Review Article

Burnout and c-reactive protein levels: an integrative literature review

Burnout e níveis de proteína c-reativa: revisão integrativa da literatura

Burnout y niveles de proteína C reactiva: revisión integradora de la literatura

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How to cite:
Maciel DM, Merces MC, Santos AS, Silva AP, Santos CV, Castro JO, et al. Burnout and c-reactive protein levels: an integrative literature review. Acta Paul Enferm. 2023;36:eAPE00242.

DOI
http://dx.doi.org/10.37689/acta-ape/2023AR002422

Keywords
Burnout; C-Reactive Protein; Occupational health; Epidemiology

Descritores
Esgotamento profissional; Proteína C-Reativa; Saúde do trabalhador; Epidemiologia

Descriptores
Agotamiento professional; Proteína C-Reactiva; Salud laboral; Epidemiología

Submitted
February 8, 2022

Accepted
October 26, 2022

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Associate Editor (Peer review process):
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Abstract

Objective: To identify the scientific evidence available in the literature on the association between Burnout Syndrome (BS) and C-reactive protein levels.

Methods: This is an integrative literature review of articles published in Portuguese, Spanish and English, with no date limit, with different study designs, available electronically in the Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine, National Institutes of Health (PubMed), Scopus, Latin American and Caribbean Center on Health Sciences Information (LILACS), Science Direct, and Springer Link databases. The selected articles were analyzed according to the Agency for Healthcare Research and Quality.

Results: Seven articles were analyzed. In most studies, there was a positive association between Burnout and high c-reactive protein levels, despite the general results being contradictory. Most articles that met the selection criteria were in English and indexed in the CINAHL database. The European continent concentrated most of studies. There was a predominance of cross-sectional study design.

Conclusion: Despite the positive association between Burnout and high c-reactive protein levels, the results of this review suggest that new, more robust studies be carried out in an attempt to explain the relationship between BS and CRP.

Resumo

Objetivo: Identificar as evidências científicas disponíveis na literatura sobre a associação entre Síndrome de *Burnout* (SB) e níveis de proteína C-reativa.

Métodos: Revisão integrativa da literatura de artigos publicados em português, espanhol e inglês, sem limite de data, com diferentes desenhos de estudo, disponíveis eletronicamente nas bases de dados do *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), *National Library of Medicine National Institutes of Health* (PubMed), *Scopus*, *Latin American and Caribbean Center on Health Sciences Information* (LILACS), *Science Direct* e *Springer Link*. Os artigos selecionados foram analisados de acordo com a *Agency for Healthcare Research and Quality*.

Resultados: Foram analisados 7 artigos. Na maior parte dos estudos, houve associação positiva entre *Burnout* e níveis elevados de proteína c-reativa, apesar dos resultados gerais serem contraditórios. A maioria dos artigos que atenderam aos critérios de seleção encontrava-se em língua inglesa e indexados na base de dados CINAHL. O continente europeu concentrou a maior parte de produção. Houve predominância de desenho de estudo transversal.

Conclusão: Apesar da associação positiva entre *Burnout* e níveis elevados de proteína c-reativa os resultados dessa revisão sugerem a realização de novos estudos mais robustos na tentativa de explicar a relação entre SB e PCR.

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Conflicts of interest: article is part of a master's thesis enttiled "Associação entre Síndrome de Burnout e Proteína c-reativa: Estudo Transversal de base populacional".

Resumen

Objetivo: Identificar las evidencias científicas disponibles en la literatura sobre la relación entre el síndrome de *burnout* (SB) y los niveles de proteína C reactiva.

Métodos: Revisión integradora de la literatura de artículos publicados en portugués, español e inglés, sin límite de fecha, con diferentes diseños de estudio, disponibles electrónicamente en las bases de datos del *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), *National Library of Medicine National Institutes of Health* (PubMed), *Scopus*, *Latin American and Caribbean Center on Health Sciences Information* (LILACS), *Science Direct* y *Springer Link*. Los artículos seleccionados fueron analizados de acuerdo con la *Agency for Healthcare Research and Quality*.

Resultados: Se analizaron siete artículos. En la mayor parte de los estudios, hubo asociación positiva entre *burnout* y niveles elevados de proteína C reactiva, aunque los resultados generales eran contradictorios. La mayoría de los artículos que cumplieron los criterios de selección estaban en idioma inglés e indexados en la base de datos CINAHL. El continente europeo concentró la mayor parte de la producción. Hubo predominancia de diseño de estudio transversal.

Conclusión: A pesar de la asociación positiva entre *burnout* y niveles elevados de proteína C reactiva, los resultados de esta revisión sugieren la realización de nuevos estudios más sólidos para explicar la relación entre SB y PCR.

Introduction

Stress can be viewed as a state produced by a change in the environment, perceived as challenging or threatening to homeostatic balance. The physiological response to a stressor, whether physical or psychological, is a protective mechanism to maintain human body balance. When a stress response occurs, the body triggers a series of neurological and hormonal processes. Stress duration and intensity can cause short- or long-term effects, compromising homeostasis and even resulting in a pathological process.[1]

In the context of work, sub-proletarianization and the proliferation of structural unemployment exposed workers to a high pace, long hours, high demands, conflicting interpersonal relationships, loss of autonomy over the work process, fragile employment relationships, unhealthy conditions, low pay and professional recognition.[2,3]

In permanent exposure to these stressors, Burnout syndrome (BS) is established, which is characterized as an occupational disease recognized by Brazilian social security since 1999and recently included in the 11th International Classification of Diseases (ICD-11), and defined as a chronic syndrome linked to work.[4,5]

The term Burnout appears in scientific literature in the mid-1970s, mainly after Freudenberger's article in 1974, to explain the process of deterioration in the care and attention given by organizations to their workers. Currently, through social psychologists Christina Maslach and Suzan Jackson, it is recognized as a multidimensional construct consisting of emotional and physical exhaustion, depersonalization and reduced personal fulfillment at work.[6]

Physical and emotional exhaustion is defined as a state of exhaustion due to the relationship/performance of one's own work; depersonalization as indifferent, cold and distant behavior towards users of a service; and reduced personal achievement as a progressive loss of idealism, energy, and desire to achieve goals.[5]

BS is the result of constant physical and psychological suffering, often exceeding the limit of an individual's ability to cope, and may even lead to other injuries, such as metabolic disorders, immunological alterations, mental disorders and abusive use of alcohol and psychotropic drugs, compromising family and social relationships. [7-10]

Regarding immunological changes, chronic work stress activates low-grade inflammatory responses through the synergistic effect of the hypothalamic-pituitary-adrenal and sympathetic-medullary-adrenal axes. Persistent stimulation of these systems can culminate in chronic inflammation with increased serum cortisol levels; alteration of the immune function by decreased Natural Killer (NK) cell activity; increase in proinflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 17 (IL-17), TNFα; and increased c-reactive protein (CRP) levels.[11-15]

CRP is pointed out as a reliable biomarker of inflammation with a constant half-life, ensuring a unique determinant correlation of production with its blood levels, as its rapid production is a response to inflammation.[14] Furthermore, low-grade inflammation detected by ultrasensitive CRP has been shown to be an independent predictor of mortality for cardiovascular disease and increased risk of overall mortality.[12,14]

Considering the context, it is known that the act of working is recognized as an essential activity to guarantee livelihoods, social bonds and personal fulfillment of individuals. However, the transformations in the world of work and its forms of precariousness expose the worker to situations of permanent stress and consequent Burnout. This situation considering the biological inability to maintain the body's homeostasis associated with chronic inflammation can trigger an increase in CRP levels and contribute to the development of chronic and degenerative clinical conditions, such as immunological and metabolic alterations, musculoskeletal pain, psychiatric disorders and metabolic syndrome, for instance. Thus, it is essential to understand the relationship between work and its impacts on health in order to create strategies to face this work reality.[16-18]

In this sense, the present study, based on the literature review, aimed to identify the scientific evidence available in the literature on the association between BS and CRP levels.

Methods

An integrative literature review was carried out with the aim of gathering, synthesizing and analyzing findings from primary studies, based on available scientific evidence on the association between BS and serum CRP levels.[19,20] To systematize this review, six stages were followed: guiding question elaboration; search or sampling in the literature; data collect; critical analysis of included studies; discussion of results; integrative review presentation.[17,18]

Based on the Statement for Reporting Systematic Reviews and Meta-Analyses of Studies (PRISMA), the PICO strategy (acronym for P: population/patients; I: intervention; C: comparison/control; O: outcome) was used to guiding question elaboration.[21]

P (target population) referred to professionals exposed to the development of Burnout and changes in CRP levels; I (intervention), the locus of stressful work; C (comparison), to comparisons between scientific evidence levels; and O (outcome), for a possible association between BS and changes in CRP levels.

Therefore, the guiding question was obtained: Is there scientific evidence available in the literature on the association between BS and CRP levels in workers?

The search for publications was carried out in December 2021, using the descriptors "Burnout, Professional", "C-Reactive Protein", "Occupational Health" and "Epidemiology", Boolean operator AND and truncation techniques, in the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Library of Medicine National Institutes of Health (PubMed), Scopus, Latin American and Caribbean Center on Health Sciences Information (LILACS), Science Direct and Springer Link.

We included articles published in Portuguese, Spanish and English, with no date limit, with different study designs, available electronically in the listed databases that had as scope the association between BS and CRP levels. We excluded articles that were unrelated to the object, monographs, dissertations, theses, abstracts in event annals, book chapters. Duplicate articles were considered only once.

Soon after, a document was prepared to assist in the collection of articles, such as identification, host institution of the study, type of publication, study methodological characteristics and methodological rigor assessment.

Eligible studies were classified by the Agency for Healthcare Research and Quality (AHRQ) scientific evidence levels, which covers six levels: (I) evidence resulting from meta-analysis and systematic review; (II) evidence obtained from randomized clinical trials; (III) evidence obtained from clinical trials without randomization; (IV) evidence from cohort and case-control studies; (V) evidence from a systematic review of descriptive and qualitative studies; (VI) evidence based on descriptive or qualitative study. Finally, a critical analysis of articles took place and a synoptic table was prepared with selected publications, containing author/year/journal, country where the study was conducted, thematic considerations, study design, summary of conclusions and AHRQ classification.

Results

Twenty-seven articles were found in the databases, including 48% (13) CINAHL, 33% (9) PubMed, 7.4% (2) Scopus, 3.7% (1) LILACS, 3.7% (1) Springer Link and Science Direct (1). Based on eligibility criteria and detailed analysis of publications, 20 articles did not meet the criteria, equivalent to 15% duplicated and 85% were unrelated to the object of study. Given the above, in this review, seven articles were selected, which are summarized in figure 1.

Of the seven eligible studies, 71% (5) were in English and 29% (2) in Spanish, mostly indexed in CINAHL. It is noteworthy that most journals were psychology and medicine. As for the years of publication, they focused between 2005 and 2020. Regarding the education of each study's main authors, 86% were doctors, of these 29% were psychiatrists and 14% with training in biotechnology. There was a higher concentration of articles in Europe, such as France, Spain and the Netherlands (43%). In Asia, the countries that conducted studies were Jordan and Israel, representing 29% of the sample. Venezuela in South America and South Africa in the African continent both represented 14% in the sample. There was a predominance of cross-sectional study design (72%), case-control (14%) and systematic review (14%). No article with a randomized clinical trial study design was found. The population investigated in the studies was mostly made up of professionals who developed work activities in health. According to the AHRQ categories, 72% of articles were classified as level of evidence VI (cross-sectional), 14%, level of evidence IV (cohort and case-control) and 14%, level of evidence V (review of literature). There were no articles selected for evidence level I (evidence resulting from meta-analysis and systematic review). A significant number of studies that made up the integrative literature review described Burnout as a predictive variable for changes in CRP. In 57% (4) of studies, there was an association between the syndrome and CRP alteration, in 29% (2) between Burnout components with CRP and in 14% (1) the association between Burnout and CRP was not found. The articles in this review are summarized in chart 1, ordered according to the year of publication.

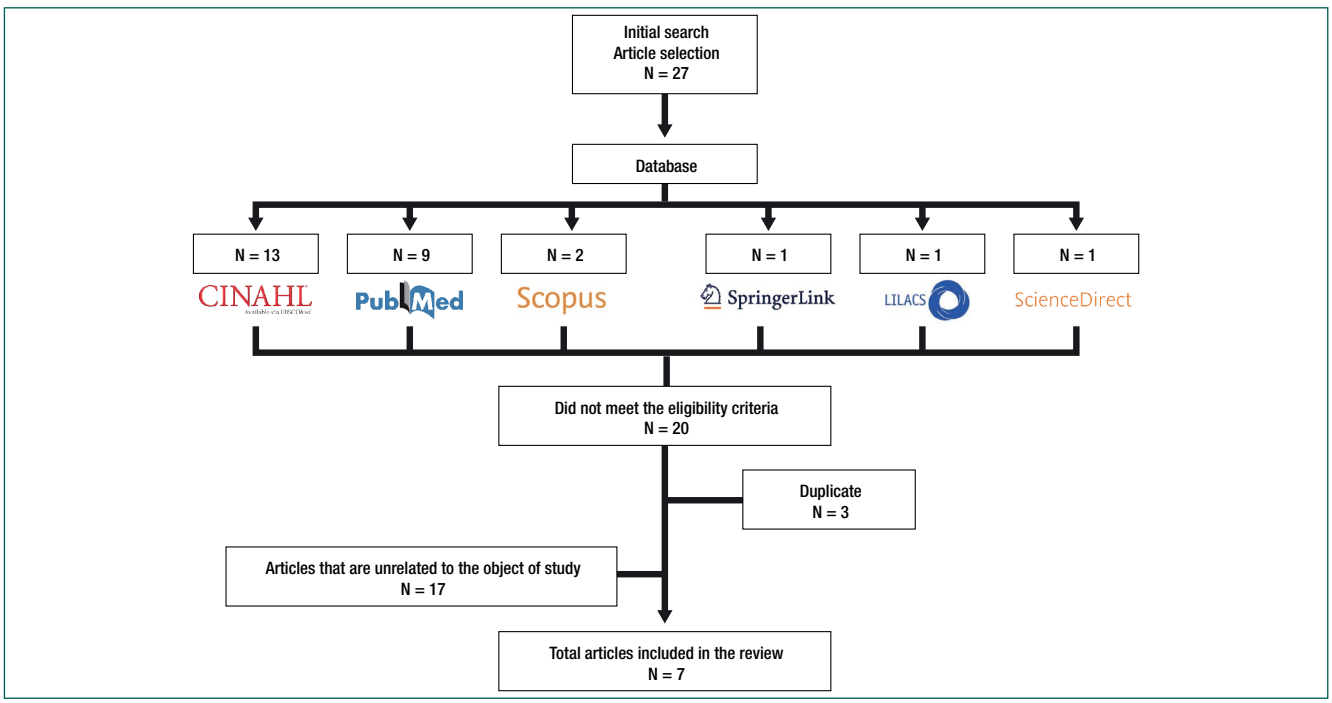

Figure 1. Flowchart of integrative review on scientific evidence between Burnout and C-reactive protein levels

Chart 1. Characterization of publications included in the integrative review

Year of publication/author/ journal	Study type and country/ level of evidence	Thematic considerations	Summary of conclusions
2005 Toker S, Shirom A, Shapira I, Berliner S, Melamed S[22] Journal Occupational Health Psychology	Cross-sectional Israel Level VI	They investigated the possibility that one of the mechanisms linking Burnout, assessed by the Shirom-Melamed Burnout Measure (SMBM) questionnaire, to cardiovascular morbidity is microinflammation, assessed in this study by ultrasensitive CRP (us-CRP) and fibrinogen concentrations. The sample included employees (630 women and 933 men) who performed routine tests at the center where the study took place.	They suggest that in women Burnout is associated with low-grade inflammation, as indicated by the association with hs-CRP and fibrinogen concentrations. This suggests that women with burnout may be at greater risk for diabetes and future cardiovascular events compared to those without Burnout. However, it does not rule out the possibility that exhausted men may also have a higher risk for the same outcomes of the disease.
2011 Danhof-Pont M, Veen T, Zitman F[23] Journal of Psychosomatic Research	Systematic review Netherlands Level V	They assessed the evidence accumulated in international literature on potential biomarkers for Burnout.	Of the 38 biomarkers found in the 31 studies, none presented potential for Burnout. However, there was incompatibility of studies due to differences in the methods used.
2012 Fernández J, Clavero F, Gutiérrez M, Segura I, Bagur M, Fernández J[24] *Atención Primaria*	Cross-sectional Spain Level VI	They investigated Burnout levels in 200 voluntary participants, who attended their periodic health examinations at the Occupational Risk Prevention Service of the *Hospital Universidad de Ceuta*, using the Maslach Burnout Inventory (MBI).	BS was present in 17.2% of workers. There was a significant relationship between work and emotional exhaustion, depersonalization and professional achievement. CRP had a higher average in professionals with Burnout than in the others.
2013 Almadi T, Cathers I, Chow C[25] Psychophysiology	Cross-sectional Jordan Level VI	They examined the relationship between occupational stress, cortisol and CRP in predicting metabolic syndrome (MS). Self-reported job stress measured by effort-reward imbalance ratio (ERI), anthropometric data, CRP, and salivary cortisol were collected from 204 healthy male workers.	The odds of MS in men with high ERI and cortisol were significantly higher than in men with low ERI and cortisol. CRP significantly was associated with MS. The odds of MS were significantly higher in obese men with elevated ERI and CRP levels. Thus, elevated ERI with high cortisol or CRP increases the risk of MS, especially among men with central obesity.
2017 Viljoen M, Claassen N [26] WORK: A Journal of Prevention, Assessment & Rehabilitation	Cross-sectional South Africa Level VI	They investigated associations between scores on the cynicism (depersonalization) subscale of the Maslach Burnout Inventory-General Survey (MBI-GS) with levels of stress, anxiety, physical health based on a questionnaire and a series of risk indicators for physiological health, in 27 volunteer workers with a workload varying between 40 and 80 hours per week.	Cynicism, as reflected by the MBI-GS, increases with increasing stress and is positively correlated with CRP and may contribute to the health decline reported in the MBI.
2018 Metlaine A, Sauvet F, Merino D, Boucher T, Elbaz M, Delafosse J, et al[27] Plos ONE	Case-control study France Level IV	They analyze chronic exposure to stress (Burnout), sleep quality and biological repercussions with metabolic and inflammatory responses among 140 employees of a financial company, from different positions (assistant, assistant, director, senior and senior manager).	Participants with Burnout had higher HbA1C, blood glucose, CRP levels, lower vitamin D levels, increased numbers of leukocytes, neutrophils and monocytes and higher total cholesterol.
2020 González-Moret YA, Guzmán-Cuárez NE [28] MEDUNAB	Cross-sectional Venezuela Level VI	They assess the relationship between BS and hs-CRP levels in 174 physicians residing at a university hospital in Caracas.	Residents with Burnout had higher CRP levels compared to the group without Burnout. Likewise, female individuals, those who slept less than 8 hours a day and those who were subjected to family stress showed a statistically significant association with the development of the syndrome.

Discussion

The selected articles reflect the recognition of the magnitude, severity and vulnerability of Burnout. Moreover, they clearly define the syndrome and use updated terms, such as cynicism (alteration of the term depersonalization in 1996 by Maslach, Jackson and Leiter).[26]

Although it is known that stress affects the body's homeostasis, only two decades ago, studies on Burnout and changes in inflammatory biomarkers began to expand in the world. Although CRP is commonly used as a general inflammation signal, low dosage detected by hs-CRP is an important marker of increased risk of all-cause mortality, mortality from cardiovascular diseases and neoplasms and slightly to moderately increased levels are associated with low-grade chronic inflammation and, consequently, chronic stress, being an important biomarker for assessing the deleterious effects of Burnout.[11,12]

Although most studies show higher CRP levels in people with BS, they were unable to sustain an association with biological plausibility, due to the various variables that can alter this marker, even though many of them are used as exclusion criteria for these studies, such as inflammatory diseases, cardiovascular disease, mental disorders and use of antibiotics, immunosuppressants, amiodarone, low molecular weight heparin.[22,24,26,27] In addition to this, an increase in CRP was observed only in women with Burnout, in the article with the largest analysis sample.[21]

The main limitations were that participants cannot be representative of the general population, due to the sample size and the influence of environmental and emotional factors specific to each place

and individual.[25-27] Cross-sectional studies brought the barrier of this type of research, which is not possible to perform cause-effect association.[22,24-28] Moreover, one of the studies questions the influence of the results of self-reported questionnaires, especially for people with Burnout, since exhausted subjects can respond more negatively due to the negative feeling when filling out the questionnaire.[26]

No Brazilian studies were found that investigated the scientific evidence between the association of BS and CRP levels, making this the first study in Brazil to investigate this association in an integrative review. This information translates the worrying lack of knowledge about important health variables of Brazilian workers and risk factors for cardiovascular diseases and metabolic syndrome, for instance, highlighting the urgency of observational and longitudinal studies on the object, as well as research on interventions in the current labor situation, focusing on Burnout and its consequences.[22,25]

The largest number of articles concentrated on the European continent (43%), certainly due to the concern that the European Union (EU) has shown in reducing the deleterious effects of work on workers' health and in the creation of public policies on the subject. Of the studies identified in this review, according to the AHRQ categories, 72% were classified as level of evidence VI (cross-sectional study), which results in a medium level of evidence.

The limitations found were the scarcity of studies that addressed the research object of this review, hindering a greater discussion on the subject. Regarding the use of different scales for measuring BS (MBI and SMBM), which, although validated, MBI assesses anxiety, depression, sleep disorders, somatic symptoms and impaired health. In contrast to SMBM, which focuses on the chronic depletion of energy resources and is similar to chronic fatigue syndrome and "vital exhaustion", making it difficult to compare studies that use different scales, differences between exclusion criteria and possible interference in the results of articles regarding CRP level and consequently in this review.

Due to the differences between the results found and the predominance of medium-level study designs, it is believed that conducting epidemiological studies with robust analyzes and well-structured methodology and randomized clinical trials will contribute more effectively with the necessary knowledge to compare and assess the effects of BS on CRP levels.

Conclusion

It is concluded that although most studies show a positive association between Burnout and high CRP levels, the results are still contradictory, demonstrating that the scientific evidence available in the literature is still insufficient to affirm the association between Burnout and CRP levels. This shows the urgency to carry out new, more robust studies, mainly national ones, in an attempt to curb BS and its possible deleterious impacts, such as CRP and its relationship with the risk of mortality. In addition to this, the encouragement and dissemination of knowledge on this topic to other professional categories due to the multifactorial complexity of Burnout and its repercussions.

Acknowledgments

We would like to thank the Coordination for the Improvement of Higher Education Personnel (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) for the master's scholarship.

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