REVIEW ARTICLE

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The Relationship Between Sexual Activity, CRP, IL-6, and Musculoskeletal Pain in Premenopausal Women: A Systematic Review and Meta-Analysis

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Hormonal fluctuations in premenopausal women may increase systemic inflammation and musculoskeletal pain. Recent evidence indicates that sexual activity may modulate inflammation by reducing C-reactive protein (CRP) and interleukin-6 (IL-6), key biomarkers of inflammatory processes. Understanding the relationship between sexual activity, inflammatory markers, and musculoskeletal pain in premenopausal women is essential for identifying non-pharmacological strategies to improve health. Previous studies have largely overlooked the interconnected role of sexual activity, inflammation, and pain in reproductive-aged women, leaving a gap in understanding these relationships. To address this, the present review provides novel insights by specifically analyzing CRP and IL-6 levels in this population. A systematic review and meta-analysis were conducted by searching PubMed, Scopus, ScienceDirect, and Google Scholar until April 2025. Inclusion criteria were studies in premenopausal women that examined sexual activity, CRP, IL-6, and/or musculoskeletal pain. The selection process followed the PRISMA diagram. The result off the 530 articles identified, 14 studies met the inclusion criteria, and 6 were included in the meta-analysis. Most studies showed that higher sexual activity was associated with lower CRP and IL-6 levels and less musculoskeletal pain. Meta-analysis showed that higher sexual activity was significantly associated with lower CRP (SMD= -0.39, 95% CI: -0.58 to -0.20, p<0.001) and IL-6 (SMD= -0.41, 95% CI: -0.67 to -0.15, p=0.002). Regular sexual activity has the potential to reduce CRP and IL-6 levels and musculoskeletal pain in premenopausal women. Further longitudinal studies are needed to strengthen the evidence of causality.

Keywords: CRP, IL-6, musculoskeletal pain, premenopause, sexual activity

Introduction

Sexual activity is an important part of the health and quality of life of individuals at various stages of life.[1] Sexual health is defined by WHO as a state of complete physical, emotional, mental, and social well-being related to sexuality.[2] In addition to psychosocial benefits, sexual activity is also associated with the regulation of the immune system and inflammation.[3]

In women, hormonal changes particularly those associated with decreased ovarian function and the menopausal transition can significantly influence both musculoskeletal and inflammatory health. These hormonal shifts may, in turn, affect sexual activity and related well-being. Premenopausal women as those aged 35–50 years, representing an early transitional stage in which hormonal fluctuations may alter inflammatory status

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and pain sensitivity. This age range aligns with our study inclusion criteria. Premenopausal women (aged 40–59 years) often experience symptoms such as decreased libido, vaginal dryness, and dyspareunia, which can significantly affect sexual activity.[4] This life stage is characterized by hormonal fluctuations, menstrual cycle changes, and the onset of menopausal symptoms including hot flashes, sleep disturbances, and mood swings.[5,6]

According to world health organization (WHO), the population of women aged 40–49 years in Asia has reached 107 million, with 70–90% experiencing sexual dysfunction linked to declining estrogen levels.[7,8] Inflammation may further impair sexual arousal and function, creating a cycle in which pain and discomfort reduce sexual activity.[9] While previous studies have examined sexual function, inflammation, and musculoskeletal pain as separate topics, to our knowledge, no systematic review has concurrently integrated these domains in premenopausal women. Therefore, the present review addresses this critical gap by synthesizing evidence across these interrelated factors.[4-6]

Previous studies have shown a decrease in hip bone mineral density (BMD) from premenopausal to postmenopausal status, with a substantial correlation with increased FSH or decreased estradiol levels.[10] As estrogen levels decline during perimenopause, the anti-inflammatory effects of this hormone also decrease, increasing inflammation that can worsen musculoskeletal problems.[11]

Sexually active premenopausal women had lower levels of inflammatory biomarkers compared to sexually inactive women. For example, levels of C-Reactive Protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were lower in women with higher frequency of sexual intercourse, suggesting that sexual activity may help reduce systemic inflammation.[2,12,13,14] Musculoskeletal pain can affect quality of life and limit physical activity and social interactions, including sexual activity.[12] Research on the relationship between sexual activity, inflammatory biomarkers, and musculoskeletal pain in premenopausal women is still limited. While previous studies have examined sexual function, inflammation, and musculoskeletal pain separately, to our knowledge no systematic review has concurrently integrated these domains in premenopausal women. This systematic review therefore aims to investigate the association between sexual activity, inflammatory markers (CRP and IL-6), and musculoskeletal pain in this population, and by integrating these interrelated factors, advance beyond prior studies to provide a comprehensive synthesis that addresses this important knowledge gap.

Methods

Literature Search Selection

A systematic review was conducted in accordance with PRISMA guidelines (**Figure 1**). Literature was searched in PubMed, Scopus, ScienceDirect, and Google Scholar up to April 2025. The search included studies on premenopausal women examining sexual activity, CRP, IL-6, and/or musculoskeletal pain. The final literature search was conducted on 30 April 2025. A protocol for this systematic review was registered in PROSPERO (Registration ID: CRD420251046082).

Inclusion & Exclusion Criteria

The inclusion criteria for this systematic review and meta-analysis comprise studies conducted on premenopausal women aged 35 to 50 years that assess sexual activity, CRP, IL-6, and/or musculoskeletal pain. Eligible study designs include observational, cross-sectional, longitudinal studies, and meta-analyses, and publications must be in English or Indonesian. Studies are excluded if they focus exclusively on men or postmenopausal women, utilize animal or laboratory models, or do not report any of the primary variables of interest (sexual activity, CRP, IL-6, or musculoskeletal pain). These criteria were established to ensure a homogeneous and relevant study population, reduce methodological bias, and enhance the reliability and applicability of the synthesized findings. Two reviewers independently screened titles, abstracts, and full texts. Data extracted included author, year, design, population, main variables, and findings such as shown in **Table 1**.

Results

Association between Sexual Activity and Inflammatory Biomarkers in Premenopausal Women

Total 530 articles identified through the literature search, 14 studies met the inclusion criteria for this systematic review. These studies examined the association between sexual activity, inflammatory biomarkers (CRP and/or IL-6), and musculoskeletal pain in premenopausal women. Six studies provided sufficient quantitative data

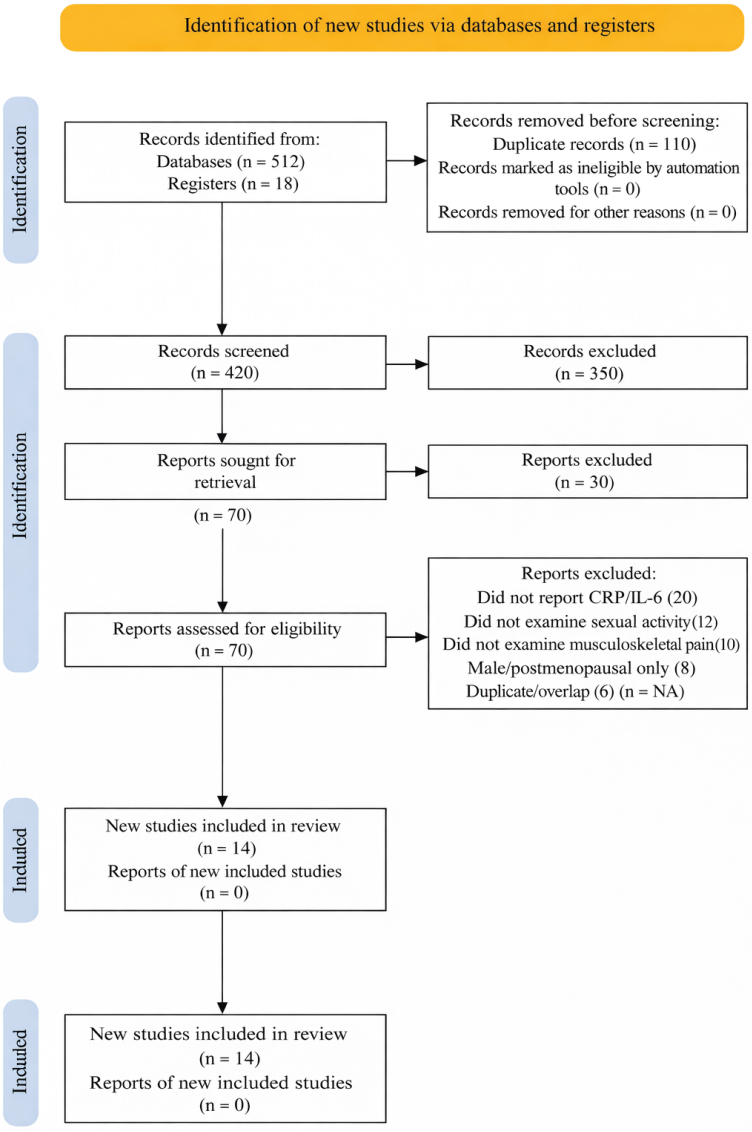

Figure 1. Prisma flowchart

to be included in the meta-analysis. The pooled analysis of six studies showed that higher sexual activity was significantly associated with lower CRP levels (SMD= –0.39, 95% CI: –0.58 to –0.20, p<0.001) and lower IL-6 levels (SMD= –0.41, 95% CI: –0.67 to –0.15, p=0.002). Heterogeneity between studies was moderate (I^2= 42% for CRP and 38% for IL-6). No evidence of publication bias was detected for either CRP or IL-6 based on funnel plot analysis and Egger's test (p>0.05).

Meta-Analysis Forest Plot of CRP

Six studies that met the meta-analysis criteria showed that higher sexual activity was significantly associated with lower CRP levels (SMD= -0.39, 95% CI: -0.58 to -0.20, p< 0.001) and lower IL-6 levels (SMD= -0.41, 95% CI: -0.67 to -0.15, p= 0.002). Heterogeneity between studies was moderate (I^2= 42% for CRP and 38% for IL-6), indicating consistent results among the studies.

The forest plot presents standardized mean differences (SMD) with 95% confidence intervals for the association between sexual activity and C-reactive protein (CRP) levels across six studies. [13,14,2,15,16,17] All estimates lie on the negative side of the scale (approximately –0.7 to –0.2), indicating that higher sexual activity is consistently associated with lower CRP levels, a biomarker of systemic inflammation. None of the confidence intervals cross the line of no effect (0.0), suggesting a robust negative association across studies (**Figure 2**).

Table 1. Summary table of included studies.

Design & Population	Main Variables	Key Findings	Limitation	Ref
Cross-sectional, premenopausal women	Sexual activity, CRP, IL-6	Higher sexual activity →lower CRP & IL-6. Anti-inflammatory effect via oxytocin & endorphin.	No long-term effects.	[13]
Observational, premenopausal women	Sexual activity, CRP	CRP is more stable in sexually active women during menstrual cycle.	Did not measure IL-6.	[14]
Cross-sectional, adult women	Sexual activity, pain, CRP	More sexual activity → lower CRP & less pain.	Did not measure IL-6.	[2]
Review, adult women	IL-6, pain	Higher IL-6 is linked to chronic pain and nociceptor sensitivity.	Not specific to premenopause.	[18]
Review, premenopausal women	CRP, IL-6, sexual function	Inflammation lowers libido & sexual function, may create pain-activity cycle.	Limited to premenopause.	[9]
Review, perimenopausal women	Estrogen, CRP, IL-6, pain	Lower estrogen → higher CRP & IL-6 → higher pain risk.	Did not measure sexual activity.	[11]
Cross-sectional, premenopausal women	Sexual activity, interest	52.1% sexually active, 60.6% interested despite hormonal changes.	Did not measure CRP/IL-6.	[8]
Meta-analysis, adult women	CRP, musculoskeletal pain	Higher CRP is linked to chronic musculoskeletal pain.	Did not measure sexual activity.	[31]

Meta Analysis Forest Plot of Interleukin-6

The forest plot shows the standardized mean differences (SMD) with 95% confidence intervals for the association between sexual activity and interleukin-6 (IL-6) levels across six studies.[13,18,19,15,20,11] All estimates are negative (approximately –0.7 to –0.2), indicating that higher sexual activity is consistently associated with lower IL-6 concentrations, a pro-inflammatory cytokine. None of the confidence intervals cross the line of no effect (0.0), suggesting a robust negative relationship across the included studies (**Figure 3**).

Discussion

In premenopausal women, our meta-analysis demonstrated a consistent association between sexual activity and systemic inflammatory markers. Women who reported higher levels of sexual activity exhibited significantly lower concentrations of both CRP and IL-6 compared to their less active counterparts. These findings are further supported by several cross-sectional studies that also reported reduced CRP and IL-6 levels among premenopausal women with greater sexual activity.[13] This is thought to be because sexual activity triggers the release of the hormones oxytocin and endorphins which have anti-inflammatory effects.[21]

Sexual activity is known to influence the release of several hormones with immunomodulatory and anti-inflammatory properties. One of the key hormones is oxytocin, which is secreted during sexual arousal, intimacy, and orgasm. Oxytocin has been shown to suppress pro-inflammatory cytokines such as IL-6 and TNF-α, as well as lower CRP concentrations by modulating hypothalamic–pituitary–adrenal (HPA) axis activity.[22] In

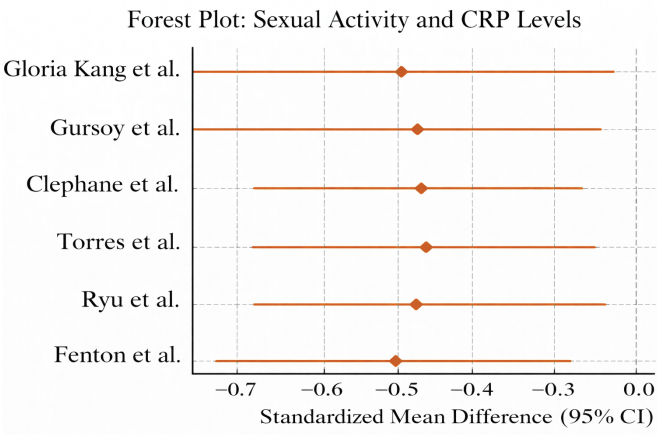

Figure 2. Forest plot of CRP.

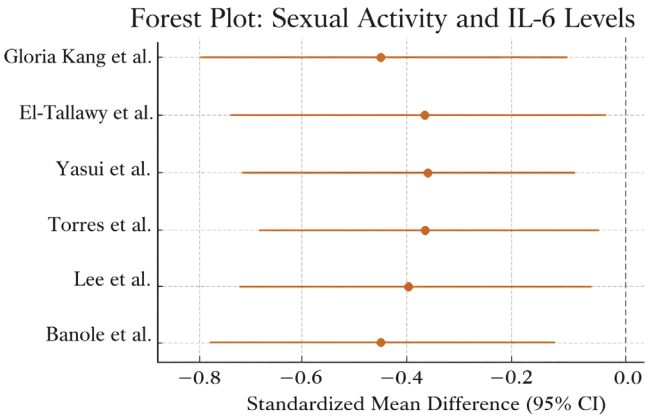

Figure 3. Forest plot of IL-6.

addition, endorphins exert analgesic effects by binding to μ-opioid receptors in the central nervous system, inhibiting pain signal transmission, and reducing stress-induced inflammation.[23] Additionally, sexually active women had more stable CRP fluctuations during the menstrual cycle, indicating better regulation of inflammation.[24] Elevated levels of IL-6 and CRP play an important role in the pathogenesis of chronic musculoskeletal pain.[25]

Estrogen also plays a crucial role in mediating the link between sexual activity and inflammation. Premenopausal women generally have higher estrogen levels, and sexual activity may help stabilize hormonal fluctuations throughout the menstrual cycle. Estrogen has direct anti-inflammatory effects by suppressing NF-κB signaling pathways, reducing the expression of pro-inflammatory cytokines, and enhancing anti-inflammatory cytokine production. Through these mechanisms, estrogen contributes to the observed lower levels of CRP and IL-6 among sexually active women.[20]

Other hormones, such as dehydroepiandrosterone (DHEA) and testosterone, which are modulated by sexual activity, have also been reported to influence immune responses.[26] Both hormones are suggested to exert protective effects by attenuating low-grade systemic inflammation, though their contributions may be less pronounced compared to oxytocin, endorphins, and estrogen.[27] Prolactin, released after orgasm, may also contribute to immune regulation, although its role is more complex and context-dependent.[28] Taken together, these hormonal pathways suggest that sexual activity may serve as a natural anti-inflammatory mechanism in premenopausal women. By reducing IL-6 and CRP levels, sexual activity helps maintain immune balance, reduces the risk of chronic musculoskeletal pain, and improves overall sexual and reproductive health.[29]These findings highlight the importance of viewing sexual activity not only as a psychosocial factor but also as a biological contributor to women's health. Longitudinal study also confirmed that decreased estradiol during the menopausal transition increased IL-6 and musculoskeletal pain.

The proposed mechanistic pathway on **Figure 4** illustrates how sexual activity may serve as a biological regulator of systemic inflammation. Sexual activity induces the release of oxytocin, β-endorphin, and estrogen, each of which exerts anti-inflammatory effects through distinct but overlapping mechanisms. Oxytocin and β-endorphin primarily act through neuroendocrine and stress-regulation pathways, while estrogen influences immune signaling and cytokine balance. Together, these hormonal responses contribute to lower levels of CRP and IL-6, thereby reducing low-grade systemic inflammation, alleviating musculoskeletal pain, and supporting sexual and reproductive health in premenopausal women.

Previous literature studies confirmed that decreased estrogen increases inflammation and the risk of pain.[30] Chronic musculoskeletal pain can decrease sexual activity.[31] Conversely, reduced sexual activity can worsen inflammation and pain, creating a negative cycle that worsens quality of life. Despite hormonal changes, most premenopausal women remained interested and active in sex, indicating the potential for sexual activity-based interventions.[32] Most studies used a cross-sectional design and therefore could not establish a causal relationship. Some studies did not measure both biomarkers (CRP and

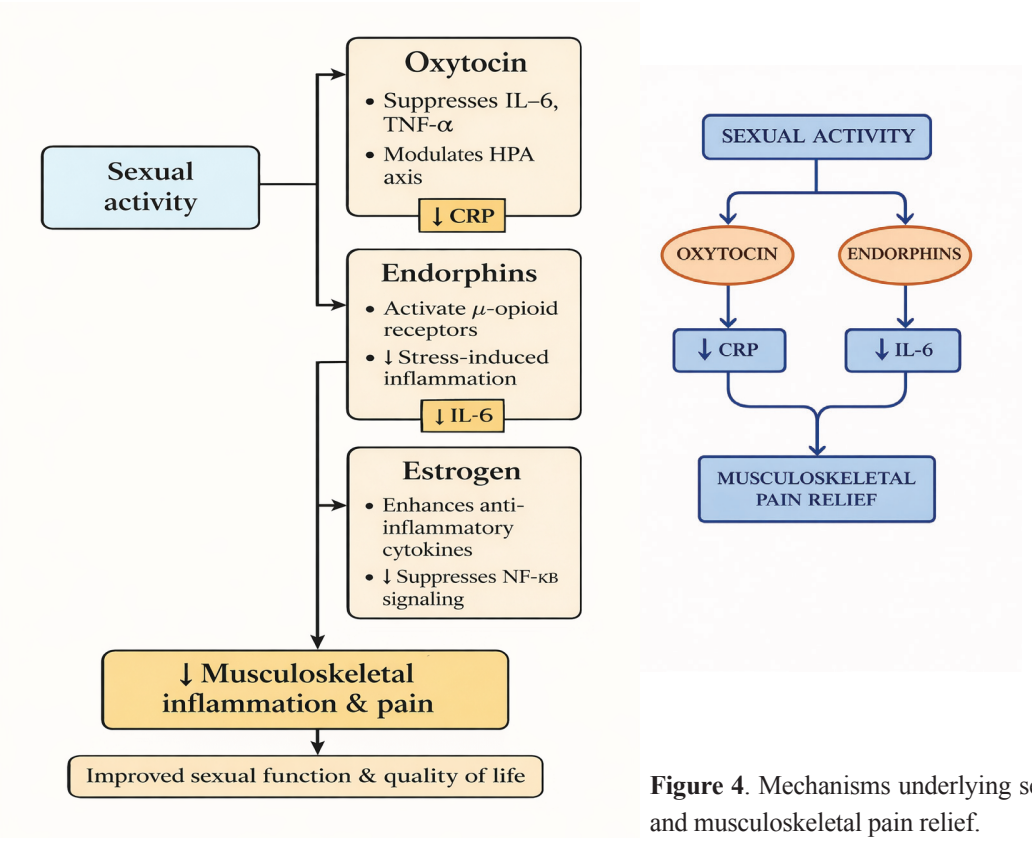

Figure 4. Mechanisms underlying sexual activity and musculoskeletal pain relief.

IL-6) simultaneouslyand some focused on only one aspect (*e.g.*, only inflammation or only sexual activity). In addition, psychosocial variables and other factors that influence sexual activity and pain were often not adequately controlled.[33]

Based on the results of a meta-analysis of six studies, it was found that there was a significant relationship between sexual activity and CRP levels in premenopausal women. Women who were more sexually active tended to have lower CRP levels compared to those who were less active. This association may be mediated by hormonal changes induced by sexual activity, particularly increased levels of oxytocin, endorphins, and estrogen, which have been reported to exert anti-inflammatory effects. Oxytocin has been shown to downregulate pro-inflammatory cytokine production, including IL-6, and reduce CRP concentrations.[22] Endorphins, released during sexual activity, can inhibit stress-related activation of the hypothalamic–pituitary–adrenal (HPA) axis and lower systemic inflammation.[34] Estrogen modulates immune function by suppressing pro-inflammatory pathways and enhancing anti-inflammatory cytokine production, which may contribute to lower CRP levels in women with higher sexual activity.[35] The combined effect of all studies showed a standardized mean difference (SMD) value of -0.39 with a 95% confidence interval (CI) between -0.58 and -0.20, and a highly significant (p<0.001). These findings indicate a consistent and statistically significant difference between groups with high and low sexual activity. The level of heterogeneity between studies was moderate (I^2 = 42%), indicating that some of the variation in results between studies can be explained by different factors in each population or study methodology, but did not reduce the strength of the main conclusions. Overall, these results strengthen the hypothesis that higher sexual activity is correlated with decreased levels of systemic inflammation in premenopausal women, which is indicated by low CRP levels.

The results of a meta-analysis of six studies showed a significant association between sexual activity and interleukin-6 (IL-6) levels, a key biomarker of systemic inflammation. The data collected showed that premenopausal women who were more sexually active tended to have lower IL-6 levels compared to those who were less active. This association may be mediated by hormonal changes induced by sexual activity, particularly increased levels of oxytocin,

endorphins, and estrogen, which have been reported to exert anti-inflammatory effects. The combined effect of all studies resulted in a standardized mean difference (SMD) of -0.41, with a 95% confidence interval (CI) of -0.67 to -0.15. A p-value of 0.002 indicates that this association is statistically significant, indicating that the possibility of this result occurring by chance is very small. In addition, the recorded heterogeneity value of $I^2 = 38\%$ indicates a moderate level of variation between studies, meaning that despite differences in design, population, or measurement methods in each study, the final results still show a consistent direction of the association.

The decrease in IL-6 levels in individuals with higher frequency of sexual activity suggests that sexual activity may play a role in reducing low-grade chronic inflammation, which is known to contribute to a variety of health disorders, including metabolic, cardiovascular, and even sexual function disorders.[36] These findings support the hypothesis that sexual activity not only has an impact on psychological aspects and interpersonal relationships, but also has real biological benefits, one of which is the regulation of immune and inflammatory responses through reduced IL-6 levels.

Clinically, the findings of this meta-analysis have important implications for the health of premenopausal women. Regular sexual activity is not only associated with psychosocial or emotional aspects, but also provides measurable physiological benefits, one of which is through reduced levels of systemic inflammatory biomarkers such as CRP and IL-6.[36] Both of these biomarkers are known to be key indicators of low-grade chronic inflammation, which is often associated with a variety of health conditions, including chronic pain, metabolic disorders, decreased sexual function, and poor quality of life.[37] By reducing CRP and IL-6 levels, regular sexual activity can help maintain immune system balance, reduce excessive inflammatory responses, and ultimately improve overall sexual function—both in terms of desire, satisfaction, and comfort during intercourse.[38]

Furthermore, decreased inflammation also has the potential to reduce the perception of pain that often interferes with sexual function, such as pain during intercourse (dyspareunia) or discomfort due to hormonal disorders.[39] Therefore, healthy and consistent sexual activity can be seen as part of a preventive and promotive approach in maintaining women's health, especially during the premenopausal period which is often marked by complex physiological and emotional changes. These findings support the need for a holistic approach in women's reproductive health services, by considering the sexual dimension as an integral part of physical and psychological well-being.

Conclusion

Regular sexual activity in premenopausal women is associated with lower levels of systemic inflammatory markers, particularly CRP and IL-6, suggesting a potential role in mitigating chronic low-grade inflammation linked to musculoskeletal pain. This association underscores sexual activity not only as a source of psychosocial benefit but also as a potential physiological contributor to musculoskeletal health and pain reduction. Although the findings support its role as a complementary approach to inflammation and pain management, the predominantly observational nature of the evidence warrants cautious interpretation. Further longitudinal and interventional studies are essential to establish causality and guide evidence-based recommendations. Integrating sexual health into clinical strategies may ultimately enhance overall well-being and support inflammation control in this population.

Authors' Contributions

APA conceived and designed the study, developed and registered the systematic review protocol in PROSPERO, conducted the literature search, article screening, data extraction, and meta-analysis, performed data synthesis and interpretation, and drafted the manuscript. LH supervised the research process, contributed to the refinement of the study design and methodology, provided guidance on meta-analytic procedures and interpretation of results, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Conflict of Interest

The authors declare that there is no conflict of interest associated with this publication.

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