Interventions in burnout and their effects on biomarkers: A systematic review

Intervenções em burnout e seus efeitos sobre os biomarcadores: Uma revisão sistemática

Intervenciones en burnout y sus efectos en biomarcadores: Una revisión sistemática

Literature Reviews

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Abstract: Although burnout is a widely studied topic, there is still no clear consensus on its definition, and many interventions are implemented without a rigorous evaluation of their actual effectiveness. This study aimed to analyze the biomarkers associated with the response to interventions applied to adults with burnout. A systematic review was conducted using the PRISMA methodology, with searches performed on PubMed, Web of Science, PsycInfo, and Embase from April to May 2023. Six articles met the inclusion criteria for the final analysis. It was found that mindfulness-based interventions are common, with cortisol collected from saliva being the most frequently evaluated biomarker. Therefore, these interventions primarily focus on analyzing stress reduction, although this is only one precursor of burnout. This study emphasizes the importance of analyzing the impact of interventions through biomarkers and behavioral measures, assessing pre- and post-intervention, to accurately determine their overall effectiveness.
Keywords: burnout, therapy, biomarkers.

Resumo: Apesar de o *burnout* ser um tema muito estudado, não existe um consenso claro sobre sua definição, e muitas intervenções são implementadas sem uma avaliação rigorosa de sua eficácia real. Este estudo objetivou analisar os biomarcadores associados à resposta às intervenções aplicadas em adultos com *burnout*. Foi realizada uma revisão sistemática utilizando a metodologia PRISMA, com buscas nos portais PubMed, Web of Science, PsycInfo e Embase, de abril a maio de 2023. Seis artigos preencheram os critérios de inclusão para a análise final. Verificou-se que as intervenções baseadas em mindfulness são comuns, sendo o cortisol coletado através da saliva o biomarcador mais frequentemente avaliado. Portanto, as intervenções focam principalmente na análise da redução do estresse, embora esta seja apenas um precursor do *burnout*. Enfatiza-se a importância de analisar o impacto das intervenções por meio de biomarcadores e medidas comportamentais, avaliando antes e depois, para conhecer com precisão sua eficácia geral.
Palavras-chave: esgotamento psicológico, terapia, biomarcadores.

Resumen: Aunque el *burnout* es un tema ampliamente estudiado, aún no existe un consenso claro sobre su definición, y muchas intervenciones se implementan sin una evaluación rigurosa de su efectividad real. Este estudio tuvo como objetivo analizar los biomarcadores asociados con la respuesta a las intervenciones aplicadas a adultos con *burnout*. Se realizó una revisión sistemática utilizando la metodología PRISMA, con búsquedas en PubMed, Web of Science, PsychInfo y Embase, desde abril hasta mayo de 2023. Seis artículos cumplieron con los criterios de inclusión para el análisis final. Se encontró que las intervenciones basadas en mindfulness son comunes, siendo el cortisol recogido de la saliva el biomarcador más frecuentemente evaluado. Por lo tanto, estas intervenciones se centran principalmente en analizar la reducción del estrés, aunque este es solo un precursor del *burnout*. Este estudio enfatiza la importancia de analizar el impacto de las intervenciones a través de biomarcadores y medidas conductuales, evaluando antes y después de la intervención, para determinar con precisión su efectividad general.
Palabras clave: agotamiento, terapia, biomarcadores.

Introduction

Studies on workers' mental health are increasingly gaining international recognition and dissemination (Mittal et al., 2021; Solmi et al., 2022). Notably, Burnout Syndrome has recently been officially acknowledged as a chronic syndrome by the World Health Organization (WHO), and it is strongly linked to the workplace. Further, it was also included in the new International Classification of Diseases, 11th Revision (ICD-11), effective as of January 1, 2022 (WHO, 2019). Burnout syndrome manifests as a state of chronic stress characterized by symptoms of emotional exhaustion, depersonalization, and a low sense of personal accomplishment (Maslach et al., 2001; Schaufeli et al., 2017). Emotional exhaustion includes feelings of being overwhelmed, helpless, or defeated. Depersonalization involves emotional detachment from work, indifference, or disconnection from the profession, often leading to the development of negative attitudes towards colleagues. A sense of low personal accomplishment is characterized by seclusion from responsibilities and inefficiency toward work challenges (Mauceri, 2023).

Concerning the latest definition of burnout, Schaufeli et al. (2020) introduced a novel conceptualization that delineates four core dimensions (exhaustion, mental distance, cognitive impairment, and emotional impairment) and three secondary dimensions (psychological distress, psychosomatic complaints, and depressed mood). The conceptualization and measurement of burnout has been a great challenge for researchers, attributed in part to the lack of a comprehensive and profound understanding of its pathophysiology (Schwenk & Gold, 2018).

From this perspective, burnout is conceptually linked to chronic stress, although it is not the same phenomena, influencing the neuro-hormonal state of the human body, such as cortisol levels (Begin et al., 2022). There are two systems associated with stress regulation: the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis. The SAM axis is associated with automatic responses to stressor events, leading to increased heart rate, blood pressure, and the secretion of hormones such as epinephrine and norepinephrine (DeVente et al., 2003). On the other hand, the HPA axis serves as the link between the brain and the endocrine system, contributing to slower responses from the body. Its activation involves secretion of corticosteroids, adrenocorticotropic hormone, and cortisol (DeVente et al., 2003; Mommersteeg et al., 2006; Raison & Miller, 2003).

A dysfunctional HPA axis is linked to several psychiatric disorders, including burnout, major depression, infectious diseases, cardiovascular problems, and autoimmune processes, such as lupus erythematosus, multiple sclerosis, neurodermatitis, fibromyalgia, among others (Kirschbaum et al., 2000; Kudielka et al., 2006; Van Cauter et al., 1990). Cortisol, associated with this dysfunction, typically exhibits the lowest secretion during the night and the highest peak level after morning awakening, steadily decreasing throughout the day. In healthy adults, free salivary cortisol shows a concentration increase of 50 to 160% within the first 27 to 29 minutes after awakening (Kudielka et al., 2006). There are studies highlighting the importance of providing evidence regarding the effect on the pathophysiology of burnout for the improvement of its measurement using biomarkers such as cortisol (Begin et al., 2022; Penz et al., 2018).

Most studies on interventions for burnout in adults mention person-directed interventions, such as cognitive-behavioral interventions, mindfulness-based interventions, and relaxation techniques, as well as interventions targeting the improvement of social-emotional skills, a psychoeducational approach, a social support approach, professional development strategies, and organizational-directed interventions (Awa et al., 2010; Iancu et al., 2018). Systematic reviews in the burnout literature affirm that interventions, such as cognitive-behavioral interventions and those based on relaxation techniques, when applied to adults diagnosed with burnout, prove more effective in reducing a specific core symptom—emotional exhaustion (Iancu et al., 2018; Maricuţoiu et al., 2016).

Previous reviews have primarily focused on understanding the effects of burnout on biomarkers (Danhof-Pont et al., 2011; Kudielka et al., 2006) or on the effectiveness of interventions for burnout through behavioral measurements (Iancu et al., 2018). However, an analysis of intervention effectiveness, specifically by comparing the changes in biomarkers caused by burnout interventions, is still pending. Understanding the relationship between biomarkers and interventions can contribute to improving treatments for burnout patients, assessing interventions, identifying the main effects on participants, comprehending mechanisms of action, personalizing treatments, and monitoring progress (Danhof-Pont et al., 2011; Jonsdottir & Dahlman, 2019). With this objective in mind, the present systematic literature review aims to investigate changes in biomarkers after interventions for burnout. The specific objectives include identifying sample characteristics, interventions applied to adults with burnout, the duration of interventions, biomarkers investigated, pre- and post-intervention behavioral measures, and values from biomarker assessments. The paper aims to summarize changes in biomarkers associated with the effects of interventions on burnout.

Methods

This systematic review was carried out following the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA; Page et al., 2021). The PRISMA methodology recommends the inclusion of preponderant items and the analysis of systematized literature.

The literature search was independently performed by two researchers across the PubMed, Web of Science, PsycInfo, and Embase databases between April 10th and May 10th, 2023 (see supplementary tables). The search strategy was specifically limited to randomized controlled trials, with appropriate filters applied in the PubMed and PsycInfo databases to exclusively retrieve controlled trials. As well, we filtered the language of the articles (english, spanish and portuguese); and open access articles. All search results were exported to Rayyan, a tool used for systematic reviews, where details of each result were documented. The final selection of studies was completed using the blind-off function within the software to ensure unbiased decisions. The search terms combined various keywords related to "burnout" and "biomarkers," incorporating both Medical Subject Headings (MeSH) and commonly used terminology for each primary concept. A comprehensive list of search terms and strategies employed in the different databases is provided in supplementary Tables 1, 2, 3, and 4.

To be included in the review, studies were required to be empirical articles involving adult participants with burnout symptoms, designed as randomized clinical trials, and include pre- and post-intervention biomarker measurements. Additionally, eligible studies had to be published in Portuguese, English, or Spanish. Studies were excluded if they were part of the "grey literature," lacked a clear definition or assessment tool for burnout, or did not include recorded biomarker measurements.

The retrieved studies were manually checked by two independent and paired reviewers, who conducted a screening by title and/or abstract, adhering to the established criteria for inclusion or exclusion, in cases of disagreement, a third researcher was consulted to decide regarding the study's eligibility. The Rayyan program facilitated this selection process. The reviewers of this systematic review consisted of a multidisciplinary team with advanced qualifications in psychology and experience in neuroscience, neuropsychology, burnout syndrome and cognitive behavioral therapy. This diverse expertise provided a thorough and well-rounded evaluation of the subject matter.

All selected studies were initially read in full. Subsequently, descriptive information from each study was extracted, encompassing details such as title, year of publication, country, and main author. Sample characteristics were also recorded, including sample size, the investigated biomarker, intervention details, intervention duration, pre- and post-intervention measures, and values from biomarker assessments. The main outcome extracted for this systematic review consisted of the changes in biomarker values observed after interventions performed for the treatment of burnout.

In order to control the risk of bias, we implemented dual independent review where one author conducted the initial selection, and a second author independently cross-checked the decisions. This process is designed to minimize the risk of selection bias and ensure a more objective assessment of the studies (Page et al., 2021). Also, the risk of bias was assessed using validation checkpoints and discussion meetings. All tasks independently conducted were cross-checked by another author to mitigate the risk of selection bias and potential assessment errors. The selection process included a checkpoint after reading and discussing the abstract, during which an impartial author reviewed all abstracts from the selected articles. PRISMA 2020 protocols were applied to the validation processes (Page et al., 2021).

As previously detailed, the main outcome under evaluation was the impact of interventions on biomarkers related to burnout. To achieve the review goals, the results were assessed considering the main intervention, the effects over time, and interactions in biomarker measures. This entailed comparing values related to pre and post biomarkers for each intervention, as well as conducting a 2 x 2 comparison between the included interventions in each study.

For each study, when available, means and standard deviations for each group, both pre- and post-interventions, were computed and tested initially to assess time effects. Furthermore, as a second step, interaction effects were tested for each study. At the end of this review, we aim to summarize the main biomarkers assessed in burnout RCTs and the potential changes across the interventions. With the computation of data from various studies, the goal is to contribute to identifying the association between biomarkers pre and post burnout interventions.

Results

Searches returned a total of 1,229 articles. After removing duplicates and records marked as ineligible by automation tools that excluded studies written in a language other than English, Spanish or Portuguese, a total of 778 studies were screened. During the screening process, researchers disagreed on 6.04% (n = 47) of the selection criteria, and a third researcher resolved the discrepancies.

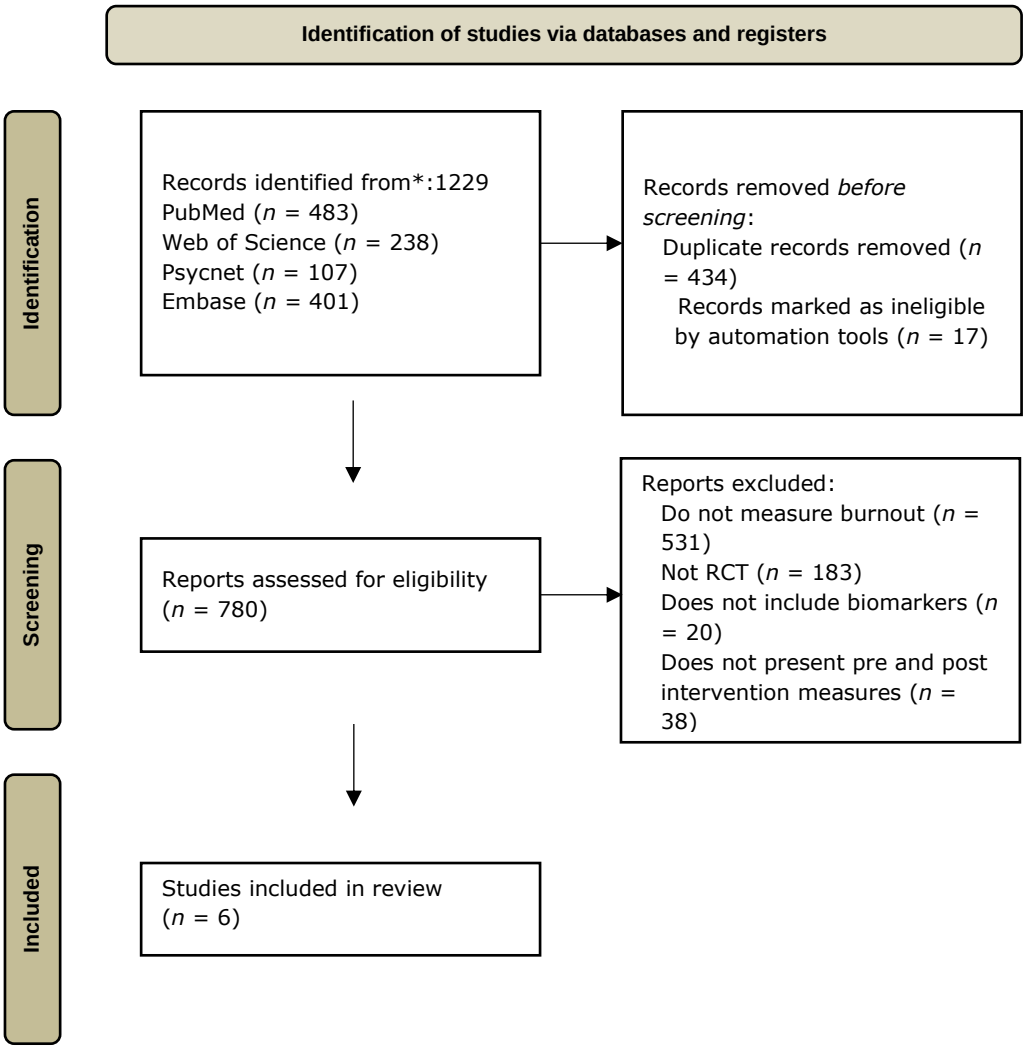

Figure 1. *PRISMA Flowchart Diagram*

Figure 1 depicts the study's identification and inclusion evaluation process. As can be seen, the primary reason for exclusion was the lack of a burnout group, followed by non-RCT studies, lack of biomarker assessments, and details about biomarkers' pre- and post-intervention measures. Thus, this systematic review included six studies, as illustrated in Figure 1, which contains details of the steps involved in the searches, filtering, and inclusion.

Sample characteristics

The sample of this systematic review was heterogeneous, the studies evaluated parents, health professionals (doctors, nurses, young surgeons in training) and workers at an automotive company. Two studies specified the time of biomarker collection in the morning (Díaz-Rodríguez et al., 2011, Jahangard et al., 2019), one in the early afternoon (Duchemin et al., 2015), one not specified (Martínez-Borrás et al., 2022). Cortisol collected at 12 AM is also a bias, considering the appropriate measurement, nocturnal cortisol should be taken to assess disruption of the circadian rhythm, which tends to better measure the effects of stress.

The results and methods were assessed and considered for the risk of bias due to procedural and theoretical issues. Various biasing variables could interfere with biomarker outcomes. Although variables such as age, gender, smoking, and the use of contraceptives or any pills influence cortisol levels (Arantes et al., 2008), none of the other studies mentioned any control for their effects on cortisol measurement (Díaz-Rodríguez et al., 2011; Jahangard et al., 2019; Martínez-Borrás et al., 2022). Furthermore, none of them presented a baseline for cortisol levels. Statistical heterogeneity could be explained by different protocols in laboratories or sample sizes (Danhof-Pont et al., 2011). One study refuted a significant decrease in saliva production, which would be a negative result of the intervention (Díaz-Rodríguez et al., 2011).

As depicted in Table 1, the general studies had sample sizes ranging from 30 to 43 participants, except for one study with a distinct sample size of 122. One study was exclusively composed of female participants (Díaz-Rodríguez et al., 2011), while the others (n = 5) evaluated mixed samples

with both males and females (Belcaro et al., 2018; Brianda et al., 2020; Jahangard et al., 2019; Martínez-Borrás et al., 2022). Most studies involved health professionals (*n* = 4; Belcaro et al., 2018; Díaz-Rodríguez et al., 2011; Duchemin et al., 2015; Jahangard et al., 2019), with only one study conducted among professionals from an automotive company (Martínez-Borrás et al., 2022) and another among parents (Brianda et al., 2020). Five articles employed the same scale to evaluate burnout symptoms (Belcaro et al., 2018; Díaz-Rodríguez et al., 2011; Duchemin et al., 2015; Jahangard et al., 2019; Martínez-Borrás et al., 2022), while one study used an adapted version specifically designed for parents (Brianda et al., 2020).

Intervention characteristics

A heterogeneity of techniques was observed in interventions for adults with burnout. Two studies applied Mindfulness as intervention (*n* = 2; Duchemin et al., 2015; Martínez-Borrás et al., 2022), while other studies used different techniques such as omega-3 supplementation (Jahangard et al., 2019), and Reiki (Díaz-Rodríguez et al., 2011). Additionally, directive, and non-directive approaches were identified for parents (Brianda et al., 2020), as was supplementation with ROBUVIT® (Belcaro et al., 2018), as illustrated in Table 1.

Biomarkers and behavioral assessments

There were three out of the six studies that presented cortisol as the measured biomarker (*n* = 3; Brianda et al., 2020; Díaz-Rodríguez et al., 2011; Jahangard et al., 2019), followed by amylase (*n* = 1; Duchemin et al., 2015), and four distinct biomarkers that were not repeated: salivary flow rate (Díaz-Rodríguez et al., 2011), body temperature (Díaz-Rodríguez et al., 2011), salivary immunoglobulin - sIgA (Martinez-Borrás et al., 2022), and plasma free radicals (Belcaro et al., 2018). Among the six studies, only one evaluated more than one biomarker (Díaz-Rodríguez et al., 2011). For cortisol assessments, all studies collected samples in the morning until 12 a.m. Saliva was the used medium for biomarker collection (*n* = 4; Díaz-Rodríguez et al., 2011; Duchemin et al., 2015; Jahangard et al., 2019; Martinez-Borrás et al., 2022), with one study employing hair collection (Brianda et al., 2020) and another using blood samples (Belcaro et al., 2018). Also, Three out of the six studies (Brianda et al., 2020; Duchemin et al., 2015; Martinez-Borrás et al., 2022) assessed psychological or behavioral measures such as parental neglect, positive and negative emotions, quality of life, perceived stress, anxiety, self-compassion, acceptance, and action, and all of them appropriately assessed burnout (Table 1).

Burnout interventions effects on biomarkers

Out of the six studies, five showed a considerable time effect on biomarkers (Brianda et al., 2020; Díaz-Rodríguez et al., 2011; Duchemin et al., 2015; Jahangard et al., 2019; Martínez-Borrás et al., 2022). Cortisol was expected to decrease after interventions (Brianda et al., 2020; Díaz-Rodríguez et al., 2011; Jahangard et al., 2019), along with a reduction in salivary alpha-amylase (Duchemin et al., 2015), sIgA (Martinez-Borrás et al., 2022), and Oxidative Stress (Belcaro et al., 2018). Conversely, an increase in body temperature (Díaz-Rodríguez et al., 2011), and salivary flow rate (Díaz-Rodríguez et al., 2011) was expected. Only Díaz-Rodríguez et al. (2011) did not observe a significant difference between cortisol levels pre- and post-intervention and reported a negative result in salivary flow (this biomarker tends to be lower in stress situations). There were no interaction effects in any study (Table 2).

Burnout interventions' effects on behavior

Results showed that four studies measured the impact of interventions on burnout using psychological instruments (Brianda et al., 2020; Duchemin et al., 2015; Jahangard et al., 2019; Martínez-Borrás et al., 2022). Brianda et al. (2020) assessed the effectiveness of two different group interventions for parental burnout: directive and non-directive conditions. The authors observed that the parental burnout symptoms decreased significantly immediately and three months after the interventions. Given that the interventions were focused on parental burnout, no significant main effects of time or group were found immediately after in the Maslach Burnout Inventory (MBI), but significant group and time interaction three months after the end of the intervention was found, indicating a reduction of job burnout symptoms only in the directive intervention.

Díaz-Rodríguez et al. (2011) used the MBI only for inclusion criteria, without assessing changes in the instrument's scores pre- and post-intervention. In Duchemin et al. (2015) study, MBI scores did not significantly change between pre- and post-intervention. However, the number of participants with scores greater than 26 on emotional exhaustion decreased by 34% in the MBI intervention group, with no change observed in the waiting list control group. Positive correlations were noted between salivary α-amylase levels and both DASS stress and Maslach emotional exhaustion scores, although neither reached statistical significance ($p = 0.0586$ and $p = 0.0660$, respectively).

Table 1. *Sample Characteristics and Interventions*

Reference	Country	Sample control group M/F	Sample intervention group M/F	Occupation	Behavioral measures	Intervention	Duration of intervention
Belcaro et al. (2018)	Italy	20/42 20/66	22/42 46/66	Young surgeons and senior professionals/ managers	Maslach Burnout Inventory	Robuvit®	4 weeks (300mg/ day)
Brianda et al. (2020)	Belgium	-	77/142 65/142	Parents	Parental Burnout Assessment; Maslach Burnout Inventory	Directive X Non-directive	8 weekly, 2-hour group sessions
Díaz-Rodríguez et al. (2011)	Spain	0/21	0/21	Healthcare professionals	Maslach Burnout Inventory	Reiki	1 session (30 minutes)
Duchemin et al. (2015)	USA	2/14	2/14	Surgical intensive care workers	Maslach Burnout Inventory and the Professional Quality of Life	Mindfulness based intervention; gentle yoga with music	8 weeks (1h/week)
Jahangard et al. (2019)	Iran	4/17	6/16	Nurses	Maslach Burnout Inventory	Omega-3-polyunsaturated	8 weeks (1000mg/ day)
Martinez-Borrás et al. (2022)	Spain	12/8	13/7	Automotive company workers	Maslach Burnout Inventory; Perceived Stress Questionnaire; Self-Compassion Scale; Acceptance and Action Questionnaire	Mindfulness and Self-compassion program	6 weeks

Table 2. *Effects of Intervention on Biomarkers*

		Intervention Group			Control Group				
		T0	**T1**	**Time effect**	**T0**	**T1**	**Time effect**	**Interaction effect**	
Reference	**Biomarker**	***M (SD)***	***M (SD)***	***t (df), p***	***M (SD)***	***M (SD)***	***t (df), p***	***F(df), p***	***p***
Belcaro et al. (2018)	Oxidative stress (plasma free radicals)	397 (33)	323 (29)		396 (19)	358 (27)	-	0.328 (1.2), 0.624	0.624
Belcaro et al. (2018)	Oxidative stress (free radicals)	388 (24)	344 (22)		378 (31)	377 (2)	-	2 (1.2), 0.29	0.29
Brianda et al. (2020)	Hair cortisol	89.19 (102.71)	56.89 (60.76)	2.53 (107), 0.012			-		
Brianda et al. (2020)	Hair cortisol	128.5 (126.35)	43.72 (20.34)	6.21 (174), 0.001			-		
Díaz-Rodríguez et al. (2011)	Salivary flow rate	1.2 (0.6)	1.1 (0.6)	0.54 (40), 0.592	1.2 (0.5)	1.3 (0.6)	0.58 (40) 0.56	2 (1.2)	0.292
Díaz-Rodríguez et al. (2011)	Salivary cortisol	0.34 (0.41)	0.12 (0.08)	2.41 (40), 0.02	0.26 (0.30)	0.11 (0.06)	2.246 (40) 0.03	0.069 (1.2)	0.817
Díaz-Rodríguez et al. (2011)	Body temperature	35.7 (0.3)	36.0 (0.3)	3.24 (40), 0.002	35.8 (0.4)	35.8 (0.4)	0 (40) 1	0.562 (1.2)	0.531
Duchemin et al. (2015)	Salivary Alpha Amylase	93.6 (15.9)	80.1 (9.2)	2.939 (30), 0.006	93.6 (15.9)	60.2 (3.3)	8.227 (30) 0.001	0.398 (1.2)	0.592
Jahangard et al. (2019)	Salivary cortisol	59.80 (21.94)	40.51 (17.29)	3.16 (40), 0.003	62.31 (17.73)	52.23 (15.13)	2.16 (42) 0.036	8.65 (1.2)	0.098
Martinez-Borrás et al. (2022)	Salivary Immunoglobulin A (sIgA)	7.44 (3.89)	13.7 (7.14)	3.09 (38), 0.003	7.07 (3.46)	8.30 (3.24)	1.16 (38) 0.25	1.296 (1.2)	0.372

Martínez-Borrás et al. (2022) found a significant decrease in the scores for perceived stress (Perceived Stress Questionnaire), emotional exhaustion (MBI), depersonalization (MBI), and experiential avoidance (Acceptance and Action Questionnaire) after the Mindfulness and Self-compassion program. Jahangard et al. (2019) identified that emotional exhaustion and depersonalization (MBI) decreased over time in the omega-3 group compared to the placebo group. The sense of personal accomplishment increased over time in the omega-3 group. Belcaro et al. (2018), also using the MBI, found that post-intervention, there were positive effects on the feeling of having a positive influence, strain from work interactions, the lack of care, and levels of interest and enthusiasm. The need for giving up and regrets for being in the profession decreased, while the level of satisfaction improved significantly.

Discussion

This systematic literature review presents studies that investigate changes in biomarkers following interventions on adults with burnout symptoms. Specific objectives included identifying sample characteristics, interventions applied, intervention duration, biomarkers investigated, pre- and post-intervention behavioral measures, and values from biomarker assessments. The sample characteristics revealed a majority of women, young adults, and economically active age groups. Consequently, the interventions described cannot be generalized to the broader burnout population, as the techniques were applied only in individuals with these characteristics. Further studies are needed to generalize interventions to diverse populations. Notably, most interventions targeted health professionals, whose symptoms of burnout considerably increased after the pandemic (Ornell et al., 2020). Thus, interventions that help these professionals to have a better relationship with their work have proved essential.

The new burnout definition (Schaufeli et al., 2020) considers four core dimensions (exhaustion, mental distance, and impaired emotional and cognitive impairment) and three secondary dimensions (depressed mood, psychological distress, and psychosomatic complaints). Regarding the interventions applied, it was found that, although burnout symptoms were evaluated, none of the interventions were specifically designed for addressing burnout as described in this new definition. The studies based their studies on the Maslach definition, and specifically addressed emotional exhaustion as burnout. Only, the study by Brianda et al. (2018), was expressly designed to intervene in parental burnout. Techniques applied to workers were mainly focused on reducing their stress symptoms, when they should consider all dimensions to treat burnout correctly.

Regarding behavioral interventions, it was found three types of interventions: reiki, mindfulness-based, and directives). Our results showed that mindfulness-based techniques were employed in 33% of the studies analyzed, consistent with literature highlighting their frequent use in stress reduction (Karo et al., 2023). Furthermore, our findings support the effectiveness of mindfulness as a strategy for reducing burnout levels (Duchemin et al., 2015; Maricuţoiu et al., 2016; Martinez-Borrás et al., 2022). In addition, Vîrgă et al. (2021) suggest that mindfulness interventions may also help enhance work engagement, offering a positive counterbalance to burnout. No effect of reiki was found on the biomarkers investigated by Díaz-Rodríguez et al. (2011). On the other hand, recent studies identified Reiki as a technique offering several benefits in pain management treatment, including stress reduction, alleviation of anxiety and depression, mitigation of work-related stress, improvement in psychosocial health, enhancement of well-being, and better quality of life and mental health (Dyer et al., 2023; Morero et al., 2021; Rosada et al., 2015; Zadro et al., 2022; Zucchetti et al., 2024). Therefore, behavioral techniques such as mindfulness, reiki and yoga should be better studied to help reduce, specifically, burnout symptoms and their effects on biomarkers. In conclusion, exploring the potential synergies and distinct benefits of mindfulness, reiki, and yoga in addressing burnout symptoms and biomarkers could offer valuable insights for future research and clinical applications.

The studies included in our analysis identified medication interventions such as omega-3 supplements and Robuvit. Omega-3 supplementation, which aims to balance fatty acids, is associated with the treatment of various behavioral and learning disorders. Ruxton et al. (2007) conducted a comprehensive evidence review demonstrating its effectiveness in treating conditions including depression and bipolar disorder (Freeman, 2000; Mischoulon & Fava, 2000; Sarris et al., 2011), as well as dementia, attention deficit hyperactivity disorder (ADHD), autism, dyslexia, and dyspraxia (Richardson, 2006). Moreover, recent research, such as the study conducted by Weichmann et al. (2021), has provided compelling evidence supporting the clinical benefits of Robuvit supplementation. These effects encompass not only reductions in fatigue but also enhancements in overall energy levels. Robuvit has been employed in interventions targeting reductions in plasma oxidative stress among chronically fatigued and burnout individuals, as well as improvements in conditions such as renal insufficiency, mild heart failure, liver insufficiency, posttraumatic stress disorder, and recovery from surgery-induced fatigue. Furthermore, studies have indicated its effectiveness in enhancing sports performance, promoting general vigor, and ameliorating erectile function.

To understand the biomarkers measured in the included studies, it is important to know that

certain dysfunctions are responsible for the physical fatigue activated in a person experiencing burnout. According to Maslach et al. (2001), burnout has been considered a disorder associated with a state of stress; it has been biologically theorized that both the autonomous nervous system (ANS) and the hypothalamus–pituitary–adrenal axis (HPA axis) are involved (Belcaro et al., 2018; Brianda et al., 2020; DeVente et al., 2003; Díaz-Rodríguez et al., 2011; Duchemin et al., 2015; Jahangard, 2019; Martinez-Borrás et al., 2022). Burnout compromises heart rate and blood pressure (overactivated), the immune system, and metabolism; consequently, burnout is accompanied by abnormal blood levels (lower) of adrenaline and cortisol, as well as their metabolites. This certainly justifies the fact that all the studies expected a reduction in stress biomarker measures.

This study provides evidence that there was a reduction in the levels of hair cortisol (Brianda et al., 2020), salivary cortisol (Díaz-Rodríguez et al., 2011; Jahangard et al., 2019), salivary alpha-amylase (Duchemin et al., 2015), salivary immunoglobulin A (sigA; Martinez-Borrás et al., 2022), and body temperature (Díaz-Rodrigues et al., 2011; Martinez-Borrás, 2022). These results suggest that health clinical professionals could improve their evaluation of burnout symptom severity and diagnostic assessment by incorporating biological measurements of patients, assisting in the identification of those at risk for mental health problems and allowing for the tracking of intervention effects. However, caution should be exercised in attributing these changes solely to time, as no interactions were observed in any measure.

However, measures of oxidative stress and salivary flow rate did not show significant differences after the interventions (Belcaro et al., 2018), suggesting that these biomarkers may not be sensitive indicators for investigating burnout symptoms or the effects of interventions. Of the six articles included in this review, four also assessed the effects of the interventions on behavioral measures utilizing the MBI (Brianda et al., 2020; Duchemin et al., 2015; Jahangard et al., 2019; Martínez-Borrás et al., 2022). While the MBI is recognized as the gold standard for measuring the levels of burnout dimensions, criticism has been raised by Schaufeli et al. (2020) regarding its outdated burnout definition and technical and practical issues. The MBI criticized concept links the definition of burnout and chronic stress, which are two different concepts that are sometimes wrongly considered the same in the literature. Despite identifying differences in biomarkers, none study observed differences in instrument scores, supporting the notion that the MBI may not be sensitive enough to gauge the severity of burnout symptoms. Therefore, it is recommended to employ more sensitive instruments in the assessment of burnout.

During the selection process of the articles, 49 articles were identified that utilized a stress assessment tool to measure burnout syndrome. For example, the study conducted by Niva et al. (2021) can be highlighted for adopting this approach. This theoretical conflict could also be an important reason for the limited number of articles found in this review. Danhof-Pont et al. (2011), in a systematic review, identified an incompatibility between studies due to differences in the methods used to diagnose and define burnout in patients. The literature review conducted for this article encountered the same limitation. Burnout is operationalized in different ways, and this issue also provided the authors with the argument for not finding specific biomarkers to burnout symptoms. It was not possible to verify if there are specific biomarkers exclusively for burnout and not related to stress.

In conclusion, it is important to note that, clinically and theoretically, burnout and stress refer to distinct constructs. Therefore, biological, and behavioral measures should be integrated into the assessment of clinician burnout symptoms, bearing in mind that none of them may be sufficient in isolation. Additionally, assessing patients' biomarkers can be used to identify risks for other mental disorders. Studies should differentiate burnout as a distinct construct from stress to achieve better behavioral and biological measurements, enhancing the understanding of the phenomenon and proposing effective interventions for the patients.

Studies demonstrating effectiveness in addressing emotional exhaustion, primarily through stress management approaches, highlight the need for innovative interventions targeting the other dimensions of burnout, such as depersonalization and personal accomplishment. This underscores the necessity of developing new strategies to comprehensively address all aspects of burnout. To obtain more accurate evidence about the effectiveness of burnout interventions using changes in biomarkers, there is still a need to address the methodological heterogeneity of burnout studies. A majority of studies focus on relaxation techniques for stress, yet the articles included in this study revealed that interventions did not significantly impact biomarkers. Overall, it can be concluded that we could not identify a relevant effect of the interventions on these biomarkers and burnout. We encountered two research papers with incomplete statistical estimates needed to compute the effect size.

Finally, this systematic literature review highlights practical applications and provides a foundation for future studies exploring the relationship between burnout interventions and biomarkers. One key takeaway is the need to develop more comprehensive interventions that address all dimensions of burnout, particularly beyond emotional exhaustion, such as depersonalization and personal accomplishment. While mindfulness-based interventions showed some promise in reducing burnout symptoms, other techniques like Reiki and stress-reduction

methods failed to show significant effects on biomarkers. This suggests a need for more targeted interventions that incorporate biological assessments alongside behavioral measures to better capture burnout's complexity. Additionally, the findings suggest that biomarkers such as cortisol and alpha-amylase are relevant for burnout assessment, though future studies should explore more sensitive instruments and interventions tailored to burnout-specific dimensions. New research should focus on addressing the methodological heterogeneity in burnout studies and refining intervention approaches to improve their effectiveness in both clinical and workplace settings.

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