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A transdiagnostic and diagnostic-specific approach on inflammatory biomarkers in eating disorders: A meta-analysis and systematic review

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ABSTRACT

Eating disorders (EDs) are severe mental illnesses with a multifactorial etiology and a chronic course. Among the biological factors related to pathogenesis and maintenance of EDs, inflammation acquired growing scientific interest. This study aimed to assess the inflammatory profile of EDs, focusing on anorexia nervosa, bulimia nervosa, and including for the first time binge eating disorder. A comprehensive research of existing literature identified 51 eligible studies for meta-analysis, comparing levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), osteoprotegerin (OPG), soluble receptor activator of nuclear factor kappa-B ligand (sRANKL), interleukin-1β (IL-1β), and interleukin-10 (IL-10) between patients with EDs and healthy controls (HCs). The systematic review explored other inflammatory biomarkers of interest, which did not meet the meta-analysis criteria. Results revealed significantly elevated levels of TNF-α, OPG, sRANKL, and IL-1β in patients with EDs compared to HCs. Additionally, the results highlighted the heterogeneity of inflammatory state among patients with EDs, emphasizing the need for further research into the association between inflammatory biomarkers and psychopathological correlates. This approach should transcend categorical diagnoses, enabling more precise subcategorizations of patients.

Overall, this study contributed to the understanding of the inflammatory pathways involved in EDs, emphasizing potential implications for diagnosis, staging, and targeted interventions.

1. Introduction

Eating Disorders (EDs) are severe mental illnesses characterized by a persistent and often chronic course (Solmi et al., 2024; Voderholzer et al., 2020), with a serious impact on physical and mental health, heightened risk of mortality, and a significant burden on healthcare services (American Psychiatric Association, 2022; Castellini et al., 2023a,b). As all main psychiatric conditions, EDs are characterized by multifactorial etiology, including both biological and environmental components (Bulik et al., 2022; Treasure et al., 2020). Within biological predisposing and maintaining factors for EDs, emerging evidence has been found regarding inflammatory mechanisms, particularly regarding Anorexia Nervosa (AN) and Bulimia Nervosa (BN) (Dalton et al., 2018; Solmi et al., 2015).

Inflammatory biomarkers are a broad category of proteins involved in cell signaling, secreted by the immune system, with a significant impact on the communication and coordination of the response to diseases and infections (Liu et al., 2021). A large body of literature highlighted the critical role of cytokines in inflammatory response, as well as their potential as targets for screening in autoimmune diseases (Sjøgren et al., 2022), cancer (DeCotiis et al., 2016) and more recently psychiatric diseases (Pinto et al., 2017). In fact, an elevation in inflammatory biomarkers has been observed in several psychiatric diseases, such as depression (Nikkheslat et al., 2020; Pitharouli et al., 2021), bipolar disorder (Solmi et al., 2021), and schizophrenia (Bigseth et al., 2023).

One recent meta-analysis confirmed the presence of significant heterogeneity in findings in patients with AN, while also highlighting higher levels of TNF-α and IL-6 in patients compared to healthy controls (HCs) (Dalton et al., 2018). Nonetheless, this recent meta-analysis focused only on AN, thus excluding other EDs such as BN and Binge Eating Disorder (BED). These limitations, coupled with the rapid evolution of the field in recent years, underscore the need for a broader perspective when considering the relevance of these results to the wider

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context of EDs.

In fact, the role of inflammatory processes in the pathophysiology and maintenance of EDs has also been described as potentially encompassing not only AN, but also BN, and BED (Butler et al., 2021; Caldas et al., 2022; Himmerich et al., 2021).

Physiological studies showed how low-grade inflammation might alter metabolic pathways, reducing the potential of the organism to reach effective homeostasis (De Baat et al., 2023; Gibson and Mehler, 2019). The alterations in homeostasis related to an heightened inflammatory profile has been described in both obese subjects, related to a reduced likelihood of weight loss (Popko et al., 2010), and patients diagnosed with AN (Caroleo et al., 2019). Moreover, inflammation and the Hypothalamic-Pituitary-Adrenal (HPA) axis have a close interplay, with each system modulating the other (Malek et al., 2015; Tian et al., 2014; Turnbull and Rivier, 1999). Signals from the gastrointestinal tract can influence brain functions, including food-seeking behaviors (Martinez De Morentin et al., 2024; Rossi and Stuber, 2018; Ursell et al., 2012). Immune-system related molecules may also have the potential to shape neurotransmission itself, both directly and acting as neuromodulators (De Simoni MG and Imeri, 1998; Nakazato et al., 2012). (Figure S1)

On the basis of these observations, several hypotheses proposed that inflammatory biomarkers play various roles in the context of EDs. They may act as predisposing factors for the disease (Ruiz Guerrero et al., 2022), be related to frequent psychiatric comorbidities (Osimo et al., 2020; Solmi et al., 2018), arise after pathological changes creating bidirectional and feedback mechanisms (such as in autoimmunity, appetite regulation, and stress modulation) (Malek et al., 2015; Sirufo et al., 2022; Smitka et al., 2021), and or result from alterations in homeostasis due to the disease (Butler et al., 2021). As current data do not allow us to infer the underlying mechanisms driving this complex interplay between ED symptoms and inflammatory biomarkers, it remains crucial to identify the specific molecules involved.

For these reasons, the inflammatory state in patients with EDs may be considered as a potential molecular target with diagnostic or therapeutic potential. Assuming a clinical stage perspective (McGorry et al., 2006), it definitely could be regarded as a factor to be assessed in order to enhance the likelihood of achieving long-term recovery by enabling earlier and targeted clinical interventions.

1.1. Aims

The primary aim of the present meta-analysis was to investigate the association between specific inflammatory biomarkers and EDs, exploring the potential divergences in the observed alteration in comparison to healthy controls (HCs) between specific diagnoses across EDs, namely: AN, BN e BED. The secondary aim was to assess the role of moderating factors on the inflammatory state of patients with EDs, specifically sex, disease onset, disease duration, pharmacotherapy, and smoke.

2. Methods

2.1. Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), as shown in Figure S2. Original studies were searched until June 2024 through PubMed, Embase and Scopus. In addition, a cross-reference search with identified studies was performed. These keywords were used to perform a systematic review of literature:

("eating disorder" OR "eating disorders" OR "anorexia nervosa" OR bulimia OR "binge eating" OR "disordered eating" OR "feeding disorder") AND (flogosis OR "inflammatory marker" OR inflammation OR inflam OR neuroinflamma* OR adipokine OR interleukin OR cytokine OR tnf OR "tumor necrosis alpha" OR tgf OR "tumor growth factor" OR "reactive protein" OR crp OR il6 OR il-6 OR s100b OR glia* OR microglia* OR noci*) NOT mice NOT rat NOT review[pt] NOT systematic review[pt] NOT meta analysis[pt].*

The study protocol was pre-registered and can be accessed via the following link: https://doi.org/10.17605/OSF.IO/ZS83U.

2.2. Study selection and data collection process

Five authors (CD, LT, GPM, AF, VZC) supervised both the search method and the choice of operators as well as the selected articles. In the screening phase, the title and abstract were also reviewed to make a first selection of the studies that fit the criteria. In the eligibility phase, the title and abstract of the screened studies were reviewed, validating the use of standardized instruments with correct psychometric properties. In the inclusion phase, the full text was reviewed to confirm their admission to the textual data synthesis phase, ensuring an exhaustive compliance with the inclusion and exclusion criteria. After identifying the included articles, data extraction was performed, annotating the following outcomes: authors list, number of participants per study, main results (in a narrative synthesis), mean and standard deviation of each inflammatory biomarker for patients' and controls' groups, sample type, assay type. Data extraction was performed by five independent authors (CD, LT, GPM, AF, VZC).

2.3. Selection criteria

English-language case-control studies reporting levels of inflammation biomarkers in patients with EDs were included if they met the following criteria: (1) studies comprising comparisons between patients with EDs (AN, BN, BED) and HCs, or patients with EDs with each other (e.g. AN vs BN) (2) patients were diagnosed with EDs (AN, BN, BED) according to any version of the Diagnostic and Statistical Manual of Mental Disorder; (3) inflammation biomarkers falling into the following categories: not-stimulated blood (e.g., serum and plasma) and cerebrospinal fluid (CSF) based. Review papers, meta-analyses, case reports, study protocols, and commentaries were excluded.

For inflammatory biomarkers with $\geq$8 studies reporting sufficient information to derive the effect size and standard error, a meta-analysis was conducted on inflammatory biomarkers comparing EDs (i.e. AN, BN, BED, EDs) with HCs. The chosen measure for the effect size adopted for the present study was the Standardized Mean Difference (SMD). A systematic review on the biomarkers which did not exceed on a numeric basis the cut-off threshold established as per $\geq$8 articles, but were found in $a \geq 3$ number of articles during the screening process was performed.

2.4. Meta-Analysis and systematic review

The random effects model (Balduzzi et al., 2023) was chosen as a method of choice to address the diversity across the studies due to the heterogeneity in terms of study design and methodology of the included articles. The standardized mean difference (SMD) along with its corresponding 95 % confidence interval (CI) was utilized. The presence of study heterogeneity was assessed using the chi-squared and I-squared statistics. Specifically, a chi-squared p-value less than 0.05 and an I-squared value $\geq$50 % were considered as indicators of significant heterogeneity. Publication bias across the studies was explored with the Pustejovsky method (Pustejovsky and Rodgers, 2019).

Subgroup analyses on different diagnostic categories of EDs were conducted, in order to assess the diversity across different categories of patients (AN, BN, BED, EDs). Subgroup analyses were performed for TNF-α, IL-1β, IL-10, CRP and IL-6, being the only inflammatory biomarkers analyzed among more than one diagnostic category among EDs. A random network meta-analysis, with the residual (restricted) maximum likelihood (REML) algorithm to estimate tau2, combined direct and indirect evidence of bias-corrected effect sizes (SMD) from multiple groups studies.

Additionally, multivariate meta-regression analysis was performed

to determine the moderating role of age and BMI on the levels of TNF-α, IL-1β, IL-10, CRP and IL-6. No other factors could be taken into account for meta-regression, due either to the homogeneity of the samples (i.e. sex) or to the overall insufficiency of data (i.e. disease onset, disease duration, pharmacotherapy, smoke) in the retrieved articles.

Moreover, a systematic review of inflammatory biomarkers of interest was conducted based on the existing literature. Non-stimulated biomarkers which did not exceed on a numeric basis the cut-off threshold established as per ≥8 articles, but were found in $a \geq 3$ number of articles during the screening process, were included for the systematic review in order to provide a more comprehensive perspective on the topic. Differently from meta-analysis inclusion criteria, articles which did not report calculated mean and standard deviations were assessed.

The figures palettes were optimized for color blindness according to Wong (2011).

The statistical analysis was performed with R 4.3.2 (*RStudio Team. RStudio: Integrated Development for R.*, 2020), with the support of the following libraries: meta (Schwarzer et al., 2015), metafor (Viechtbauer, 2010), netmeta (Balduzzi et al., 2023), tidyverse (Wickham et al., 2019), ggplot2 (Wickham, 2016).

2.5. Risk of bias

Four authors (CD, LT, GP, AF) independently assessed the risk of bias for individual studies using the JBI critical appraisal checklist for included studies (Munn et al., 2019). In case the opinion was not unanimous, a majority vote would have been taken between all authors. These four authors agreed on all the eligibility assessments of the studies, and no consensus vote needed to take place. A figure representing the detailed assessment of the risk of bias for each article included in the review was given in the Supplementary Materials (Figure S3).

3. Results

3.1. Search strategy

The initial literature search generated 4428 papers. After eliminating duplicate abstracts, a total of 2152 article abstracts were screened. 109 full texts were assessed for eligibility. As reported in Fig. 1, data on more than one inflammatory mediator were reported in most of the 109 studies, yielding 137 data points. Ultimately, 51 studies were eligible for the meta-analysis, comparing levels of TNF-α, CRP, OPG, sRANKL, IL-6, IL-1, IL-1β (Agnello et al., 2012; Ahrén-Moonga et al., 2011; Allende et al., 1998; Amerio et al., 2023; Brambilla, 1998; Brambilla et al., 2001; Caldas et al., 2022; Caroleo et al., 2019; Caso et al., 2020; Corcos et al., 2001; Dolezalova et al., 2007; Gabriel et al., 2023; Gołąbek et al., 2015, 2015; Haluzíková et al., 2009; Himmerich et al., 2021; Kahl et al., 2005; Keeler et al., 2021, 2024; Křížová et al., 2002, 2008; Limone et al., 2000; Mikolajczak et al., 2017; Misra et al., 2006; Mörkl et al., 2017; Muñoz-Calvo et al., 2007; Nagata et al., 1999, 2006; Nakai et al., 1999; Nilsson et al., 2020; Nogueira et al., 2010; Ohwada et al., 2007; Ostrowska et al., 2016a, 2012a, 2012b, 2016b, 2013, 2014, 2015, 2022; Pomeroy et al., 1994; Prochazkova et al., 2021; Raymond et al., 2000; Roczniak et al., 2020; Roubalova et al., 2021; Ruiz Guerrero et al., 2022; Shimizu et al., 2005; Tabasi et al., 2020; Tomášová et al., 2022; Tyszkiewicz-Nwafor et al., 2022; Vaisman et al., 1996; Víctor et al., 2015).

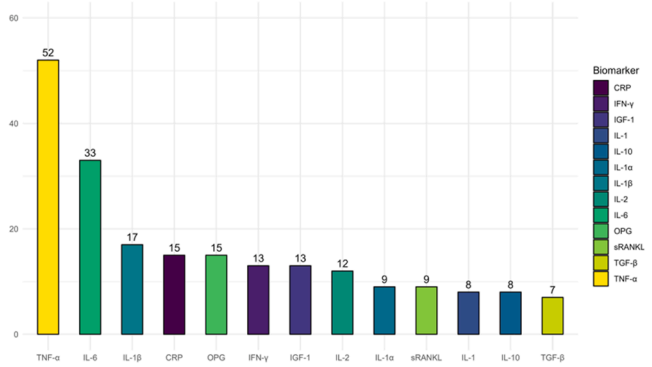

Fig. 1. Bar graph showing the data points retrieved after assessing the eligibility of the 109 full texts article.
Legend. TNF-α = tumor necrosis factor-α; IL-6 = interleukin-6; IL-1β = interleukin-1β; CRP = *c*-reactive protein; OPG = osteoprotegerin; IFN-γ = interferon-γ; IGF-1 = insulin like growth factor-1; IL-2 = interleukin-2; IL-1α: interleukin-1α; sRANKL: soluble receptor activator of nuclear factor kappa-B ligand; IL-1 = interleukin-1; IL-10 = interleukin-10; TGF-β = transforming growth factor-β.

3.2. Mean difference and subgroup analysis

The results of the comparative meta-analysis for the selected inflammatory biomarkers showed that the overall concentrations of TNF-α (SMD 0.64, 95 % CI 0.11–1.17, $p = 0.019$) (Fig. 2), OPG (SMD 1.92, 95 % CI 0.96–2.88, $p < 0.001$) (Fig. 3), sRANKL (SMD 1.67, 95 % CI 0.32–3.02, $p = 0.015$) (Fig. 4) and IL-1β (SMD 0.63, 95 % CI 0.02–1.24, $p = 0.042$) (Fig. 5) were significantly higher in patients with EDs compared to HCs, whereas no difference was found for CRP (SMD −0.20, 95 % CI −0.91–0.50, $p = 0.572$) (Figure S4), IL-6 (SMD 0.36, 95 % CI −0.07–0.80, $p = 0.098$) (Figure S5) and IL-10 (SMD 0.05, 95 % CI 0.91–1.01, $p = 0.921$) (Figure S6).

No publication bias across studies were found through Pustejovsky method for TNF-α ($p = 0.919$), CRP ($p = 0.720$), IL-1β ($p = 0.334$), IL-6 ($p = 0.380$), IL-10 ($p = 0.720$), OPG ($p = 0.380$), sRANKL ($p = 0.063$), as further shown in Table S1.

Additionally, subgroup analysis was performed for TNF-α, IL-1β, IL-10, CRP and IL-6 based on the diagnostic category of individuals with EDs. Significant heterogeneity on biomarkers levels across the different diagnostic categories were found for TNF-α ($p = 0.043$), IL-6 ($p = 0.010$) and IL-10 ($p < 0.001$), whereas no significant results were found for CRP ($p = 0.458$), IL-1β ($p = 0.091$). Subgroup analysis was not performed for OPG and sRANKL as all the studies included only patients diagnosed with AN.

3.3. Multivariate meta-regression analysis

The multivariate meta-regression analysis results revealed that age had a significant positive moderating effect on OPG levels ($b = 0.27$, $p = 0.001$) and sRANKL levels ($\beta = 9.91$, $p < 0.001$). In contrast, age did not significantly moderate the levels of TNF-α ($\beta = 0.01$, $p < 0.891$), IL-1β ($\beta = -0.10$, $p = 0.132$), IL-10 ($\beta = 0.29$, $p = 0.164$), CRP ($\beta = -0.07$, $p = 0.386$), and IL-6 ($\beta = -0.01$, $p = 0.807$). Additionally, BMI showed significant moderation effects on TNF-α ($\beta = 0.16$, $p = 0.001$), OPG ($\beta = -0.98$, $p < 0.001$), and sRANKL ($\beta = -3.70$, $p < 0.001$) levels. No significant moderation was observed between BMI and IL-1β ($\beta = -0.06$, $p = 0.577$), IL-10 ($\beta = -0.49$, $p = 0.060$), CRP ($\beta = 0.05$, $p = 0.577$), and IL-6 ($\beta = -0.01$, $p = 0.807$) levels (Table 1).

3.4. Network meta-analysis

A NMA was conducted on TNF-α, and included 28 studies. Patients with EDs showed higher TNF-α levels than HCs. Regarding different diagnostic categories, patients with BN showed higher TNF-α levels if compared to patients with AN, BED and EDs. It is noteworthy, however, that while a trend was observed, no findings achieved statistical significance - potentially due to the limited number of retrieved pairwise comparisons. Results are shown in Fig. 6.

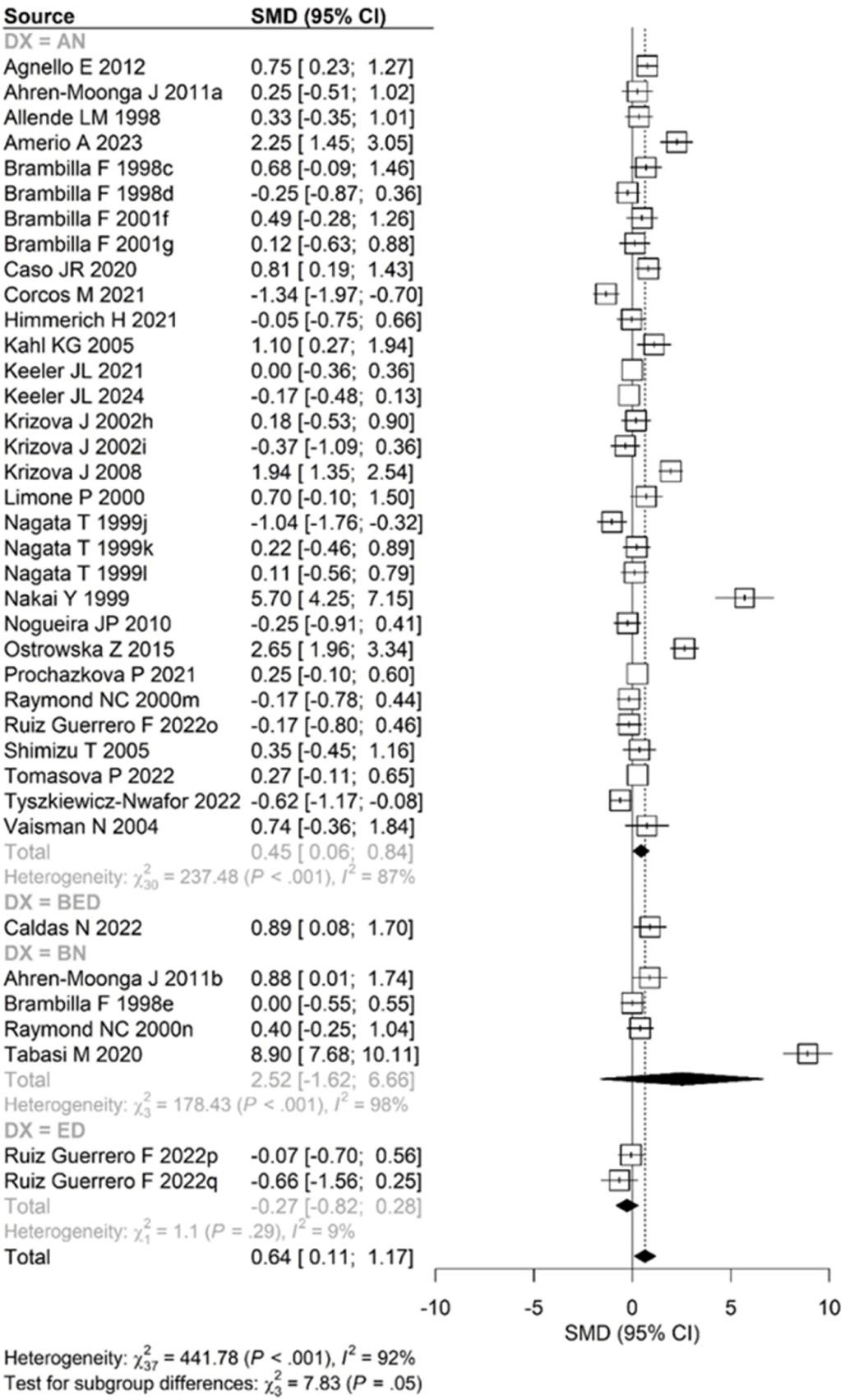

Fig. 2. Forest plot of SMD in TNF-α between patients with EDs and HCs. Abbreviations: SMD = standardized mean difference; CI = confidence intervals; DX = diagnostic category; AN: anorexia nervosa; BED: binge eating disorder; BN: bulimia nervosa; ED: eating disorders.
Legend. a: AN; b: BN; c: AN-r; d: AN-bp; e: BN; f: AN-r, g: AN-bp; h: AN; i: AN partial refeeding; j: AN <65 % standard body weight (SBW); k: AN >65 % SBW; l: AN >75 % SBW; m: AN; n: BN; o: female with AN; p: female with other EDs; q: male with EDs.

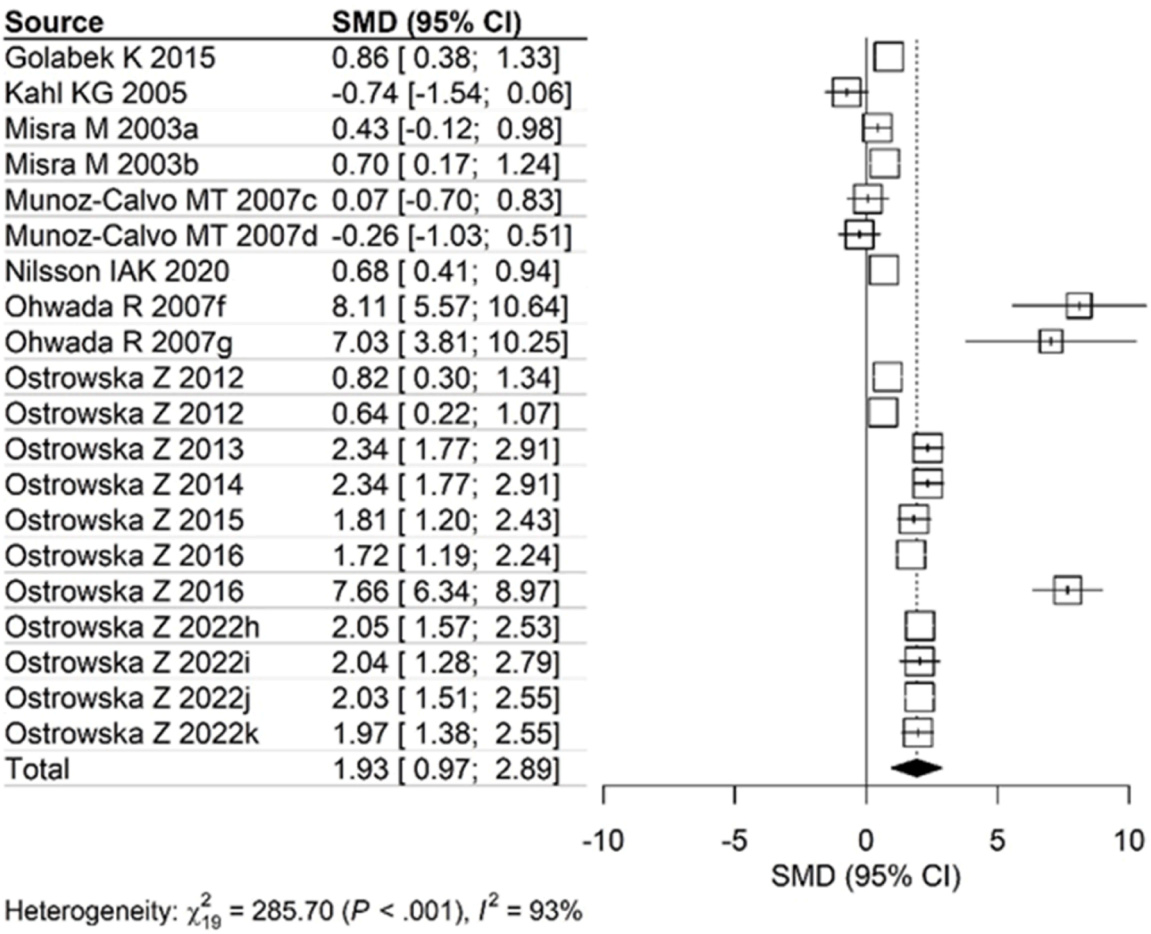

Fig. 3. Forest plot of SMD in OPG between patients with AN and HCs. Abbreviations: SMD = standardized mean difference; CI = confidence intervals. Legend. a: AN with lumbar z-score > −1; b: AN with lumbar z-score ≤ −1; c: AN amenorrhea > 1y; d: AN amenorrhea ⟨ 1y; e: AN; f: AN-r; g: AN-bp; h: AN with lumbar z-score ⟩ −2; i: AN with lumbar z-score ≤ −2; j: AN with total body z-score > −2; k: AN with total body z-score ≤ −2.

3.5. Systematic review of inflammatory biomarkers of interest

A systematic review of inflammatory biomarkers of interest (less than 8, but more than 3 retrieved articles, see Methods Section 2.3) was conducted based on the existing literature. The following biomarkers were selected as per the aforementioned criteria: IL-1 (Bessler et al., 1993; Corcos et al., 2001; Tyszkiewicz-Nwafor et al., 2022; Vaisman et al., 1996), IL-1α (Caroleo et al., 2019; Himmerich et al., 2021; Raymond et al., 2000), IL-2 (Caroleo et al., 2019; Corcos et al., 2001; Himmerich et al., 2021; Keeler et al., 2021; Pászthy et al., 2007; Tabasi et al., 2020), IL-4 (Caroleo et al., 2019; Corcos et al., 2001), IL-15 (Himmerich et al., 2021; Käver et al., 2024; Keeler et al., 2021; Roczniak et al., 2020), IL-17 (Prochazkova et al., 2021; Roubalova et al., 2021; Tomášová et al., 2022), IFN-γ (Caroleo et al., 2019; Corcos et al., 2001; Gabriel et al., 2023; Himmerich et al., 2021; Keeler et al., 2021; Nagata et al., 1999), TGF-β (Amerio et al., 2023; Corcos et al., 2001; Ostrowska et al., 2016a, 2016b; Pomeroy et al., 1994), GFAP (Doose et al., 2022; Ehrlich et al., 2008; Hellerhoff et al., 2021, 2023), NPY (Baranowska et al., 2001, 2003; Turan et al., 2021), BDNF (Eddy et al., 2015; Homan et al., 2015; Nakazato et al., 2012; Tyszkiewicz-Nwafor et al., 2022), αMSH (Grigioni et al., 2022; Moriya et al., 2006; Roubalova et al., 2021), TAU Protein (Doose et al., 2022; Hellerhoff et al., 2021, 2023), NF-L (Doose et al., 2022; Hellerhoff et al., 2021, 2023). Results in percentages are shown in Fig. 4.

The analyzed articles predominantly focused on patients affected by AN, revealing significantly higher levels of TGF-β, IL-15, GFAP, NF-L, TAU Protein, and lower levels of BDNF compared with HCs. No significant difference was found in articles regarding IL-2, IL-1, IL-1α, IL-4, IL-17, IFN-γ, NPY and α-MSH. With regards to patients with BN, they showed higher significant levels in NPY and comparable levels in percentage in BDNF levels. No significant difference was found in IL-1α, IL-2, IL-4 and TGF-β. Only 4 studies were conducted comparing biomarkers levels of patients with BED to levels of HCs: IFN-γ and NPY levels were higher in patients with BED than HCs, whereas IL-1α levels were significantly lower compared with HCs group. No significant differences were found on IL-2 and IL-4. See Fig. 7 for further details.

4. Discussion

In the authors' knowledge, this is the first meta-analysis about inflammatory biomarkers in patients with EDs that adopts a transdiagnostic approach, encompassing patients with AN, BN and BED. Considering the overall category of EDs, TNF-α, IL-1β, OPG and sRANKL were significantly higher in comparison to HCs. Conversely, no significant difference was found for CRP, IL-6 and IL-10.

In addition, the subgroup analysis performed across diagnostic categories of EDs (AN, BN, BED) supported the heterogeneity on biomarkers levels between singular entities among EDs. In particular, TNF-α, IL-6, and IL-10 showed evidence of higher levels in patients with EDs if compared with HCs. Finally, a systematic review provided valuable insights into the inflammatory state among EDs diagnostic categories. However, even if many inflammatory biomarkers exhibited consistent evidence across studies, IL-1, IL-1α, IL-2, IL-4 and α-MSH showed preliminary evidence of heterogeneity across studies. Further studies might

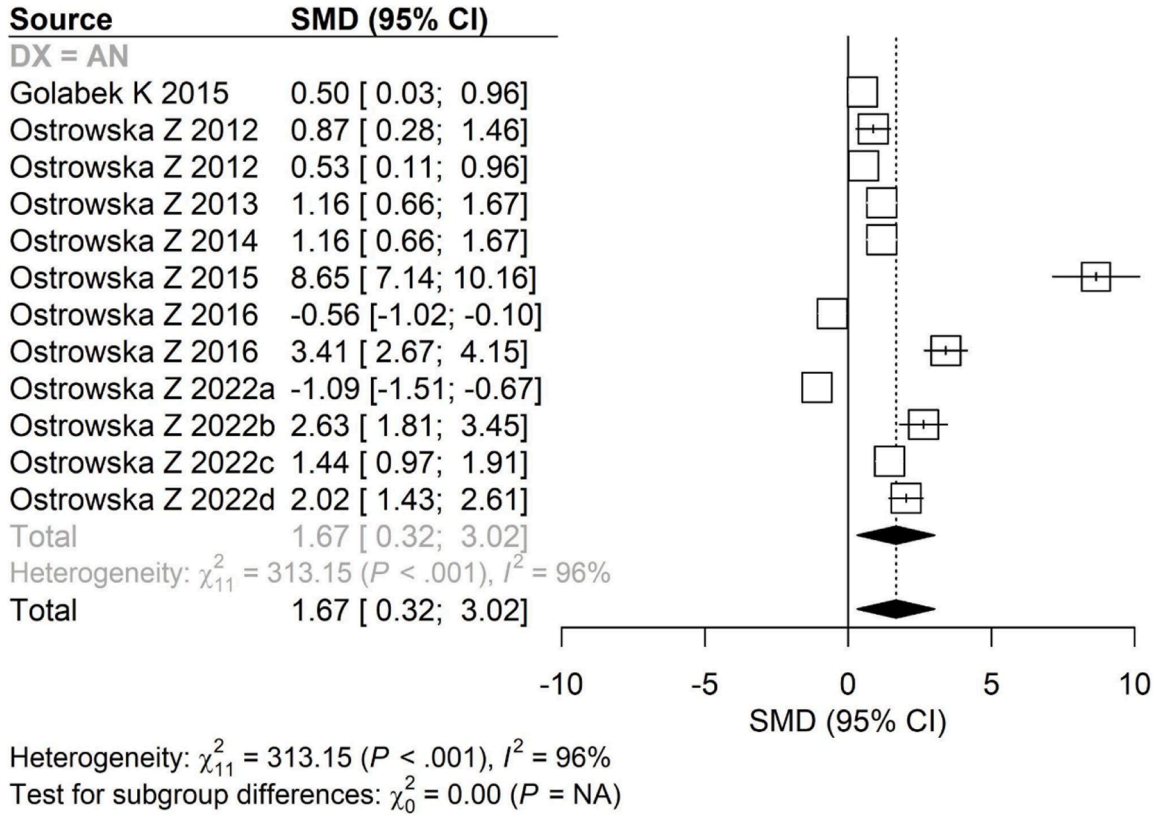

Fig. 4. Forest plot of SMD in sRANKL between patients with AN and HCs. Abbreviations: SMD = standardized mean difference; CI = confidence intervals. Legend. a: AN with lumbar z-score > −2; b: AN with lumbar z-score ≤ −2; c: AN with total body z-score > −2; d: AN with total body z-score ≤ −2.

therefore be needed in order to better inform current clinical practice and future research applications.

4.1. Meta-analytical results

Current results on TNF-α levels in EDs replicate those identified in patients with AN in previous meta-analyses (Dalton et al., 2018; Solmi et al., 2015). On the contrary, the lack of significant difference in IL-6 levels observed among individuals with EDs compared to HCs contrasted with the findings reported by the same authors, possibly for the wider inclusion of patients with BN and BED (Dalton et al., 2018). Notably, the current study also identified a significant increase in IL-1β levels in patients with EDs compared to HCs, also contrasting with previous evidence collected in AN only (Solmi et al., 2015). These discrepancies could be attributed to the greater number of included studies, the inclusion of more recent studies, and the consequent increased heterogeneity of the sample populations.

Moreover, OPG and sRANKL, whose concentrations were not previously meta-analyzed among patients with EDs, exhibited higher levels in patients with AN than HCs. The increased levels of these two bone metabolism biomarkers (Boyce and Xing, 2008; Fazeli, 2019) could explain the peculiar characteristics of bone metabolism in AN, which is characterized by a decrease in levels of both bone formation and increased bone turnover (Fazeli and Klibanski, 2018).

The meta-regression analysis using age and BMI as moderators, if compared with the past meta-analysis (Dalton et al., 2018; Solmi et al., 2015), confirmed the role of IL-1β and uncovered an association between TNF-α and BMI. IL-6 was not found associated with age, aligning with Solmi et al. (Solmi et al., 2015) but in contrast with Dalton et al. (Dalton et al., 2018). These discrepancies might be due to the larger number of studies included in the current analysis, comprising different diagnostic categories. In addition, this kind of analysis was performed for the first time on OPG and sRANKL, revealing for both biomarkers a positive association with age and a negative association with BMI, in support to the severe alterations on bone metabolism in patients with AN (Ostrowska et al., 2016a, 2022; Rogers and Eastell, 2005). Furthermore, IL-10, CRP, and IL-6 did not show any association with age or BMI.

4.2. Systematic review

Most of the studies retrieved for the narrative review of existent literature found significantly higher levels of IFN-γ, TNF-α, GFAP, NF-L, and Tau protein in patients with AN compared to HCs. Conversely, BDNF concentrations were consistently found to be lower in patients with AN than HCs in most of the studies. IL-1, IL-1α, IL-2, IL-4, α-MSH concentrations were not found as significantly different in most existing articles regarding all diagnostic categories among EDs. However, no sufficient comparisons were found to reliably estimate the direction of effect possible for IL-15, IL-17 and NPY.

4.2.1. General inflammatory biomarkers

Higher NPY in both patients with BN and BED (compared to HCs) suggested that this peptide may be associated with a clinically relevant dysregulation in appetite stimuli processing and energy homeostasis, previously described as altered in both disorders (Wen et al., 2019). Patients affected by BN showed no alterations of TNF-α compared with HCs. This finding suggests the need for further investigation into specific aspects of TNF-α biology in patients with BN. IL-1α, IL-2, IL-4 levels were found not to be significantly different between patients with EDs and HCs. Regarding patients diagnosed with BED, only a few studies on inflammatory biomarkers were retrieved. Insufficient evidence precludes definitive conclusions regarding IL-2 and IL-4 levels, which did not differ compared with HCs in the only two studies conducted.

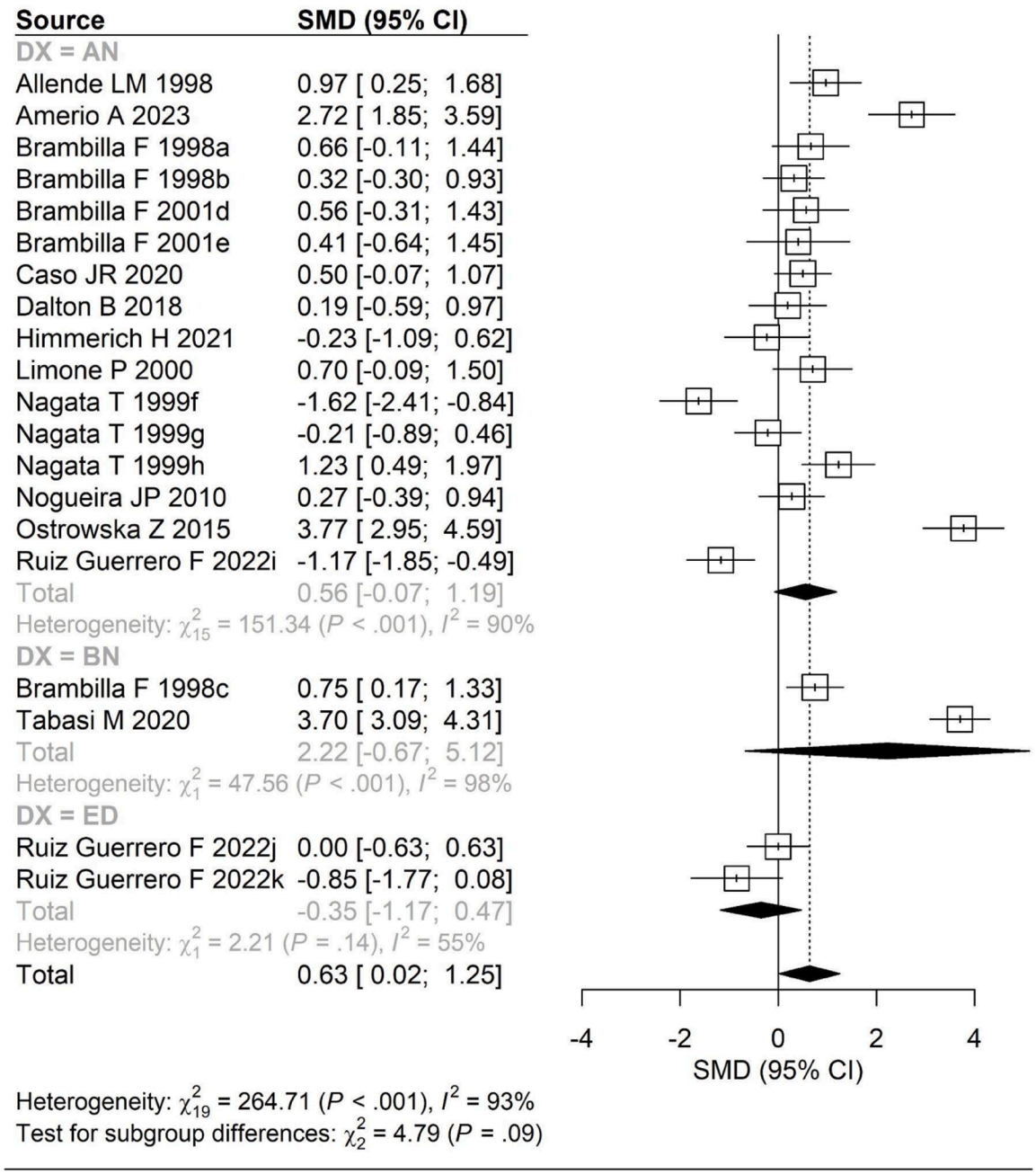

Fig. 5. Forest plot of SMD in IL-1β between patients with EDs and HCs. Abbreviations: SMD = standardized mean difference; CI = confidence intervals; DX = diagnostic category; AN: anorexia nervosa; BN: bulimia nervosa; ED: eating disorders.
Legend. a: AN-r; b: AN-bp; c: BN; d: AN-r, e: AN-bp; f: AN; g: AN partial refeeding; h: female with AN; i: female with other EDs; j: male with EDs.

Table 1
Meta-regression analysis of moderating effects of age and BMI on selected biomarker levels. b coefficients along their p- values are shown.
Legend: BMI: body mass index; TNF-α = tumor necrosis factor-α; OPG = osteoprotegerin; sRANKL: soluble receptor activator of nuclear factor kappa-B ligand; IL-1β = interleukin-1β; IL-10 = interleukin-10; CRP = *c*-reactive protein; IL-6 = interleukin-6.

Moderator	TNF-α	OPG	sRANKL	IL-1β	IL-10	CRP	IL-6
Age	0.01	0.27**	9.91***	−0.10	0.29	−0.07	0.00
BMI	0.16**	−0.98***	−3.70***	−0.06	−0.49	0.05	−0.01

4.2.2. Neuroinflammatory biomarkers

The overall reduction in BDNF levels in AN may suggest that compromised immune function due to eating restraint may negatively impact neurotrophic support (Brandys et al., 2011; 2013). No sufficient studies regarding BDNF levels between patients with BN were found. Future studies on circulating levels of BDNF in patients with BN may therefore be warranted.

Increased levels of GFAP were observed in AN compared to HCs. This result may suggest an alteration in neuroinflammatory processes in AN due to a heightened astroglial activation (Ehrlich et al., 2008). Indeed,

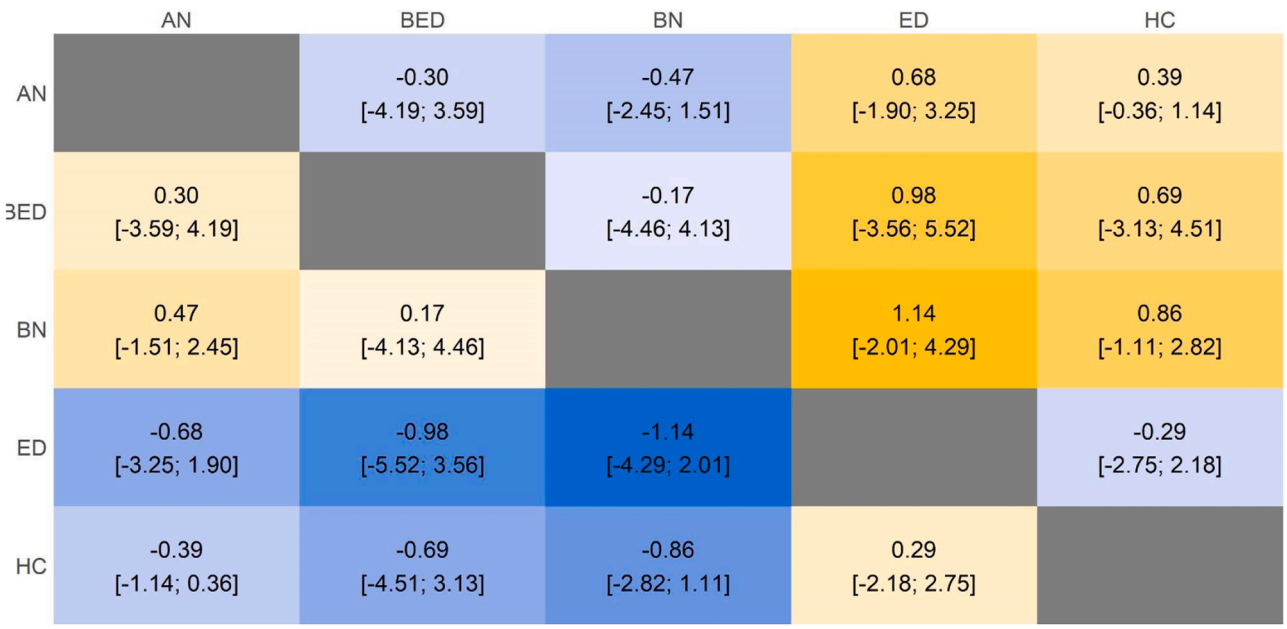

Fig. 6. Net Heat Plot of SMD with Standard Errors and 95 % CI in TNF-α levels between ED participants and HCs, from $n = 28$ studies.
Legend. AN = anorexia nervosa, BN = bulimia nervosa, BED = binge eating disorder, ED = eating disorders, HC =healthy controls.

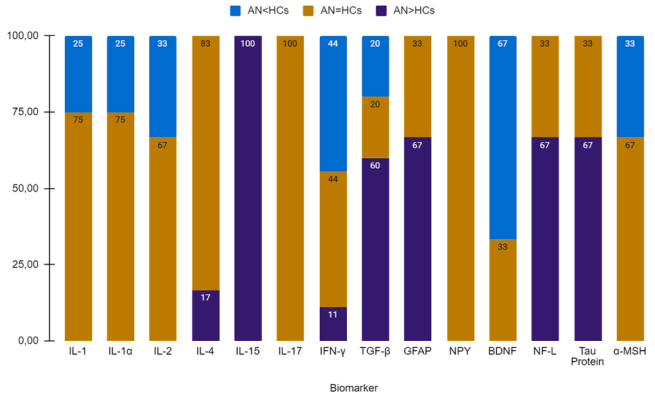

Fig. 7. Agreement within the literature on inflammatory biomarkers in participants with AN compared to HCs in $n = 58$ studies. Results in percentages are shown.
Legend. AN = anorexia nervosa, HCs = healthy controls. IL-1 = interleukin-1; IL-1α = interleukin-1α; IL-2 = interleukin-2; IL-4 = interleukin-4; IL-15 = interleukin-15; IL-17 = interleukin-17; IFN-γ = interferon-γ; TGF-β = transforming growth factor-β; GFAP =glial fibrillary acidic protein; NPY = neuropeptide Y; BDNF = brain-derived neurotrophic factor; NF-*L* = neurofilament light polypeptide; α-MSH =alpha-melanocyte stimulating hormone.

the aforementioned higher levels of NF-L and Tau protein in patients with AN supported the hypothesis of higher risk of axonal damage in AN, which is a primary activator of cellular repair processes mediated by the astroglia. In fact, recent studies described how NF-L might be positively correlated with cortical thickness alterations in AN, further reinforcing the notion that axonal damages underlie most of the neuroinflammatory processes observed in AN (Doose et al., 2022; Hellerhoff et al., 2021). Moreover, increasing concentrations of BDNF might be associated with longitudinal restorations of hippocampal volumes, further suggesting a role for neuroinflammatory regulation as shaping cortical plasticity in AN (Hellerhoff et al., 2023). In summary, general inflammation does not seem to be associated with reduced cortical thickness in AN, whereas specific neurotrophic factors might be implicated in cortical thickness restoration after weight-recovery (Bernardoni et al., 2024).

4.3. Interaction between inflammatory biomarkers, HPA and clinical correlates

The current systematic review offered evidence of inflammatory processes in individuals with EDs, as evidenced by altered cytokine profiles, increased activity by immune cells, and a heightened stress response mediated by circulating endocrine modulators. As a reaction to stress, cytokines normally act in modulating the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis by influencing the release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), ultimately impacting cortisol production (Knezevic et al., 2023).

Regarding HPA activation, patients with AN often showed an elevated cortisol awakening response (CAR), particularly those with binge-purging subtype as opposed to restrictive subtype (Monteleone et al., 2017). Conversely, this phenomenon was not observed in patients with BN, and the heightened CAR tended to normalize in AN patients after weight-restoration, reinforcing its association with malnutrition (Monteleone et al., 2016). Interestingly, patients with AN and BN with a history of childhood maltreatment (CM) showed particular alterations in HPA axis (Rossi et al., 2024), indicative of deficiencies in HPA axis functioning, compared to those with AN and BN who had not been exposed to CM (Monteleone et al., 2015). The alteration in the stress response of patients with AN was also demonstrated through Trier Social Stress Test (TSST), as a higher cortisol production was observed regardless of the presence of CM (Monteleone et al., 2021).

Elevated stress at the same time was demonstrated to have a crucial contribution for the altered cytokine profile observed in EDs, creating a feedback that may exacerbate the underlying pathology (Dalton et al., 2018; Solmi et al., 2015). In addition, chronic low-grade inflammation was associated with disruptions in appetite regulation and the modulation of satiety signals, potentially contributing to the maintenance of pathological eating behaviors (Butler et al., 2021).

Patients with AN also exhibited elevated IgM autoantibodies against α-MSH, while patients with AN and BN were demonstrated to show altered IgG autoantibody levels, forming immune complexes that chronically activate the melanocortin system, potentially triggering the disease onset (Acres et al., 2012; Fetissov and Hökfelt, 2019). In addition, an elevation in NPY levels was proven to exhibit a protective role in

AN and BN through preventing the exhaustion of energy reserves (Smitka et al., 2021). Increased levels of TNF-α and IL-6, but more specifically in levels of cytokines directly implied in appetite regulation and orexigenic response such as α-MSH and NPY, might contribute to alterations in physiological homeostasis and promote the maintenance of the EDs (Butler et al., 2021; Smitka et al., 2021). At the same time, the elevation of anti-inflammatory cytokines - such as IL-10 - could be interpreted as an attempt to reach homeostasis, restraining inflammation through the downregulation of pro-inflammatory cytokines through negative feedback signaling (De Waal Malefyt et al., 1991).

The concomitant alteration in activation of the HPA axis and inflammatory state of patients with EDs might appear in contradiction to the anti-inflammatory effects of glucocorticoids (Cohen et al., 2012). This phenomenon could potentially be attributed to stress-induced glucocorticoid resistance (Gordon et al., 2000), as already demonstrated for depression (Horowitz et al., 2020) and brain cancer (Miller et al., 2008). On the other hand, glucocorticoids could act as potential enhancers of inflammatory processes under stressogenic circumstances, in addition to the recognized inhibitory effects (De Pablos et al., 2014; Espinosa-Oliva et al., 2011).

The limited evidence available on many inflammatory biomarkers - such as IL-1α, IL-2 and IL-4 - underscores the need for further comprehensive studies to draw definitive conclusions about the inflammatory response across EDs. In fact, additional studies in this field could potentially lead to the timely development of clinical staging models for EDs (McGorry et al., 2006), currently lacking, and urgently needed due to the limited availability of treatment, in particular for AN (Bulik et al., 2021), even in a perspective of personalized interventions depending on the stage of the illness and according to the patient's inflammatory profile.

4.4. Strength and limitations

The primary strength of this article is the analysis of the largest and most updated sample of studies currently present in literature regarding inflammatory biomarkers in EDs. Moreover, this research expanded the previous meta-analyses with the inclusion of studies conducted on patients with AN, BN, BED.

No longitudinal data were assessed, thus reducing the possibility to derive evidence on recovery trajectories and the potential impact of inflammatory biomarkers as moderating treatment response. Future studies might focus on longitudinal data, especially in the perspective of personalized medicine. Furthermore, the present meta-analysis noted significant heterogeneity among the included studies. The different methodologies, populations of study, and variables across the analyzed studies may introduce variability that could impact the robustness of our findings, thus reducing its potential for wider generalizability.

5. Conclusions

The current meta-analysis provided a comprehensive examination of inflammatory biomarkers in patients diagnosed with AN, BN and BED. The observed elevation in levels of several inflammatory biomarkers in comparison with HCs, proposed to confirm the crucial impact of inflammatory processes in the pathophysiology of EDs. Moreover, the findings of this meta-analysis supported the integration of a clinical staging model for EDs. The understanding of the comprehensive role of inflammatory biomarkers in EDs has indeed significant clinical implications, as it may contribute to the development of novel diagnostic biomarkers, help identify subgroups of patients who are more susceptible to inflammatory processes, and provide insights into potential targets for therapeutic interventions from a clinical staging perspective (McGorry et al., 2006). Moreover, a better understanding of the inflammatory pathways involved in EDs may inform future personalized treatments and improve patient outcomes.

CRediT authorship contribution statement

Cristiano Dani: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Livio Tarchi:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Emanuele Cassioli:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Eleonora Rossi:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Giuseppe Pierpaolo Merola:** Writing – review & editing, Data curation. **Arianna Ficola:** Writing – review & editing, Data curation. **Valentina Zofia Cordasco:** Writing – review & editing, Data curation. **Valdo Ricca:** Writing – review & editing, Visualization, Validation. **Giovanni Castellini:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The code and data supporting the current study can be shared upon reasonable request to the corresponding author, upon agreement with the other authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116115.

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