S. men," (Breiding et al., 2015). Data also shows that during their lifetime, almost 1 in 11 women (8.8%) have been raped from a current or former intimate partner (Breiding *et al*., 2015). Almost 9.2% of women and 2.5% of men have been stalked by an intimate partner in their lifetime (Breiding et al., 2015). According to another study, in 2010, the global prevalence of women aged 15 and over who have experienced some form of IPV in their lifetime was 30.0% [95% confidence interval (CI) 27.8 to 32.2%] (Devries *et al*., 2013). Taken together, these statistics point to a significant, global public health issue which has a multitude of deleterious effects on the human body, both physically and mentally, and quality of life, underscoring the need for the relationship between IPV and immunity to be urgently and thoroughly assessed.

IPV relationships include both present and former relationships, as well as married spouses, domestic partners, boyfriends/girlfriends, dating partners, as well as ongoing sexual partners of the same or opposite sex (Breiding *et al.*, 2015). Coercion is also a form of physical violence (Breiding *et al.*, 2015). Physical violence is defined as "the intentional use of physical force with the potential for causing death, disability, injury, or harm," (Breiding et al., 2015) Sexual violence is defined as a "sexual act that is committed or attempted by another person without freely given consent of the victim or against someone who is unable to consent or refuse,"(Breiding *et al.*, 2015). Stalking is defined as "A pattern of repeated, unwanted, attention and contact that causes fear or concern for one's own safety or the safety of someone else (e.g., family member, close friend) (Breiding et al., 2015). Lastly, psychological aggression can be defined as, "Use of verbal and non-verbal communication with the intent to: a) harm another person mentally or emotionally, and/or b) exert control over another person," (Breiding et al., 2015)

It has been well-documented in the literature that IPV has many consequences on both physical and mental health. When comparing women who experienced abuse to women who did not, women who experienced abuse demonstrated a 60% higher rate of health problems compared to women who did not experience abuse (J. Campbell *et al.*, 2002). The most commonly stated health problems ranged from headaches, vaginal infections, back pain, digestive problems, sexually transmitted infections and urinary tract infections (J. Campbell et al., 2002; Maman et al., 2002). As for mental health, literature has shown that the chronic nature of IPV can lead to neurological and neuropsychological alterations which lead to mental health disorders such as anxiety and depression (Wong, Fong, Lai, & Tiwari, 2014). Women who experience abuse have been shown to develop "fear conditioning," which is a conditioned fear

response induced by linking certain objects and situations to unrelated objects and situations (Wong *et al*., 2014). Normally, this response functions to protect ourselves from perceived threats and danger and is a useful mechanism of self-protection (Wong *et al*., 2014). However, women who experience IPV become hyperresponsive and the overactivity of the fear response predisposes those individuals to develop anxiety disorder, panic disorder or PTSD (Wong et al., 2014). In female IPV survivors, rates of PTSD range from 45% to 81%, with the severity of PTSD influenced by the frequency and severity of IPV (Golding, 1999; Houskamp & Foy, 1991; Stein & Kennedy, 2001). Further, survivors of IPV are more likely to report mood problems, such as depression, and dissociative symptoms such as subjective feelings of detachment, distortion of reality, depersonalization and derealization (Dorahy, Lewis, & Wolfe, 2007).

All of these disorders and health problems have a significant effect on the immune system. The immune system of survivors of IPV must adapt to the chronic, high levels of stress that they experience (Heath et al., 2013). In fact, this cycle of violence, characterized by a period of tension that reaches a peak and results in an act of violence, followed by a period of calm until this cycle repeats, suggests that there may exist a link between the physical health and immunological responses of victims of IPV (Yim, 2019). In one systematic review of PTSD in victims of domestic violence, 31% to 84% of women who had experienced abuse exhibited PTSD symptoms (Jones, Hughes, & Unterstaller, 2001). Together, this suggests that individuals who experience violence may exhibit an altered immune response as a result of PTSD that results from sustained and traumatic re-experiencing of abuse (Heath *et al*., 2013).

In addition to its effects on mental health, IPV has been linked to greater susceptibility to communicable diseases including HIV, STIs, UTIs and respiratory infections in this population (J. Campbell et al., 2002; J. C. B. Campbell, M. L.: Ghandour, R. M.: Stockman, J. K.:

Francisco, L.: Wagman, J., 2008). The relationship between IPV and HIV has been extensively studied. Internationally, among HIV-positive women, the risk of IPV was found to be higher than in HIV-negative women (J. C. B. Campbell, M. L.: Ghandour, R. M.: Stockman, J. K.: Francisco, L.: Wagman, J., 2008). IPV has been linked to greater HIV risk through high-risk sexual contact (i.e. through forced sex with an intimate partner, unsafe sexual practices, or increased risk of sexual risk-taking behaviors) (J. C. B. Campbell, M. L.: Ghandour, R. M.: Stockman, J. K.: Francisco, L.: Wagman, J., 2008; Maman et al., 2002). The same factors place IPV survivors at risk for contracting STIs. IPV survivors describe being unable to practice protective sexual health behaviors due to fear of retaliation from sexual partners (Seth, Wingood, Robinson, Raiford, & Diclemente, 2015). In a study done by Seth et al., they found that participants who experienced IPV reported higher cases of trichomonas vaginalis (Seth et al., 2015). Increased rates of UTIs in this population are explained by the fact that these women are subject to forced anal, vaginal and other abusive sex practices and are therefore highly susceptible to contracting UTIs (J. Campbell et al., 2002). Although there are fewer studies on the association between IPV, and respiratory tract infections, a study done by Bonomi et al., showed that women who experienced IPV were 1.33 times more likely than women who did not experience abuse to develop a respiratory tract infection (Bonomi, 2009). Thus, the many studies demonstrating the link between IPV and communicable diseases, suggests that IPV may also have effects on immunity.

Many studies have evaluated the effects of IPV on the hypothalamic-pituitary-adrenal axis. The HPA axis is triggered during time of stress, activating the fight or flight response (Wong et al., 2014). Cortisol, known as a “stress hormone” is released into the blood circulation and is responsible for regulating glucose metabolism in order to mobilize energy for the body to

respond to the stressful stimuli (Wong et al., 2014). In a review conducted by Yim and colleagues, they found that abuse chronicity was associated with suppressed morning cortisol secretion and that women who had experienced physical and psychological IPV had higher evening cortisol levels than women who did not (Yim, 2019).

The immune system is the body's defense mechanism against pathogens and injury (Cota & Midwinter, 2015). The body can respond either through the non-specific, innate immune response or through the more specific adaptive immune response (Howell & Shepherd, 2018). Innate immunity includes polymorphonuclear cells such as neutrophils, eosinophils, etc. and natural killer cells (Howell & Shepherd, 2018). An important response of innate immunity includes inflammatory mediators, such as chemokines, prostaglandins and leukotrienes (Howell & Shepherd, 2018). The role of these cells is to attract inflammatory and immune cells to sites of damaged or infected tissue, among many other functions (Howell & Shepherd, 2018). Adaptive immunity includes both cellular and humoral immune responses. Humoral immunity describes the B-lymphocyte response which secretes antibodies, such as immunoglobulins (Howell & Shepherd, 2018). Cellular immunity describes the T-cell response. This includes cytotoxic, helper and regulatory cell types, which regulate humoral and cellular-immune responses; CD8 cells destroy tissue containing intracellular pathogens or tumor cells and regulatory T cells (Tregs) regulate the immune response by suppressing the action of helper and cytotoxic T-cells (Howell & Shepherd, 2018).

Conversely, few studies have examined the association between IPV perpetration and immunity. It is possible that perpetrators of IPV exhibit higher levels of aggression and altered activation (Mommersteeg et al. 2008) which may in turn have an impact on their immunity. One study showed that a pro-inflammatory profile is linked to hostility and can lead to adverse health

outcomes (Mommersteeg, Vermetten, Kavelaars, Geuze, & Heijnen, 2008). In fact, men who displayed high levels of aggression also showed a significant decrease in levels of IL-6 as well as an increase in levels of TNF-a, and demonstrated poorer wound healing (Mommersteeg et al., 2008). This could be due to excessive testosterone or reduced serotonin activity (Pinto et al., 2010). It is also associated with higher levels of mortality and morbidity, one reason being that these individuals are more likely to develop cardiovascular disease, which is caused by an inflammatory process (Suarez, Lewis, & Kuhn, 2002).

Statement of Purpose

The aim of this systematic review is to analyze the breadth of literature available on the topic, assess the gaps in knowledge among what has been studied (i.e. by population, by disease outcome, study design), and explore trends across studies in association between IPV and innate and adaptive (i.e. cellular and humoral) immunity.

Methods

A systematic review of published literature was conducted using search engines and key words relevant to the research question, applying inclusion and exclusion criteria to first assess article title and abstract relevancy and then full text relevancy when appropriate, and lastly, conducting data extraction of articles deemed eligible. In place of conducting a meta-analysis (not possible due to the heterogeneity of outcomes), we performed a narrative review of the selected studies. The systematic review did not require review by the Institutional Review Board (IRB).

The systematic review utilized three search engines: Pubmed, Embase and Web of Science. These databases were determined to be the most relevant for the type of literature necessary for the review based on discussions from a qualified librarian as well as an advisor for this review.

The same search was conducted for each of the three searches. No changes to the search terms or to the dictation of the search terms was needed to conduct a search successfully in the three data databases. Details regarding search terms are shown in Table 1. Search terms were determined after conducting a preliminary search of relevant articles and consulting with professionals in the field of public health who had previously done work in this subject area.

Table 1: Search Terms Used in Databases

Databases	**Search Terms**
Pubmed	("Intimate Partner Violence" OR "Domestic Violence" OR "Abusive relationship" OR "Mistreatment in a relationship" OR "Violent relationship" OR "Spousal abuse") AND ("Cellular Immunity" OR "Humoral Immunity" OR "Cell-mediated immune response" OR "Humoral immune response" OR "Adaptive immunity" OR "Immune response" OR "Antibody response" OR "Immunity" OR "Innate immunity" OR "Innate immune response")
Embase	
Web of Science	

After the search was conducted in all three databases, the citations were exported to EndNote and all duplicates were deleted. Titles and abstracts of all the papers were reviewed and evaluated using pre-determined inclusion and exclusion criteria. In order to be considered for inclusion, the literature had to:

- Be published in English
- Available through Emory library or another catalog system
- Evaluate the link between intimate partner violence (perpetration or experience) and immunity

Exclusion criteria included:

- Published in a language besides English
- Gray literature

- Commentaries, Systematic Reviews, and Meta-analyses or papers not analyzing original data

No time period limits regarding article publication dates were set as correlation between intimate partner and immunity has not been documented widely, and time would be unlikely to shape the association. To achieve a comprehensive understanding of the association, we included articles examining intimate partner violence against individuals of any gender, age, or ethnicity, and geographic location.

Articles were first examined against the eligibility criteria using the article's title and abstract to assess relevancy. Those deemed relevant or requiring more information to determine relevancy underwent full text review. Full text was obtained for these articles and aggregated using Kopernio. If only the abstract was available through the institutional library, it was not included for the review. Full text of the articles was again examined using the eligibility criteria. Those deemed irrelevant were excluded, those deemed relevant included, and those which the primary author was unsure about were discussed with the second author until consensus on whether to include them was reached. Finally, the relevant references from the previous two searches were also reviewed using the same methodology. Data was extracted from the final selected literature and were input in an Excel spreadsheet; these data were organized by citation, study population, study design, predictor variable (IPV), tool used to measure IPV (i.e. instruments, single question), immune outcomes assessed, methods used to measure the outcome variable, and study findings. In order to assess the methodological quality of the articles included for review, a single reviewer conducted a quality assessment of the articles using a modified version of the Effective Public Health Practice Project Quality Assessment tool

(EPHPP) (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings 2012). (See Table 2: EPHPP Quality Assessment Tool)

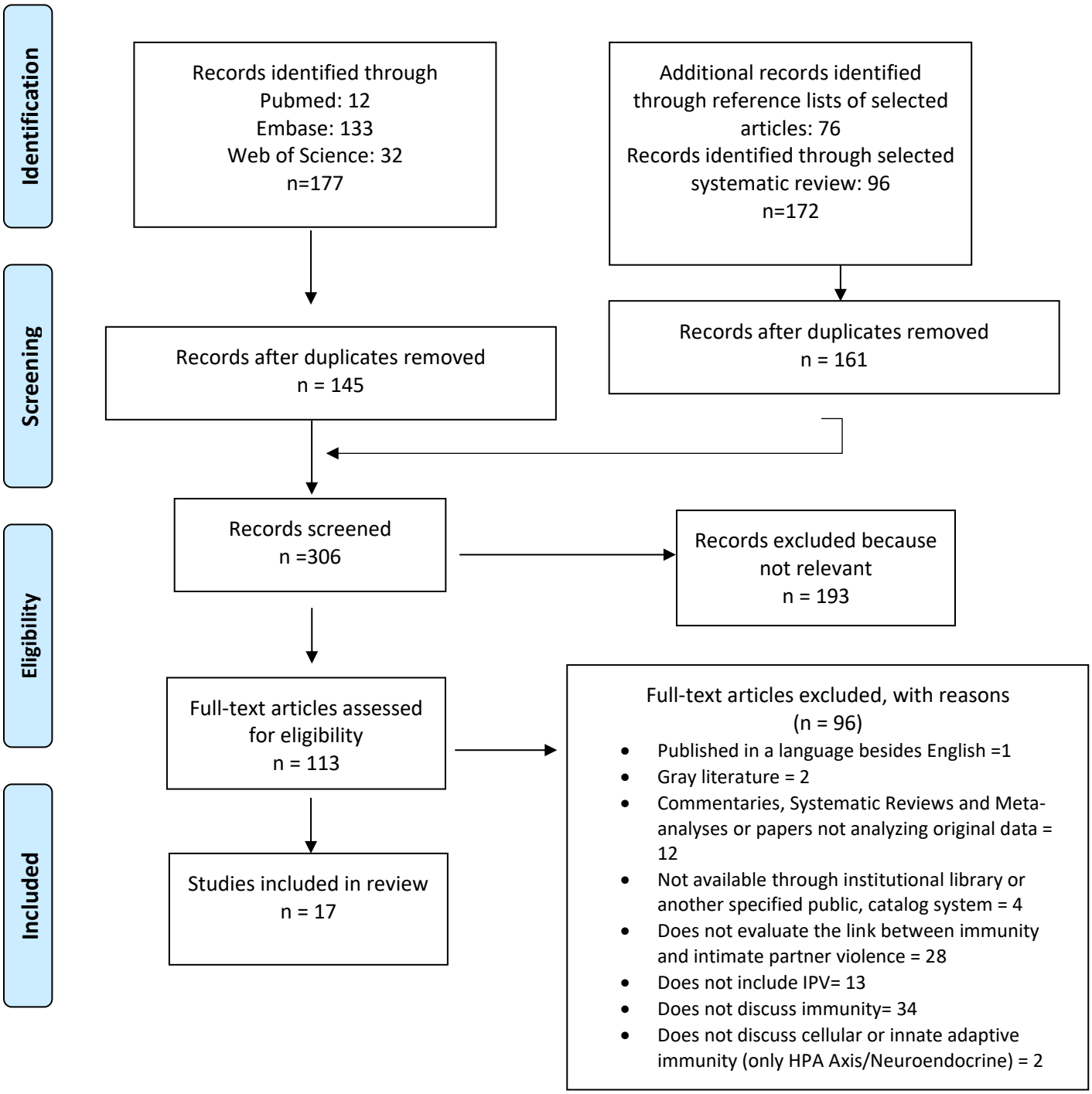
Results

Article Yield

Using the above described search strategy, there were a total of 177 articles found through either PubMed, Embase, and Web of Science. Additional articles (n=172) were identified through the reference list of selected articles as well as through a related systematic review. After duplicates were removed, a total of 306 articles underwent title and abstract screening for relevancy. From this, 193 articles were excluded as they were irrelevant, and the full text of 113 articles were assessed for eligibility. Of the remaining articles, 1 was excluded as it was published in a language besides English, 2 were excluded as they fell into the category of grey literature, 12 were excluded as they were either commentaries, systematic reviews or meta-analysis or papers which did not analyze original data, and 4 were excluded because they were not available at the authors' institutional library. Additionally, articles were excluded as they did not evaluate the relationship between immunity and intimate partner violence (n=28), did not examine IPV (n=13), did not examine immunity (n=34), or solely examined the association between IPV and the hypothalamic-pituitary-axis and neuroendocrine pathways (n=2). Thus, ultimately 17 articles were deemed eligible and included in the systematic review (See Figure 1 PRISMA Flow Diagram).

Figure 1: PRISMA Diagram

**HPA-axis – hypothalamic-pituitary-adrenal axis*



Study Population

Of the 17 articles, 3 articles examined women who reported being abused and compared them to a group of women who did not report being abused (Constantino, Sekula, Rabin, & Stone, 2000; Sanchez-Lorente, 2010; Woods et al., 2005), 1 article examined only women who reported abuse (Out, 2012), 2 articles examined women who had ever been divorced or separated from a stressful relationship (Fernandez-Botran, Miller, Burns, & Newton, 2011; Newton et al., 2011), 3 articles studied women who were either at risk for, or infected with HIV (Illangasekare et al., 2012; Jewkes, 2015; Kalokhe, 2016), 5 articles examined women from the general population (Danielson, Matheson, & Anisman, 2011; Garcia-Linares, Sanchez-Lorente, Coe, & Martinez, 2004; Halpern et al., 2016; Heath et al., 2013; Robertson Blackmore et al., 2016), 1 article examined families but restriction analysis to the mother-newborn dyad (Wright, 2010), and the last 2 articles examined men who had perpetrated IPV and men who had not perpetrated IPV as controls (Romero-Martínez, 2014; Romero-Martinez, 2016). (See Table 1)

Six studies recruited participants from a clinic or hospital setting (Halpern et al., 2016; Heath et al., 2013; Illangasekare et al., 2012; Kalokhe, 2016; Robertson Blackmore et al., 2016; Woods et al., 2005), 4 studies recruited from community-based settings, through various programs for legal aid, female support, or through community targeted recruitment efforts (Constantino et al., 2000; Jewkes, 2015; Newton et al., 2011; Sanchez-Lorente, 2010). One study recruited their participants through the university (Danielson et al., 2011), 1 study recruited through domestic violence shelter (Out, 2012) and for 5 studies, the setting was not specified (Fernandez-Botran et al., 2011; Garcia-Linares et al., 2004; Romero-Martínez, 2014; Romero-Martinez, 2016; Wright, 2010).

Six of the studies were conducted in the United States (Heath et al., 2013; Illangasekare et al., 2012; Kalokhe, 2016; Out, 2012; Woods et al., 2005; Wright, 2010), 4 were conducted in Spain (Garcia-Linares et al., 2004; Romero-Martínez, 2014; Romero-Martinez, 2016; Sanchez-Lorente, 2010), 1 in South Africa (Jewkes, 2015), and for 6 of the studies, the geographic location was not specified (Constantino et al., 2000; Danielson et al., 2011; Fernandez-Botran et al., 2011; Halpern et al., 2016; Newton et al., 2011; Robertson Blackmore et al., 2016).

Study Design

Most of the studies included in this review utilized a cross-sectional study design (n= 11) (Constantino et al., 2000; Garcia-Linares et al., 2004; Halpern et al., 2016; Heath et al., 2013; Illangasekare et al., 2012; Kalokhe, 2016; Newton et al., 2011; Romero-Martínez, 2014; Romero-Martinez, 2016; Sanchez-Lorente, 2010; Woods et al., 2005). Four of the studies were prospective cohort studies (Fernandez-Botran et al., 2011; Out, 2012; Robertson Blackmore et al., 2016; Wright, 2010) and 2 were randomized control trials (Danielson et al., 2011; Jewkes, 2015). One of the RCTs was a cluster randomized controlled trial (Jewkes, 2015). Of these 6 studies, the articles by Out *et al.*, Robertson Blackmore *et al.*, and Jewkes *et al.* examined the association between IPV and immunity longitudinally.

Predictor Variable – Assessment of the various forms of IPV

As per inclusion criteria, all studies examined IPV, but they varied in their assessment of the different forms of IPV (i.e. sexual, physical and/or psychological violence and stalking). One article focused on all four of these subcategories (Fernandez-Botran et al., 2011), 5 articles focused on physical, sexual and psychological IPV (Constantino et al., 2000; Jewkes, 2015; Kalokhe, 2016; Newton et al., 2011), 4 focused on physical and psychological IPV(Danielson et al., 2011; Garcia-Linares et al., 2004; Robertson Blackmore et al., 2016; Sanchez-Lorente,

2010), 1 focused on sexual or physical IPV (Heath et al., 2013), 2 articles focused on just physical IPV(Halpern et al., 2016; Illangasekare et al., 2012) and 2 articles did not specify the type of IPV studied (Out, 2012; Wright, 2010). 5 studies assessed lifetime IPV abuse (Heath et al., 2013; Kalokhe et al., 2016; Newton et al., 2011; Robertson Blackmore et al., 2016; Woods et al., 2005). Five studies assessed IPV abuse over the past 1 year (Constantino et al., 2000; Fernandez Botran et al, 2011; Garcia-Linares et al., 2004; Illangasekare et al., 2012; Woods et al., 2005) with the study conducted by Woods *et al.,* also examining lifetime and Illangasekare *et al.,* not specifying the time period for some of the women. One study examined women who experienced IPV over an average of 5.35 years (Out et al., 2012) and 1 study examined IPV over a 3-year time frame (Sanchez-Lorente et al., 2010). One study examined abuse over a period of 3 months (Danielson et al., 2011) and 5 studies did not specify the time frame studied (Halpern et al., 2016; Jewkes et al., 2015; Romero Martinez et al., 2014; Romero Martinez et al., 2016; Wright et al., 2010).

Instrument used to assess IPV

The majority of these studies used validated questionnaires to obtain self-reported responses to assess if and what type of IPV the participants were exposed to. One study used the Life Experiences Survey (Constantino et al., 2000), and 3 studies used The Conflict Tactics Scale -revised (Danielson et al., 2011; Fernandez-Botran et al., 2011; Newton et al., 2011). Two studies used the Partner Abuse Symptom Scale (Halpern et al., 2016; Woods et al., 2005) and Halpern *et al*. also used the Partner Violence Screen. One study used the WHO violence against women instrument (Jewkes, 2015), Kalokhe *et al.* also used the Index of Psychological Abuse in addition to the Severity of Violence Against Women Scale (Kalokhe, 2016). Two studies used the Trauma History Questionnaire (Heath et al., 2013; Illangasekare et al., 2012). Newton *et. al*

used the National Violence Against Women Survey (Newton et al., 2011). One study used a modified version of the Pennebaker Inventory of Limbic Languidness survey (Out, 2012). Two studies used the Spanish version of the State-Trait Anger Expression Inventory (Romero-Martínez, 2014; Romero-Martinez, 2016). One study, the Romero-Martinez 2014 study also used the Trier Social Stress Test. One study used the Abuse Assessment Screen (Woods et al., 2005). One study used the Difficult Life Circumstances scale (Wright, 2010) and finally, 3 studies used non-validated questionnaires (Garcia-Linares et al., 2004; Robertson Blackmore et al., 2016; Sanchez-Lorente, 2010)

Outcome Variable

Four articles used T-cells as their measure of outcome. One of those studies used total mitogen response in order to approximate T-cell function (Constantino et al., 2000), 1 study measured CD4 levels (Illangasekare et al., 2012) , 1 study used rates of change in CD4+ and CD8+ T-cell counts (Jewkes, 2015) and 1 study assessed rate of CD4+ T-cell activation and differentiation as well as T-reg differentiation (Kalokhe, 2016). Four studies assessed IgA response, with 3 studies assessing salivary levels of total IgA (Garcia-Linares et al., 2004; Romero-Martínez, 2014; Romero-Martinez, 2016). Eleven studies assessed cytokines, with 3 studies assessing IL-6 levels (Danielson et al., 2011; Fernandez-Botran et al., 2011; Newton et al., 2011; Robertson Blackmore et al., 2016), 1 assessing IL-10 (Danielson et al., 2011), 1 assessing TNF-a (Robertson Blackmore et al., 2016) 1 assessing Il-8, TNF-a, IL-13 and IFN-g (Wright, 2010), 1 assessing IFN-y (Woods et al., 2005), and 1 article assessing IL-6 alongside C-reactive protein (CRP) (Newton et al., 2011). An additional 3 articles studied CRP levels exclusively (Halpern et al., 2016; Heath et al., 2013; Out, 2012).

Method of Assessment

The majority of these studies (n=9) specified ELISA as their method of assessment (Danielson et al., 2011; Fernandez-Botran et al., 2011; Garcia-Linares et al., 2004; Heath et al., 2013; Jewkes, 2015; Newton et al., 2011; Robertson Blackmore et al., 2016; Sanchez-Lorente, 2010; Woods et al., 2005). Three studies used radioimmunoassay as their method of assessment (Halpern et al., 2016; Romero-Martínez, 2014; Romero-Martinez, 2016). Two of these 3 additionally used BN-II nephelometry (Romero-Martínez, 2014; Romero-Martinez, 2016). One study used the PHA assay to study T-cell function (Constantino et al., 2000), 1 study retrieved CD4 counts from medical records (Illangasekare et al., 2012), 1 study used the BD FASOUNT analysis (Jewkes, 2015). One study used whole blood flow cytometry (Kalokhe, 2016), 1 study used a commercially available immunoassay but did not specify which one (Out, 2012), and lastly, 1 study used a bead-based multiplex assay as their method of assessment (Wright, 2010).

Findings

T-Cell Function

The Constantino et. al study found that abused women had lower T-cell function as measured by total mitogen response (TMR) ($t = –5.62$, $p < 0.01$), with a mean of 16,955 (SD=4300), compared to non-abused women, with a mean of 27, 356 (SD=4763) (Constantino et al., 2000). Another study found that in 103 young women infected with HIV aged 15-26 who developed HIV after recruitment from a HIV-prevention program in South Africa, physical and sexual IPV was not associated with a change in CD4 and CD8 counts but exposure to emotional IPV was deemed a risk factor for faster decline in CD4 and CD8 counts, after adjusting for available indicators of duration of HIV and other risk factors (Jewkes, 2015). Illangasekare and colleagues found that in a sample of 196 women recruited from an HIV clinic in Baltimore,

Maryland, there was no difference between the CD4 count of women who reported experiencing IPV and those who did not (Illangasekare, 2012). Lastly, Kalokhe and colleagues found that lifetime IPV exposure was associated with increased CD4+ activation ($r = 0.331$, $P = 0.004$), a shift in CD4+ phenotype from naïve to effector memory ($r = 0.343$, $P = 0.003$), and a decrease in naive (%HLA-DR+/CD45RA-) Treg frequency ($r = -0.337$, $P = 0.003$) (Kalokhe, 2016).

Il-6 and Il-10 Levels

There was significant variation in findings among studies that assessed Il-6 and IL-10 levels. One study found that among abused women exposed to a stressor condition, which was either an abuse stressor related to dating abuse, or a control stressor which detailed an interaction that was common for all participants to experience but did not describe abuse behavior, emotions such as anger and sadness were positively correlated with increased levels of IL-6, but not IL-10 levels (Danielson et al. 2011). This remained true even when they were exposed to the abuse stressor (Danielson et al. 2011). One study found that in women who experienced violence, there were significantly smaller changes in levels of IL-6 ($\beta = -0.36$, $p = 0.04$) across time when compared to women who had not experienced violence (Robertson Blackmore et al., 2016). However, a study done by Fernandez-Botran *et al.*, found that there were no significant differences in IL-6 levels in women who experienced abuse compared to women who did not experience abuse (Fernandez-Botran et al. 2011). In contrast, Newton *et al* found that a history of physical assault was significantly negatively correlated with PHA-stimulated IL-6 production (Newton et al., 2011). As discussed in the Newton *et al*. study, a steady pro-inflammatory response is not common and that stressor history is related to decreased levels of IL-6 and increased response to CRP levels (Newton et al., 2011).

Changes in IgA Levels

In one study examining HSV-1 virus neutralization capacity, physically abused women had the lowest virus neutralization, much more than the other two groups (psychologically abused women and non-abused women) (Garcia-Linares, Sanchez-Lorente, Coe, & Martinez, 2004). The study also found that the HSV-1 antibody was lower in physically abused women, however, they hypothesized that decreased bioactivity was attributed to the loss of other antiviral factors, such as cystatins and proline-rich proteins in saliva, but they were unable to validate this theory. (Garcia-Linares et al., 2004). Mental health status did not have a significant bearing on the effect of IPV on immune function (Garcia-Linares et al., 2004). A follow-up study, conducted three years after an initial study, found that the women regained full neutralization capacity against HSV-1 for the physical and psychological IPV group (Sanchez-Lorente, 2010). At baseline (year 1) only 27.3% of psychologically and physically abused women had saliva that neutralized HSV, however when levels were checked 3 years later, 90% of the same group of women showed saliva that neutralized HSV-1 (Sanchez-Lorente, 2010). Conversely, women who continued to experience physical and psychological abuse showed that physiological dysfunction persisted (Sanchez-Lorente, 2010).

CRP Levels

There was also considerable variation among the findings in the studies that assessed CRP levels. One study found that intrusive reexperiencing of traumatic events was associated with higher levels of CRP (Heath, 2013). Further, PTSD is a potential mechanism by which traumatic stress is converted into chronic inflammation as chronic experiences of stress lead to long-term inflammation (Heath, 2013). The study also found that depressive symptoms were

significantly but inversely associated with decreased levels of CRP, suggesting that PTSD is a more reliable predictor of higher levels of CRP in IPV survivors (Heath, 2013). However, another study found that CRP levels were not significantly different between those who had experienced IPV and those who had not (Halpern et al., 2016). A third study included in this review was conducted in the context of IPV, however, they studied CRP levels in saliva as a possible method of measurement compared to CRP levels in plasma in women who experienced IPV. They found that in a group of women who reported experiencing IPV, salivary CRP reliably distinguished between individuals with high and low plasma CRP levels and that saliva CRP significantly differentiated between the risk categories for cardiovascular disease based on plasma CRP, thereby concluding that salivary CRP levels are an acceptable alternative to plasma CRP levels (Out, 2012).

Other measures of Immune Response

One study which examined the levels of IFN-y found that survivors of IPV had significantly greater levels of the proinflammatory cytokine IFN-y compared to women who had not experienced abuse (Woods et al., 2005). Greater levels of CRP were also found in women with current symptoms of PTSD compared to women without psychopathology symptoms (Woods et al., 2005). Here however, they found that mental health effects of IPV did in fact help explain why there are differences in IFN-y in victims of IPV (Woods et al., 2005). Another study that was conducted in families during the prenatal period, and analyzed mothers and newborn children, included IPV as part of a larger composite stress measure, which was associated with increased IL-8 and TNF-alpha, IL-13 and decreased IFN-g in stimulated CBMC. No IPV-specific analysis was performed in the study (Wright et al. 2010).

Perpetrators of IPV

Lastly, two studies examined the immunological response in perpetrators of IPV. These studies found that IPV perpetrators had higher sIgA levels than controls in response to acute stress, especially during the preparation period for the stress-inducing task the participants were asked to perform (Romero-Martínez, 2014). In a follow up study by the same authors, conducted two years later, authors found that in IPV perpetrators, anger expression was associated with less reporting of respiratory and gastrointestinal complaints and the effects were mediated through reductions in sIgA (Romero-Martinez, 2016).

Quality Assessment of Included Studies

Of the studies included in this review, three studies did not select individuals which would be representative of their target population (Constantino et al. 2000; Woods et al 2005). A higher number of studies (n= 7) did not report on non-participation in their studies (Danielson et al. 2011; Fernandez-Botran et al. 2011; Garcia-Linares et al. 2004; Heath et al. 2013; Romero-Martinez et al. 2016; Sanchez-Lorente et al. 2010; Wright et al. 2010) and the research design was appropriate for all but one study (Out et al. 2012). One limitation of the majority of these studies was that their sample size was inadequate to power the study (Constantino et al. 2000; Halpern et al. 2016; Heath et al. 2013; Ilangasekare et al. 2012; Jewkes et al. 2015; Kalokhe et al. 2016; Newton et al. 2011; Romero-Martinez et al. 2014; Romero-Martinez et al. 2016; Sanchez-Lorente et al. 2010). While most studies used validated questionnaires that had high reliability, 3 studies did not (Garcia-Linares et al. 2004; Out et al. 2012; and Sanchez-Lorente et al. 2010). The statistical analysis conducted seemed appropriate for the studies included here, although confidence intervals or standard errors were not reported for seven of the studies

(Constantino et al. 2000; Danielson et al. 2011; Garcia-Linares et al. 2004; Kalokhe et al. 2016; Romero Martinez et al 2014; Woods et al. 2005; Wright et al. 2010). Confounders were included and adjusted in the final analysis in all except two studies (Constantino et al. 2000; Out et al. 2012). Eight studies did not report any bias in their studies (Fernandez-Botran et al. 2011;Garcia-Linares et al. 2004; Halpern et al. 2016; Kalokhe et al. 2016; Out et al. 2012; Romero-Martinez et al. 2014; Romero-Martinez et al. 2016; Wright et al. 2010), but all studies did taken into the ethical considerations associated with conducting a study of this nature.

Table 2: Characteristics of Articles Included in Review

**IPV-Intimate Partner Violence, PHA Assay -Phytohemagglutinin Assay, sIl-6R- soluble interleukin 6 receptor, ELISA- Enzyme-linked immunosorbent assay, CRP- C-reactive protein, HSV-1 – Herpes simplex virus -1, TNF-a – Tumor necrosis factor alpha, IgA- Immunoglobulin A, IFN-y – Interferon gamma*

Citation	**Study Population**	**Study Design**	**Predictor Variable (IPV* and its different forms)**	**Instrument to assess IPV**	**Immune Outcome Variable**	**Method of Assessment**
Constantino et al. (2000).	12 women who reported abuse by their spouse or intimate partner and 12 women who did not report abuse recruited from the local Neighborhood Legal Services pro bono program- location not specified.	Cross-sectional study (women who had experienced abuse more than once over the past 1 year)	Physical, Sexual, Psychological IPV	Life Experiences Survey	1. T-Cell function- measured through mitogenic proliferation, TMR (total mitogen response)	PHA* assay
Danielson et al. (2011).	75 University women currently involved in heterosexual dating relationships of 1 month to 3 years - location not specified	Randomized control trial: abuse-related stressor (n= 44) vs. a control scenario (n= 31)- women who experienced >4 instances of psychological abuse in the past 3 months	Psychological, Physical IPV	Manipulation checks, The Conflict Tactics Scale-Revised (CTSR)	Il-6 and IL-10*	ELISA*
Fernandez-Botran et al. (2011).	67 women ever divorced or separated from "extremely" stressful relationships - location, setting not specified	Prospective cohort study (no IPV in the past year)	Physical, sexual, psychological IPV, stalking by intimate partner	Revised Conflict Tactics Scale	IL-6 and sIL-6R* levels	ELISA
Garcia-Linares et al. (2004).	182 women from the Valencian community of Spain	Cross-sectional study (abused women residing with partner at least 1 year)	Physical and psychological IPV	Non-validated questionnaire - # of questions not specified	salivary levels of HSV-1* antibody and total IgA	Cell cultures, ELISA

Halpern et al. (2016).	78 English-speaking women recruited from the Oral Surgery Clinic	Cross-sectional study (time period of IPV not specified)	Physical IPV	Partner violence screen (PVS), Partner Abuse Symptom Scale (PASS)	CRP levels	Radioimmunoassay
Heath et al. (2013).	139 female patients presenting for routine gynecologic care at a major urban medical center in the Midwestern United States	Cross-sectional study (lifetime IPV)	Sexual or physical IPV	Trauma history questionnaire (THQ),	CRP levels	HsCRP ELISA CRP kit
Illangasekare et al. (2012).	196 women recruited from Johns Hopkins HIV* Clinic, in Baltimore, Maryland	Cross-sectional survey study (27% experienced IPV within past year, remaining not specified)	Physical IPV	Partner Violence Screen	CD4 count	CD4 count
Jewkes et al. (2015).	103 young women infected with HIV aged 15-26 who developed HIV after recruitment from a HIV-prevention program in South Africa	Cluster randomized controlled trial (various time periods)	Physical, sexual, and psychological IPV	WHO violence against women instrument	Rates of change in CD4+ and CD8+ T-cell counts	BD FASOUNT analysis
Kalokhe et al. (2016).	75 women who are HIV-negative and high risk recruited from clinic-based setting in south-eastern US	Cross-sectional study (Lifetime IPV)	Physical, sexual and psychological IPV	Index of Psychological Abuse (IPA), Severity of Violence Against Women Scale (SWAWS),	Rate of CD4+ T-cell activation and differentiation and T-reg differentiation	Whole blood flow cytometry
Newton et al. (2011).	69 midlife women ever divorced or separated from a stressful relationship, recruited through mailings and community advertisements - location not specified	Cross-sectional study (lifetime IPV)	Physical, sexual and psychological IPV	The Revised Conflict Tactics Scale (CTS2), National Violence Against Women Survey,	Circulating levels of CRP and IL-6, along with in vitro IL-6 production by peripheral blood mononuclear cells (PBMC)	ELISA, turbidimetry CRP assay
Out et al. (2012).	107 ethnically diverse women seeking help from domestic violence crisis-shelters-agencies in midwestern US	Prospective cohort study. (average of 5.35 years of IPV)	IPV - type not specified	Modified version of the Pennebaker Inventory of Limbic Languidness (PILL)	salivary CRP	Commercially available immunoassay

Robertson Blackmore et al. (2016).	171 women receiving obstetric care from a hospital-based practice serving a predominantly low-income minority population - location not specified	Prospective, longitudinal cohort study (lifetime IPV)	Physical and psychological IPV	IPV assessed through two non-validated questions	Serum levels of IL-6, TNF-a*	ELISA
Romero-Martínez et al. (2014).	38 healthy male volunteers: 19 IPV perpetrators and 19 controls in Valencia, Spain.	Cross-sectional study (not specified)	Perpetration of IPV - physical and psychological	Spanish version of the State-Trait Anger Expression Inventory (STAXI-2), the Trier Social Stress Test (TSST)	Salivary IgA* levels	RIA (radioimmunoassay), BN-II nephelometry
Romero-Martinez et al. (2016).	40 male volunteers, 19 IPV perpetrators and 21 controls, Valencia, Spain.	Cross-sectional study (not specified)	Perpetration of IPV - physical and psychological	The State-Trait Anger Expression Inventory - 2	Salivary IgA levels	RIA (radioimmunoassay), BN-II nephelometry
Sanchez-Lorente et al. (2010).	60 women who had been either physically and psychologically (n=22), or psychologically abused (n=14) by their partners and a control group of women (n=24) recruited through Centers for Helping Women in the three provinces of the Valencian community of Spain (Alicante, Castellon, and Valencia).	Cross-sectional study evaluated participants after a 3 year period (T-2) (from a previous study (T-1)	Physical and psychological IPV	Comprehensive questionnaire was designed for face-to-face interview. Duke-UNC scale to measure functional social support	Recovery of immune control over HSV-1, IgA	ELISA
Woods et al. (2005).	62 women with IPV and 39 non-abused women recruited from primary care clinic for the uninsured in Baltimore, MD-identified as high risk for mental health symptoms	Cross-sectional, study (lifetime and current – past year)	Physical, sexual, psychological IPV	Abuse Assessment Screen (AAS), Partner Abuse Scale (PAS), Physical (PH) and non-physical (NP)	IFN-y levels*	ELISAF17
Wright et al. (2010).	557 families recruited during the prenatal period in Baltimore Boston, New York and St. Louis. Unit of analysis for review: mothers and newborn child	Prospective, longitudinal cohort study (not specified)	Prenatal maternal stress including domestic violence - type not specified	Difficult Life Circumstances scale - questionnaire not publicly available	Cord blood mononuclear cell (CBMC) cytokine responses: TNF-a, IL-8, IL-13, IFN-g	Bead-based multiplex assay

Table 3: Quality assessments of quantitative studies.

EPHPP Item	Constantino et al. (2000)	Danielson et al. (2011)	Fernandez-Botran et al. (2011)	Garcia-Linares et al. (2004)	Halpern et al. (2016)	Heath et al. (2013)	Illangasekaret al. (2012)	Jewkes et al. (2015)	Kalokhe et al (2016)
Domain 1- Selection Bias									
Were the individuals selected to participate in the study likely to be representative of the target population?	X	✓	✓	✓	✓	✓	✓	✓	✓
Was any information regarding non-participation in the study included?	✓	X	X	X	✓	X	✓	✓	✓
Domain 2 - Study Design									
Was there a clear statement of aims/objectives of the study?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Is the research design appropriate for the objective?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Domain 3 - Sampling									
Was the sampling strategy appropriate to the objective?	X	✓	✓	✓	✓	✓	X	✓	✓
Is the sample size adequate for the objective?	X	✓	✓	✓	X	X	X	X	X
Domain 4 - Data Collection tools									
Was the Data collection tool reliable?	✓	✓	✓	✓	✓	✓	X	✓	✓
Was the data collection tool valid?	✓	✓	✓	X	✓	✓	✓	✓	✓
Domain 5 - Data Analysis									
Is the statistical analysis appropriate for the study design?	✓	✓	X	✓	✓	✓	✓	✓	✓

Has the confidence intervals or standard errors been reported?	X	X	✓	X	✓	✓	✓	✓	X
Were the various confounders included and adjusted in the final analysis?	X	✓	✓	✓	✓	✓	✓	✓	✓
Domain 6 - Bias									
Has any other bias been reported? What were those biases?	✓	✓	X	X	X	✓	✓	✓	X
Have ethical issues been taken into consideration?	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3 Continued

EPHPP Item	**Newton et al. (2011)**	**Out et al. (2012)**	**Robertson et al. (2016)**	**Romero-Martinez et al (2014)**	**Romero-Martinez et al. (2016)**	**Sanchez-Lorente et al. (2010)**	**Woods et al. (2005)**	**Wright et al. (2010)**
Domain 1- Selection Bias								
Were the individuals selected to participate in the study likely to be representative of the target population?	✓	✓	✓	✓	✓	✓	X	✓
Was any information regarding non-participation in the study included?	✓	✓	✓	✓	X	X	✓	X
Domain 2 - Study Design								
Was there a clear statement of aims/objectives of the study?	✓	✓	✓	✓	✓	✓	✓	✓
Is the research design appropriate for the objective?	✓	X	✓	✓	✓	✓	✓	✓
Domain 3 - Sampling								
Was the sampling strategy appropriate to the objective?	✓	X	✓	✓	✓	✓	✓	✓
Is the sample size adequate for the objective?	X	✓	✓	X	X	X	✓	✓
Domain 4 - Data Collection tools								

Was the Data collection tool reliable?	✓	✓	X	✓	X	✓	✓	✓
Was the data collection tool valid?	✓	✓	X	✓	✓	X	✓	✓
Domain 5 - Data Analysis								
Is the statistical analysis appropriate for the study design?	✓	✓	✓	✓	✓	✓	✓	✓
Has the confidence intervals or standard errors been reported?	✓	✓	✓	X	✓	✓	X	X
Were the various confounders included and adjusted in the final analysis?	✓	X	✓	X	✓	✓	✓	✓
Domain 6 - Bias								
Has any other bias been reported? What were those biases?	✓	X	✓	X	X	✓	✓	X
Have ethical issues been taken into consideration?	X	✓	✓	X	X	✓	✓	✓

Table 4: Summary of Findings included in the review.
**IPV-Intimate Partner Violence, PHA Assay -Phytohemagglutinin Assay, sIl-6R- soluble interleukin 6 receptor, ELISA- Enzyme-linked immunosorbent assay, CRP- C-reactive protein, HSV-1 – Herpes simplex virus -1, TNF-a – Tumor necrosis factor alpha, IgA- Immunoglobulin A, IFN-y – Interferon gamma*

Citation	Findings
Constantino et al. (2000).	Abused women had lower T-cell function as measured by total mitogen response (TMR) ($t = –5.62$, $p < 0.01$), with a mean of 16.955 (SD=4300), compared to non-abused women, with a mean of 27, 356 (SD=4763) (Constantino et al., 2000).
Danielson et al. (2011).	When abused women were exposed to the stressor condition, emotions such as anger and sadness were positively correlated with increased levels of IL-6, but not to IL-10 levels, even when they were exposed to the abuse stressor (Danielson et al. 2011)
Fernandez-Botran et al. (2011).	This study investigated correlations among plasma CRP and levels of IL-6 and soluble IL-6 receptor (sIL-6R) in plasma, saliva and OMT in a population of middle-aged women with histories of past IPV (Fernandez-Botran et al. 2011). They found that women who experienced IPV reported significantly higher levels of CRP compared to non-abused women, but there were no significant differences in IL-6 levels in women who experienced abuse compared to women who did not experience abuse and that there was only a modest correlation between CRP levels and IL-6 levels (Fernandez-Botran et al. 2011).
Garcia-Linares et al. (2004).	Physically abused women had the lowest virus neutralization, much more than the other two groups (psychologically abused women and non-abused women) (Garcia-Linares, Sanchez-Lorente, Coe, & Martinez, 2004). The study also found that the HSV-1 antibody was lower in physically abused women, however decreased bioactivity was attributed to the loss of other antiviral factors (Garcia-Linares et al., 2004). Mental health status did not have a significant bearing on the effect of IPV on immune function (Garcia-Linares et al., 2004).
Halpern et al. (2016).	CRP levels were not significantly different between those who had experienced IPV and those who had not (Halpern et al., 2016).
Heath et al. (2013).	Intrusive reexperiencing of traumatic events was associated with higher levels of CRP (Heath, 2013). Further, PTSD is a potential mechanism by which traumatic stress is converted into chronic inflammation, suggesting that the effects were the same as if the event was repeatedly occurring (Heath, 2013). The study also found that depressive symptoms were actually associated with decreased levels of CRP, suggesting that PTSD is a more reliable predictor of higher levels of CRP in these victims (Heath, 2013).
Illangasekare et al. (2012).	There was no difference between the CD4 count of women who reported experiencing IPV and those who did not (Illangasekare, 2012).
Jewkes et al. (2015).	Physical and sexual IPV was not associated with a change in CD4 and CD8 counts but exposure to emotional IPV is a risk factor for faster decline in CD4 and CD8 counts, after adjusting for available indicators of duration of HIV and other risk factors (Jewkes, 2015).
Kalokhe et al. (2016).	Lifetime IPV was associated with increased CD4+ activation ($r = 0.331$, $P = 0.004$), a shift in CD4+ phenotype from naïve to effector memory ($r = 0.343$, $P = 0.003$), and a decrease in naive (%HLA-DR+/CD45RA-) Treg frequency ($r = -0.337$, $P = 0.003$) (Kalokhe, 2016).

Newton et al. (2011).	A history of physical assault was significantly negatively correlated with PHA-stimulated IL-6 production (Newton et al., 2011). A uniform, pro-inflammatory response is not seen, and stressor history is related to increased CRP levels as well as decreased stimulation of IL-6 production. IL-6 production reflects the in-vitro response of a particular type of leukocyte (e.g. monocytes vs. T-cells) in response to a given stimulation," (Newton et al., 2011). Whereas CRP levels reflect a cumulative downstream effect of multiple inflammatory mediators and cell types (Newton et al., 2011).
Out et al. (2012).	Although this study was conducted in the context of IPV, it did not specifically study effects of IPV on immune outcome. Rather, they found that in a group of women who experienced domestic violence, salivary CRP reliably distinguished between individuals with high and low plasma CRP levels and that saliva CRP significantly differentiated between the risk categories for CVD based on plasma CRP, thereby concluding that salivary CRP levels are an acceptable alternative to plasma CRP levels (Out, 2012).
Robertson Blackmore et al. (2016).	Women with a history of IPV had significantly higher levels of TNF-α at 18 weeks ($z = -2.29$, $p < 0.05$), but significantly smaller changes in levels of IL-6 ($\beta = -0.36$, $p = 0.04$) across time (Robertson Blackmore et al., 2016).
Romero-Martínez et al. (2014).	IPV perpetrators had higher sIgA levels than controls in response to acute stress, especially during the preparation period for the stress-inducing task the participants were asked to perform (Romero-Martínez, 2014). The perpetrators found the stress test they were given – the Trier Social Stress Test (TSST) as less stressful than controls (Romero-Martínez, 2014).
Romero-Martinez et al. (2016).	In IPV perpetrators, the sIgA response to acute stress is similar to the men with no history of violence (Romero-Martinez, 2016). However, they did find that in preparation for the stress test, the IPV perpetrators presented higher sIgA levels than the non-violent controls (Romero-Martinez, 2016).
Sanchez-Lorente et al. (2010).	Three years following the initial study, the women regained full neutralization capacity against HSV-1 for the physical and psychological IPV group (Sanchez-Lorente, 2010). At baseline (year 1) only 27.3% of psychologically and physically abused women had saliva that neutralized HSV, however when levels were checked 3 years later, 90.0% of the same group of women showed saliva that neutralized HSV-1 (Sanchez-Lorente, 2010). The main factor which contributed to this recovery was the termination of physical IPV, after controlling for age (Sanchez-Lorente, 2010). When these women were exposed to physical and psychological IPV a second time, the concentrations of antibody against HSV-1 had increased (Sanchez-Lorente, 2010). Conversely, women who continued to experience physical and psychological abuse or developed PTSD from the abuse, showed that physiological dysfunction persists (Sanchez-Lorente, 2010).
Woods et al. (2005).	Victims of IPV had significantly greater levels of the proinflammatory cytokine IFN-y compared to women who had not experienced abuse (Woods et al., 2005). Greater levels of CRP were also found in women with current symptoms of PTSD compared to women without psychopathology symptoms (Woods et al., 2005). Here however, they found that mental health effects of IPV did in fact help explain why there are differences in physical health and immune function outcomes in victims of IPV (Woods et al., 2005).
Wright et al. (2010).	IPV was included as part of a larger composite stress measure, which was associated with increased IL-8 and TNF-alpha, IL-13 and decreased IFN-g in stimulated CBMC. No IPV specific analysis was performed.

Discussion

In recognition of the well-established link between IPV and various communicable diseases, this review was conducted in order to analyze the breadth of literature available on the link between IPV and immunity, assess the gaps in knowledge among what has been studied, and explore trends across studies examining the association. By understanding the relationship between IPV and immunity, researchers and health care professionals can form a more nuanced understanding of how this population responds to clinical trials, or to vaccines and develop a protocol that is better tailored for this population in order to provide the highest quality of care.

This review examined 349 original, peer-reviewed articles and ultimately included 17 of them. Other reviews that have been conducted have focused on multiple outcomes – including the hypothalamic–pituitary–adrenal (HPA) axis and the neuroendocrine response, IPV in relation to HIV, and the immunological response in the context of multiple other outcomes including mental health. This review uniquely focuses on studies that have primarily evaluated immunological response, and thereby explicitly and thoroughly evaluated all available studies examining this link.

The literature reviewed highlighted several gaps in the design and findings of existing studies examining this topic. First, most of the studies included in this review conducted their study on female victims of IPV in the US and Spain. The immune effects of IPV among men should be further studied. In a study by Reid *et al*., it was reported that in the United States, approximately 4.7% to 16.4% of men have reported experiencing IPV (Reid et al., 2008), with gay and bisexual men reporting much higher rates of IPV experience, ranging from 12% to 45% (Stephenson et al. 2016). Stigma around male victims of IPV have possibly shrouded the realities of this topic, which makes this area of study to be even more important in order to more comprehensively

understand the different forms of IPV and how its effects may differ significantly between genders (Reid et al., 2008). Equally important, is to understand how experience of IPV in same-sex and LGBTQ+ individuals also affects immunity. Although the socioeconomic status varied among populations across different studies, the majority of the studies were conducted in developed countries, which skews the results towards a more high-income population. Future studies that focus on low-income and developing countries could add valuable knowledge to the existing literature. In addition, racial and ethnic differences by geographic region may exist that impact the relationship between IPV and immune response, highlighting the need to examine this question in other contexts.

Most of the studies in this review conducted cross-sectional studies, limiting the ability to draw causal inferences of the effect of IPV on immunity. Only one study conducted a RCT ((Danielson et al., 2011), and found that IL-6 levels are moderated by depressed mood states, which are more common in women who have experienced IPV (Danielson et al., 2011) Longitudinal assessment of the impact of IPV in immunity has likely been limited by various ethical implications in using this design. Specifically, it would be unethical to not intervene when IPV was detected, thus studying the effects of IPV longitudinally is complicated.

Additionally, a high amount of variability was present among the different questionnaires used to assess IPV. Although most studies used validated instruments, the question remains whether this contributed to a variability amongst the answers that would not have been present had the same, standardized questionnaire been used across all studies. Especially as answers are self-reported, the possibility of bias or various modes of interpretation are likely and could influence study results. While there was a high variability amongst the forms of IPV that were assessed, it should be noted that sexual IPV was not assessed as extensively as the either physical

or psychological IPV and stalking by an intimate partner was assessed only examined by one study (Fernandez-Botran et al., 2011).

Among the immune outcomes examined across articles, the most highly studied areas included cytokine response (specifically IL-6 and IL-10), CRP levels, T-cell numbers, differentiation, and functionality (especially in the context of HIV), and HSV-specific antibody responses. Further research studying the link between IPV and other domains of immunity, such as humoral immunity or adaptive cellular responses to other bacterial and viral pathogens, or effects on innate immune response are still needed.

Interestingly, most of the studies that focused on interleukins, focused on Il-6 and Il-10. When surveying the literature, it was shown that IL-6 and IL-10 production increased significantly under psychological stress, along with IFN-y, IL-1, and TNF-a (Maes et al., 1998). Studies that have evaluated the link between psychosocial stressors, such as depression, and cytokine response, found that IL-6 production is increased and IL-10 production is decreased and that both of these cytokines act as a biomarker for depression and depressive behavior (Voorhees et al., 2013). This could help explain why most of the studies in the review chose to focus on these two cytokines specifically. One major limitation that was observed in the majority of studies was that confounders were not adjusted for in the final analysis. However, many studies did discuss this as a possible limitation and also outlined what the possible confounders were, which could form the basis of future research examining the association.

The findings in this review vary greatly. For example, the study done by Danielson et. al found that there was an increase in IL-6 levels in women who experienced abuse (Danielson et al., 2011), but in the Fernandez-Botran study, they found no significant difference in IL-6 levels in women who experienced abuse compared to women who did not experience abuse

(Fernandez-Botran et al., 2011), and the study done by Newton et al. found that physical assault was negatively correlated with IL-6 production (Newton et al., 2011). The discrepancy in findings could be linked to many factors. One reason that could be posited is that these studies have evaluated the relationship between IPV and immune response at varying lengths of time between when the study was conducted and how recent the abuse was. As pointed out by Newton et al., a uniform pro-inflammatory response is not seen and stressor history has a significant bearing on what the immunological response will be (Newton et al., 2011). This could be attributed to the previously mentioned confounders that were not adjusted for in the final analysis.

In the studies reviewed, a significant focus was on the potential immune effects of IPV to explain the link between IPV greater HIV susceptibility and HIV disease progression. Jewkes *et al.*, found that emotional IPV is a risk factor for faster decline in CD4 and CD8 counts, and Kalokhe *et al*. found that lifetime experience of IPV is associated with increased CD4+ activation (Jewkes, 2015; Kalokhe, 2016). It is equally imperative to study how the immune system functions in regard to other types of infectious diseases. A few studies have discussed the link between STIs and IPV and respiratory infections and IPV (Seth et al. 2015) but this area of research could be expanded upon.

Interestingly, there was high variability in findings among studies evaluating IPV effects on CRP levels. This may have been due to the differences in period of time when the abuse occurred and when the study was conducted. While the study done by Halpern *et. al* found that CRP levels did not differ significantly between those who had experienced IPV and those who had not, Heath et al. found that individuals who experienced IPV (and consequently developed PTSD) did show higher levels of CRP (Halpern et al., 2016; Heath et al., 2013). For this reason, it would be

interesting to study how CRP levels are affected within the same time frame as the previous studies. While two studies examined the association between IPV and HSV-1 salivary IgA levels, my search did not identify studies examining the effects of IPV on other humoral responses in IPV survivors. Further, studies examining immune profiles associated with IPV perpetration have been limited to examination of sIgA levels (Romero-Martínez, 2014; Romero-Martinez, 2016).

Using the Effective Public Health Practice Project Quality Assessment tool, we found the quality of studies varied. The major limitation in most of these studies were the small sample size. This hindered the studies from being able to generalize their results to a more representative target population. Additionally, because most studies used cross-sectional study designs, causality between IPV and immune response could not be determined. Due to the sensitive nature of this subject matter, finding appropriate answers to these issues are inherently difficult, but are imperative to do, in an ethical manner, so that the findings from these studies can be used to better develop evidence-based practices and resources for this population.

This literature review has several key strengths. First, it utilized 3 different databases and comprehensive search terms to capture the breadth of available studies. Second, it was conducted in a systematic manner to identify and retain only relevant articles on the subject. Article eligibility assessments and data extraction, while conducted by only one reviewer, were discussed between two reviewers if concerns were raised by Reviewer 1 to foster accuracy. The PRISMA flowchart and the Cochrane guidelines for systematic reviews were followed to develop the review protocol and help standardize the process. Only original, peer-reviewed articles were included so the studies that were included for review had already undergone a rigorous vetting process. Further, the references of relevant commentaries, systematic reviews

and meta-analyses were examined for articles meeting inclusion that were not identified through the searches.

A few of the limitations of this review are that it included only articles that were published in English, which may have excluded articles that demonstrated a link between IPV and immunity in other languages. Additionally, only publicly available articles were included, that were available through the aforementioned databases or the institutional catalog – articles that required payment to be accessed or were otherwise inaccessible were not included in this review. Further, assessments of article eligibility and extracting solely using data presented in the articles – authors were not contacted to clarify insufficiencies in the reported data and methods. Additionally, the lack of multiple reviewers could be considered a limitation as there may have been biased inclusion or exclusion of studies, however in order to mitigate those effects, clear inclusion and exclusion criteria were set out and articles that required a second opinion were discussed with an advisor for the review.

Public Health Implications

Understanding the link between intimate partner violence and immunity has various, important public health implications. The literature has shown that there is an increased susceptibility to disease, and this finding is important to understand more thoroughly in order to provide the best quality of care to survivors of IPV. Additionally, when the immune system is affected, it can change how these individuals respond to vaccinations and other biomedical prevention strategies. A more thorough understanding of the link between IPV and immunity may highlight the need to modify biomedical prevention and treatment protocols for survivors of abuse to be more effective in this population. For example, in a study done by Glaser *et. al,* it was found that participants who exhibited depressive symptoms and negative mood states

demonstrated a higher IL-6 response when administered the influenza vaccine (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003). Additionally, enhanced understanding of the immune effects of IPV could add to the literature demonstrating that IPV survivors have a lower quality of life, higher utilization of health services and poorer health status, and thus motivate a stronger public health response to the IPV epidemic (J. Campbell et al., 2002). Future research in this area could shape the way health care professionals design resources that are better tailored to this population, form policies and practice methods and improve translation and implementation of prevention and support programs for violence survivors.

Future research on this topic should include studies that evaluate this relationship across different ethnicities, socioeconomic status, sexual presentation and also on communicable diseases outside the realm of HIV, such as respiratory diseases, especially in low- and middle-income countries. Conducting more prospective, longitudinal cohort studies could help to better define these effects, although it would be important to conduct these studies in the most ethical way possible. Additionally, future studies should aim to include a larger sample population in order to adequately power the study. They should also aim to ensure their sampling strategies capture the full universe of their target population and validate findings across study populations so that the results are generalizable. By doing so, it would be possible to evaluate the efficacy of using biologic markers to validate if immune markers can be considered as reasonable risk indices in victims of IPV for a magnitude of potential health outcomes.

Ultimately, the effects of IPV have long-lasting consequences even after the abuse stops (Plichta, 2004). Women who have experienced IPV are more likely to exhibit worse health behaviors, such as smoking, drinking and substance abuse (Coker, Smith, Bethea, King, & McKeown, 2000; Hathaway et al., 2000; Lemon, Verhoek-Oftedahl, & Donnelly, 2002).

According to the Trauma theory, “a perceived threat to oneself or others leads to changes in arousal, attention, perception, and emotion, and following the threat there is a state of sustained alertness or “relaxed attention” as though the danger might return at any moment,” (Bloom, 1999). By studying the effect of the link between IPV and immune response, these studies could have a meaningful impact on the way IPV prevention programs are implemented and could increase funding to further research this vital topic, thereby providing a higher quality of care to this population.

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