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Sex differences in the association between peripheral inflammation and melancholia symptoms

Christopher F. Sharpley [a,*], Vicki Bitsika [a], Wayne M. Arnold [a], Ian D. Evans [a], Emmanuel Jesulola [a,b], Linda L. Agnew [a,c]

[a] Brain-Behaviour Research Group, University of New England, Armidale, New South Wales, 2350, Australia
[b] Department of Neurosurgery, The Alfred Hospital, Melbourne, Australia
[c] Griffith University, Qld, Australia

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ABSTRACT

Melancholia represents a particular subtype of depressive symptomatology. Unlike Major Depressive Disorder (MDD), Melancholia has not been conclusively associated with peripheral inflammation, although there may be some methodological reasons confounding that finding. To overcome some of those methodological limitations, the correlation between one index of peripheral inflammation (C-Reactive Protein: CRP) and Melancholia was investigated in a community sample of 40 male and 51 female participants (aged 18–75 years) who provided a blood sample and self-report data on an established measure of Melancholia (MEL). Results indicated that females had significantly higher concentrations of CRP than males, and that there were different patterns of association between the MEL items and CRP for males and females. Although the predominant differences were for the MEL symptoms of cognitive confusion (females only) and feelings of low self-worth (males only), each sex had distinct networks of associations between CRP and the eight MEL items used here. These findings may provide some explanation of the lack of clear results regarding the CRP-Melancholia link in the previous literature, and also argue for development of clinical assessment and treatment approaches that differ for males and females.

1. Introduction

1.1. Depression

Depression represents a major disease burden and source of personal distress (WHO, 2017), for which first-line treatments are only moderately efficacious (Cuijpers et al., 2012, 2021; Rush et al., 2006). It has been suggested that one of the major reasons for this limited efficacy is the heterogeneity of depression (Ostergaard et al., 2011). For example, Major Depressive Disorder (MDD) is based upon nine diagnostic criteria (APA, 2022), which can produce different symptom profiles across patients with an MDD diagnosis, each of which requires a different treatment approach (Fried and Nesse, 2015a). Based in part upon this heterogeneity of depression, plus challenges to the universal efficacy of standard treatments, a good deal of research has focused upon the potential biomarkers of MDD, including genetic (Dall'Aglio et al., 2021), hormonal (Morssinkhof et al., 2020), and neurocognitive variables (de Aguiar Neto and Rosa, 2019). The aim of that research is to identify a reliable biologically-based indicator of depression, preferably one which is specific in predicting different depression symptom profiles, and contributes to the formulation of targeted, or individualised treatments (Insel, 2013). One potential biomarker of depression that has shown promise is inflammation (Lee and Giuliani, 2019; Majd et al., 2020; Osimo et al., 2019). Although there are a range of inflammatory factors that may be associated with depression, one which has received attention is C-Reactive Protein (CRP) (Köhler-Forsberg et al., 2017).

1.2. CRP

CRP is a major acute-phase plasma protein that recognizes pathological or invasive molecules and stimulates phagocytosis of those entities (Agrawal et al., 2020; Black et al., 2004). Concurrently, CRP is related to chronic stress (Danese et al., 2007), and is elevated in depressed patients (Chang et al., 2017; Milton et al., 2021; Osimo et al., 2019; Wysokinski et al., 2015), an association that is free from confound due to poor health, unhealthy behaviour patterns, or acute infections, as

* Corresponding author. School of Science & Technology, University of New England, Queen Elizabeth Drive, Armidale, New South Wales, 2351, Australia.
E-mail address: csharpl3@une.edu.au (C.F. Sharpley).

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confirmed in over 30 studies (see Baumeister et al., 2015, for a review). CRP collected from blood is significantly correlated with CRP in cerebrospinal fluid (Felger et al., 2020), thus providing generalizability to inflammation in the brain.

1.3. CRP and depression

As an overview of research into the associations between CRP and depressive symptomatology, Frank et al.'s (2021) recent review of data from 15 cohort studies including 56,351 participants, indicated that higher CRP concentrations were associated with six of seven physical symptoms of depression, two of three cognitive symptoms of depression, five of nine emotional symptoms, two of four biased self-perceptions, and one symptom of self-harm. Overall, CRP was most strongly linked with the physical symptoms of appetite changes, lethargy (or anergia), and sleep difficulties; the cognitive symptoms of poor concentration, and apathy; and the emotional symptoms of feeling sad and depressed. These results suggest that further investigation of the association between CRP and specific MDD symptoms may facilitate pathways towards individualised diagnosis and treatment of depression, particularly studies that focus upon different forms of depression, sometimes referred to as 'subtypes' of depression.

1.4. Melancholia

One of those MDD subtypes is Melancholic Depression, or Melancholia. Described in the DSM-5-TR as a Specifier for Depressive Disorder (APA, 2022, pp. 211–212), the key characteristics of this subtype of MDD include anhedonia, anergia, and resistance to the anti-depressive effects of pleasant events. However, a precise definition of Melancholia has proven evasive (Parker and McCraw, 2017), and is the subject of some disagreement (Tondo et al., 2020). One path out of this uncertainty has been proposed by Parker and colleagues (1990; 1994), who developed the "CORE" scale for distinguishing melancholic from non-melancholic depressed patients (Parker and McCraw, 2017), and the Sydney Melancholic Prototype Index (SMPI) which has been shown to distinguish melancholic from non-melancholic participants in community samples (Parker et al., 2019). These scales are primarily focused on symptoms of anhedonia, low energy, loss of interest, impaired concentration, lack of improvement in mood/being able to be cheered up, and thoughts of death/suicide, which may also be associated with severity of depression (Parker et al., 2019).

Several research issues that relate to the study of the correlates of Melancholia have been identified by recent reviews of this field. In particular, Bruder et al. (2017) and Bruun et al. (2021) noted that (i) the identification of melancholic participants needed to be conducted with reference to some validated and reliable method (i.e., scale), and (ii) statistical power should be a stated requirement for these investigations, particularly when sex of participant is a targeted independent variable. To these may be added the acknowledged heterogeneity of depression (Milaneschi et al., 2020; Ostergaard et al., 2011), and the implication that this also applies to investigation of Melancholia and its correlates (Parker et al., 1994, 2019). Additionally, although much of the previous literature on correlates of depression and Melancholia has relied on dichotomous classification systems (i.e., melancholic *vs* non-melancholic), this technique has been criticized because it limits the actual range of participants' severities (Cohen, 1983) to sometimes meaningless differences (e.g., different classifications for participants who are one point above *vs* one point below the cutoff threshold for group classification).

1.5. Sex differences

In addition, one of the long-standing and consistent findings from research on depression is the presence of differences in prevalence and symptomatology between biological males and females (Nolen-Hoeksema, 1987), found in many nations (Hopcroft and Bradley, 2007), and commonly of the order that women are twice as likely to report being depressed, or to receive a formal clinical diagnosis of depression, than men (Salk et al., 2017). Several reviews have focused upon the neurobiological reasons for this (Bangasser and Cuarenta, 2021; Eid et al., 2019; Slavich and Sacher, 2019), particularly differences in brain structure and function (Ma et al., 2019; Rubinow and Schmidt, 2019). There has also been some focus on the role of immunological factors (e.g., Bakunina et al., 2015; Haapakoski et al., 2016), with the exhortation that "it is imperative that sex is taken into account and is considered a factor" when investigating the association between depression and the immune system (Kropp and Hodes, 2023, p. 41). Some evidence supports the presence of sex differences in the inflammation-depression association (Siwek et al., 2017), and in differences in the inflammatory pathways between stress and depression in males and females (Rothermundt et al., 2001). However, the specific role of sex in determining the association between CRP and Melancholia remains largely unexamined.

Finally, although there are some data that describe different inflammatory factors as predictors of melancholic versus non-melancholic depression (Dunjic-Kostic et al., 2013), a review of the available literature found little evidence on which to conclude that CRP was a significant correlate of melancholic depression (Yang et al., 2018). Subsequent studies have also largely reported ambiguous findings on this association (Brydges et al., 2022; Primo de Carvalho Alves & Sica da Rocha, 2020). All of these studies have applied a dichotomous categorization process to Melancholia, often based upon subscales of other depression inventories rather than the psychometrically-valid measure developed by Parker and colleagues (Parker and McCraw, 2017; Parker et al., 2019), which may limit the possible outcomes.

1.6. Study aims

Therefore, this study aimed to explore the effect of participant sex upon the association between CRP and Melancholia, with reference to the symptoms listed in the SMPI as a validated measure of Melancholia suited for use with community samples (i.e., Parker et al., 1990; Parker et al., 1994; Parker et al., 2019). Additionally, Melancholia was investigated at the total score level and also at individual symptom level, so as to detect any subtle differences in the way that Melancholia manifests itself in males and females, and whether CRP was differentially linked with specific symptoms across males and females. For the purposes of this study, only biological sex differences were examined. To address the limitations of using dichotomous indices of Melancholia, a correlational approach was used for data analysis, allowing the full range of scores on Melancholia to be included. On the basis of the reviewed literature above, it was hypothesised that CRP would be directly correlated with the total severity of Melancholia. However, due to a lack of previous research on this issue, no directional hypotheses were made regarding the individual symptoms of Melancholia.

2. Methods

2.1. Participants

Following the recommendations made by Bruder et al. (2017) and Bruun et al. (2021) mentioned above, *a priori* power analysis (Faul et al., 2007) was undertaken, and indicated that a sample of 33 would be needed to identity the presence of a moderate level correlation (i.e., at least $r = 0.3$: Cohen, 1988), with alpha = 0.05 and power $\geq$0.80. On this basis, 51 female and 40 male adults (based on sex assigned at birth) between the ages of 18 years and 75 years were drawn from a community sample previously described (Sharpley et al., 2023b). These participants were recruited from the New England region of New South Wales, for a study "about how you think". Exclusion criteria were presence of a previous medical history of severe physical brain injury,

brain surgery, or past or current history of epilepsy or seizure disorder.

2.2. Measures

2.2.1. Background questionnaire

Participants responded to questions about their age (years) and sex.

2.2.2. The self-rating Depression Scale (SDS), Melancholia subscale

The 20-item SDS (Zung, 1965) includes the Diagnostic Criteria and several Associated Features of the most recent definition of Major Depressive Disorder (APA, 2022). Respondents indicate the frequency of each of the 20 SDS items by answering: 'None or a little of the time' (scored as 1), 'Some of the time' (2), 'Good part of the time' (3), or 'Most or all of the time' (4), providing total raw scores from 20 to 80 (used in this study). SDS raw scores of 40 or above indicate the presence of "clinically significant depression" (Zung, 1973, p. 335). The SDS has demonstrated split-half reliability of 0.81 (Zung, 1965), 0.79 (DeJonge and Baneke, 1989) and 0.94 (Gabrys and Peters, 1985), and internal consistency (Cronbach's alpha) of 0.88 for depressed patients and 0.93 for non-depressed patients (Jokelainen et al., 2019; Schaefer et al., 1985; Sepehry, 2021). As a supplementary analysis to the total score-level and symptom-level analyses, the SDS total score was used to classify participants into 'depressed' versus 'non-depressed' on the basis of Zung's cutoff score of at least 40.

To obtain the Melancholia score (henceforth referred to as MEL) described by Parker et al. (2019), items were selected from the SDS to comprise the list shown in Table 1, plus the additional item "I do not feel much better even when good things happen". Although the SDS item identified as primarily representing anhedonia ("I still enjoy sex") is limited in the range of activities that it refers to, it has previously been found to be a major indicator of anhedonia in depressed patients (Celik et al., 2021; Thakurdesai and Sawant, 2018). Sexual anhedonia is nearly three times more common in depressed patients than in non-depressed persons (Angst, 1998), and there is an association between sex-specific biomarkers and molecular mechanisms of anhedonia in depressed patients (Lin et al., 2023). When combined with the more global anhedonia item from Parker et al. (2019) ("I do not feel much better even when good things happen"), anhedonia may be satisfactorily measured in the MEL scale.

2.3. Procedure

Participants read an Explanatory Statement and completed a Consent Form, and asked any questions they had. After consent, participants completed a background questionnaire (age, sex) and the SDS and MEL scale. Ethics approval for this study was provided by the Human Research Ethics Committee of the University of New England, Australia (Approval No. HE14–051).

Table 1
Items used to measure Melancholia (MEL).

Melancholia symptoms[a]	Item
Anhedonia	I still enjoy sex[b] (R)
Low energy	I get tired for no reason[b]
Loss of interest	I still enjoy doing the things I used to do[b] (R)
Impaired concentration	My mind is as clear as it used to be[b] (R); I find it hard to make decisions[b]
Thoughts of death/suicide	I feel that others would be better off if I was dead[b]
Poor self-regard	I feel that I am useful and needed[b] (R)
Lack of improvement in mood/able to be cheered up	I do not feel much better even when good things happen[c]

R = reverse-worded item in SDS.
[a] Based on Parker et al. (1994, 2019).
[b] SDS item.
[c] Item derived from Parker et al. (1994, 2019) and framed in SDS item format.

2.4. Statistical analyses

Scale internal consistency, normality, and differences between male and female, and depressed and non-depressed participants were calculated for the SDS and MEL. To achieve the major aim of this study to measure the association between CRP and MEL, the advice of Kołodziej et al. (2021) to use correlation-based procedures as the major analytic process was followed. To detect meaningful effects, reference was made to both the traditional $p < 0.05$ level of significance and also the presence of a medium-strength correlation coefficient of at least 0.3. Due to the presence of non-normality in the SDS, MEL and CRP data, non-parametric correlational analysis was used rather than normalisation of these data because transformation can hinder interpretation of data (Feng et al., 2014; Sharpley et al., 2023a). Thus, in the present study, Spearman's Rank-Order Correlation was used as the primary data analytic procedure, plus ANOVA and MANOVA for secondary analyses, because these are relatively robust to the effects of non-normality when cell sizes are at least 20 (Tabachnik and Fidell, 2013, p. 253). Visualisations of the Spearman correlations between CRP and MEL items, undertaken within male and female subgroups, were drawn with *qgraph* (Epskamp et al., 2012) using RStudio (RStudio Team, 2022) and employed the Fruchterman and Reingold (1991) layout algorithm averaged across the two groups (male and female). Despite the argued value of correction to p values when multiple tests of significance are undertaken so as to reduce the likelihood of a Type I error, this can also increase the chances of a Type II error. Consequently, following recommendations for exploratory studies such as this (Rothman, 1990; Streiner and Norman, 2011), no correction was made.

3. Results

3.1. Data

Internal consistency (Cronbach's alpha) was satisfactory for both the SDS (0.92) and the MEL (0.88) scales. Inspection of the histograms and Normal Q-Q plots indicated the presence of non-normality in the CRP, SDS and MEL data. There were no significant correlations between age and SDS $\rho = 0.027$, $p = 0.798$, MEL $\rho = 0.068$, $p = 0.519$, or CRP $\rho = -0.036$, $p = 0.737$ values. For the entire sample, CRP concentrations ranged from 4.288 mg/L to 26.40 mg/L ($M = 5.632$ mg/L, SD = 4.328 mg/L), and SDS scores from 18 to 75 ($M = 33.470$, SD = 14.437) out of a possible range from 20 to 80. Table 2 presents the breakdown of the sample according to sex and SDS status. Outliers were minimal: 3 were present of CRP, but only one was >20 mg/L; there was one outlier for SDS total (score = 66) but this was within the accepted range of scores on the SDS; and two outliers for MEL score (scores = 30, 27).

3.2. Effects of sex and depression status

Allowing for the disparate cell sizes, MANOVA (sex, SDS status) using Type II Sums of Squares and referring to Pillai's Trace (Tabachnik and Fidell, 2013), was performed on CRP, age, SDS total score, and the eight MEL items. There were significant main effects for sex F (9,79) =

Table 2
SDS[a] status, mean (SD), range MEL scores, and mean (SD), range CRP concentrations for 40 male and 51 female community participants.

Sex/SDS status	Male	Female	Total	MEL score	CRP concentration[b]
Not depressed	29	33	62	11.93 (2.72), 8-19	5.59 (4.58), 0.55–26.4
Depressed	11	18	29	21.75 (3.86), 14-30	5.70 (3.63), 1.18–16.70
Total	40	51	91		

[a] SDS = Self-rated Depression Scale (Zung, 1965).
[b] mg/L.

2.441, $p = 0.017$, $\eta_p^2 = 0.218$ (a large effect size: Cohen, 1988) and SDS status $F = 19.041$, $p < 0.001$, $\eta_p^2 = 0.684$, but no significant interaction between sex and SDS status $F = 1.235$, $p = 0.286$, $\eta_p^2 = 0.139$.

Univariate tests indicated that males had significantly lower CRP concentrations ($M = 4.08$ mg/L, SD = 2.20 mg/L) than females ($M = 6.85$ mg/L, SD = 5.08 mg/L: $F(1,90) = 10.122$, $p = 0.002$, $\eta_p^2 = 0.104$), but not SDS (males: $M = 35.35$, SD = 9.88; females: $M = 37.17$, SD = 12.27: $F = 0.033$, $p = 0.856$, $\eta_p^2 = 0.001$) or MEL total scores (males: $M = 14.22$, SD = 5.10; females: $M = 15.72$, SD = 5.84: $F = 1.648$, $p = 0.203$, $\eta_p^2 = 0.018$.) There were no significant sex differences in any of the MEL individual items, including when CRP was entered as a covariate (all $p > 0.05$, $\eta_p^2 < 0.044$).

When divided according to their SDS clinical significance status, those participants whose SDS score was less than the cut-off of 40 had significantly lower total MEL scores than participants who met the cut-off for clinically significant depression (Table 2: $F = 195.251$, $p < 0.001$, $\eta_p^2 = 0.687$) and individual MEL items (all $p < 0.001$, all $\eta_p^2 > 0.220$), but there was no significant difference in the CRP values (Table 2: $F = 0.033$, $p = 0.856$, $\eta_p^2 = 0.001$), or age ($F = 0.852$, $p = 0.358$, $\eta_p^2 = 0.009$) for the clinically depressed versus the not-clinically depressed subgroups.

3.3. Sex, CRP and melancholia

On the basis of the significant difference between male and female CRP values, the associations between CRP and MEL symptoms were investigated for males and females separately to avoid confounds. Table 3 presents the Spearman correlation coefficients between CRP and each of the MEL items for males and females, using bootstrapping of 1000 cases to enhance generalizability of the results. Some major differences were apparent between the sexes for the ways in which aspects of Melancholia were associated with CRP (shown in the last column of Table 3).

The most obvious sex difference was for the two CRP-MEL symptom correlations that reached the defined level of meaningfulness described in Methods (i.e., $p < 0.05$ and effect size ≥ 0.3). For males, that was the correlation between CRP and the MEL item "Others would be better off if I were dead" $\rho = 0.352$, $p = 0.026$, 95% CI (0.041, 0.577), which was not meaningful for females $\rho = 0.038$, $p = 0.793$, 95% CI (−0.206, 0.280). The MEL item "My mind is unclear" had a meaningful correlation with CRP for females $\rho = 0.331$, $p = 0.018$, 95% CI (0.065, 0.566) but not for males $\rho = 0.165$, $p = 0.308$, 95% CI (−0.197, 0.482). These relatively wide CIs may be a consequence of the sample sizes and lack of variability due to the use of single items from the MEL scale. The outcomes of these correlation analyses did not change in significance when CRP and MEL outliers were removed from the analyses.

Although these two MEL items are those on which the sex differences in the CRP x MEL item associations were clearest, Table 3 also indicates that there was some variation in males' and females' associations between CRP and other aspects of Melancholia. Most of these were relatively small associations with CRP concentration, accounting for less than 5% of the variance.

As noted by de Plinio (2022, p. 1), even effects that are relatively minor in terms of p values can be "scientifically relevant", and several of the eight MEL items fall into that category (i.e., correlations of 0.10–0.29: Cohen, 1988), highlighting sex differences. That is, the items "I get tired for no reason", "I don't enjoy doing the things I used to", and "I feel useless and not needed" all reached the cutoff for a small effect for males but not for females. Similarly, the items "I find it hard to make decisions", and "I don't feel better when good things happen" reached the small effect cutoff for females but not for males. When added to the two MEL items that reached the medium level of association between CRP and MEL, these two sets of MEL items illustrate sex differences in CRP and Melancholia, depicted in Fig. 1.

The two sexes' profiles of their CRP-MEL item relationships are shown as networks and juxtaposed in Fig. 2 for ease of comparison not available in Table 3 or Fig. 1. The length of each line connecting variables corresponds to their respective absolute magnitude of correlation averaged across the two groups, and the thickness of the lines indicates the relative magnitude of correlation within each group (rather than

Table 3
Spearman's correlation coefficients for CRP concentration[a] x MEL[b] items for 40 males and 51 females, plus difference between sexes' correlation coefficients.

MEL item	Males	Females	Difference between sexes' correlation coefficients
Others would be better off if I were dead	0.352*	0.038	0.314
I don't enjoy doing the things I used to	−0.024	0.169	0.193
My mind is unclear	0.165	0.331*	0.166
I find it hard to make decisions	0.147	−0.004	0.151
I get tired for no reason	0.056	0.176	0.120
I feel useless and not needed	0.075	0.138	0.063
I don't feel better when good things happen	−0.130	0.082	0.212
I don't enjoy sex	−0.087	−0.003	0.084

[a] mg/L.
[b] Melancholia Scale items.

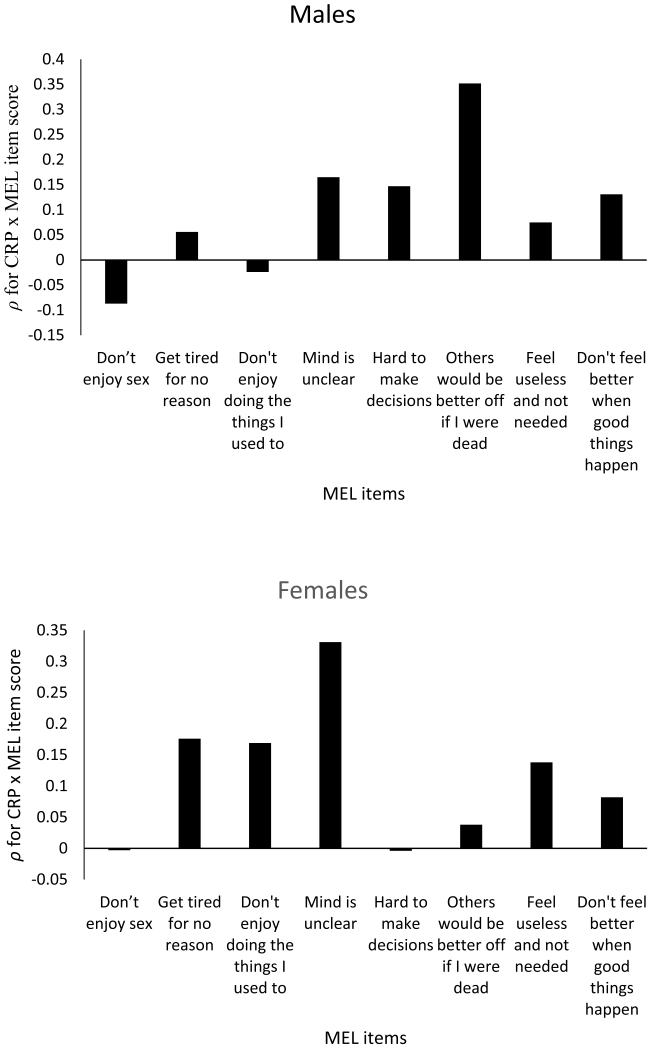

Fig. 1. Spearman correlation coefficients for the association between CRP concentrations[1] and MEL[2] items for 40 males and 51 females. [1] mg/L; [2] Melancholia Scale items.

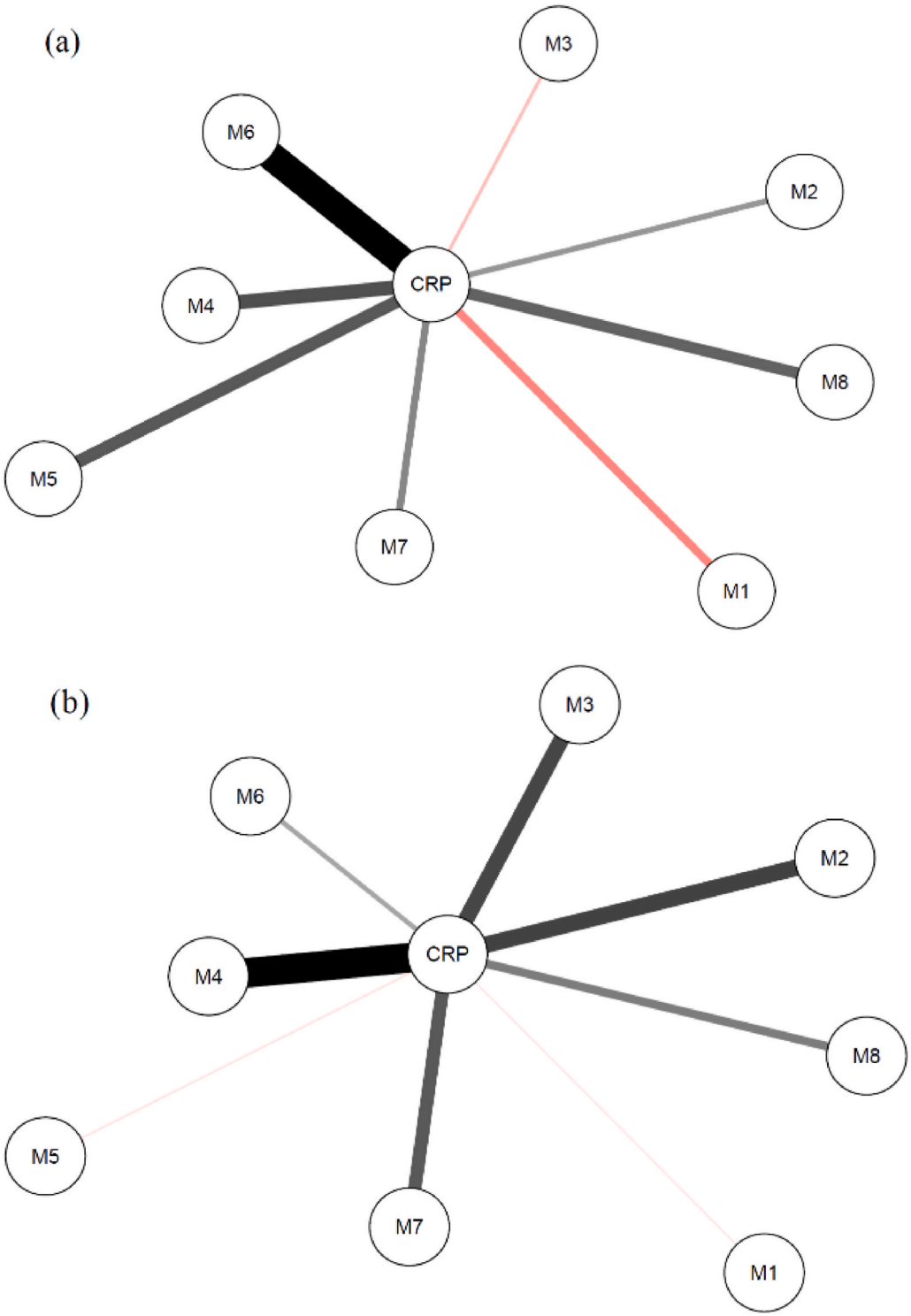

Fig. 2. Networks of Spearman's correlations between C-reactive protein (CRP) and each of the eight MEL items for (a) males (n = 40) and (b) females (n = 51). Black lines indicate positive correlations and red lines indicate negative (inverse) correlations.
M1 = "I don't enjoy sex". M2 = "I get tired for no reason". M3 = "I don't enjoy doing the things I used to". M4 = "My mind is not as clear as it used to be". M5 = "I find it hard to make decisions". M6 = "I feel that others would be better off if I were dead". M7 = "I feel that I am useless and not needed". M8 = "I do not feel much better, even when good things happen. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

averaged across the two groups). These findings confirm that, despite there being no significant sex differences in either MEL total or item scores (even when CRP was included as a covariate in the MANOVA), the ways that CRP concentration was associated with MEL items differed across males and females, so as to form distinct networks of CRP and MEL symptoms.

4. Discussion

4.1. Major findings

The major aim of this research was to investigate the possible influence of biological sex upon the association between CRP and

Melancholia as defined by reference to the content of the SMPI (Parker et al., 2019) developed for use with community samples (i.e., MEL). Several methodological steps were taken to increase the relevance of the results to the underlying issue of the heterogeneity of depression apart from the SMPI basis, notably testing of the hypothesis at the total MEL score level as well as individual MEL items, the use of peripheral CRP as an indicator of brain state CRP, and the division of the sample into males and females according to biological sex. Females had significantly higher CRP concentrations than males, but no significant differences in their SDS and total MEL scores. Further, depression severity as measured via the SDS total score was not significantly associated with CRP concentrations. These findings argued for analysis of the association between CRP and MEL separately for males and females, and the results of those analyses comprise the most important aspect of this research.

There were different patterns of association between CRP and MEL items across males and females, as shown in Fig. 2. The principal differences were that, for males, CRP concentration was significantly associated with feelings of worthlessness, but that was not the case for females. Conversely, females exhibited a significant correlation between CRP concentration and being unable to think clearly, but males did not. Other minor sex-based differences were for the association between CRP concentration and: fatigue, anhedonia, and feeling useless (males), and decision-making and not being able to respond positively when good things happen (females). Comparatively, these two sets of associations between CRP and MEL items describe clear sex effects, and also extend the previous literature that was based only upon dichotomous classification of Melancholia.

4.2. Sex, CRP, and Melancholia

Based upon those different sets of CRP-MEL item associations found for males and females, it is relevant to reflect upon the effect of this sex-based heterogeneity in the association between CRP concentration and Melancholia in general. The previously-reported largely ambiguous findings regarding the effects of sex upon the association between CRP and Melancholia (Brydges et al., 2022; Primo de Carvalho Alves & Sica da Rocha, 2020; Yang et al., 2018) may be partially explained by these results because of the potentially confounding effects of considering Melancholia as a unitary construct rather than a heterogeneous collection of different symptoms. Like MDD, the MEL scale used here is composed of quite different aspects of the overall Melancholia construct (as shown in Table 1), and the different associations between CRP concentration and those MEL items reflect the heterogeneity of that construct. In particular, the lack of consistent positive correlations between MEL items and CRP that was found in both sexes suggests a marked degree of difference in the way that inflammation is related to selected symptoms of Melancholia *per se*. Although the inverse correlations between MEL items and CRP concentration were small, they suggest that the assumed association between inflammation and global depression may not be universally direct across all symptoms of (for example) MDD. Whether this implies that (a) some aspects of Melancholia are, in fact, inversely associated with peripheral inflammation, (b) this particular association is isolated to CRP but not to other indices of inflammation, or (c) there is potential sex-based variability in whether the MEL construct can be considered unidimensional on the basis of the symptoms that comprise this MEL scale, remains to be determined. Regardless of which of these (and other) explanations is ultimately found to be valid, the argument against assuming a unitary model of depression (including the subtype that is Melancholia) is supported by these results.

A recent review of possible biomarkers of Melancholia including endocrinological, neurological, and immunological factors concluded that overall findings could not be drawn because of the substantial heterogeneity in how studies had defined Melancholia, which may have been "responsible for the between- and within-group variability observed in the candidate biomarkers that were examined" (Spoelma et al., 2023, p. 1). Because of that variability in measurement of Melancholia, those authors argued that definitive conclusions were limited, and that further research was needed that used well-defined measures of Melancholia, among which the SMPI was suggested. To the extent that the current study used the items based upon the SMPI, measured an established inflammation index, and did so within a community sample, the findings of sex differences in the ways that CRP was associated with Melancholia symptomatology constitute the kind of research that was recommended by those authors, and which commences the process of identifying biomarkers for aspects of the wider construct of Melancholia.

There is widespread and well-established acceptance that males and females experience depression differently (Grigoriadis and Erlick Robinson, 2007; Hyde and Mezulis, 2020). Recent attempts to explain these differences in terms of brain circuitry and mechanisms (Bangasser and Cuarenta, 2021) and immune function (Majd et al., 2020), included some attention to CRP and Melancholia in particular (Křenek et al., 2023). However, these studies almost universally assumed a unitary model of depression and Melancholia, and did not actively investigated the role of biological sex in the association between inflammation and the individual symptoms of depression and/or Melancholia. This is a gap in the literature, underscored by the focus upon differences in depression symptom profiles that have been found to influence the efficacy of standardized treatments (Fried and Nesse, 2015a, 2015b; Nasstasia et al., 2019). The need to further investigate that variable symptom-efficacy outcome is supported by the current findings.

4.3. Clinical implications

Although this study did not evaluate the outcomes of treatment models for depression and Melancholia, some initial suggestions may be made for the overall approach that might be taken when using traditional treatments for Melancholia, bearing in mind that the MEL is a unique measure and not completely congruent with the SMPI or other measures of Melancholia. However, as noted in section 1.4, the exact definition and measurement of Melancholia is the subject of some disagreement (Tondo et al., 2020), and so the minor discrepancies between the MEL and other measures may be accepted at this stage of research into Melancholia. Second, the SDS data were collected via self-report, which does not necessarily equate to a formal clinical diagnostic interview. Similarly, even though there is a robust agreement between the SDS classification of "clinically significant depression" defined by Zung (1973) and clinician diagnoses, the lack of a subsample of participants with a formal diagnosis of MDD limits the clinical implications made here.

Keeping those caveats in mind, several suggestions may be made from these exploratory data. First, if an association is accepted between inflammation and Melancholia (as it is for general depression), then examination of patient treatment possibilities needs to be done at the Melancholia symptom level rather than the total score level. This suggestion follows recommendations to incorporate symptom profiles rather than global depression indices during treatment planning (Fried and Nesse, 2015a) and applies equally well to Melancholia as it does to MDD. Second, male and female depression symptom profiles differ (Smith et al., 2008), and the current data suggest that differences are also present for the specific symptoms that comprise the Melancholia scale used here that was derived from the SMPI (Parker et al., 2019). Therefore, treatment planning ought also to be done on the basis of the patient's biological sex and the specific profile of Melancholia symptoms exhibited by each individual. Third, it has been suggested that inflammation is associated with disrupted neurotransmitter pathways in brain circuits that influence motivation and motor activity, which are key symptoms of Melancholia (Miller and Raison, 2015). Some initial studies have been conducted using anti-inflammatory agents such as glycyrrhizic acid (Cao et al., 2020), statins (Ma et al., 2016) and exercise (Ding and Du, 2022) to treat inflammation-related depression: see Hayley

et al. (2021) for a review. Whether these approaches would be effective for specific Melancholia symptoms remains to be determined. Finally, there are emerging aspects of the association between peripheral inflammation and depression that might be profitably explored with Melancholia rather than general depression as the target variable. One of these is the association between peripheral inflammation and functional connectivity within the brain of depressed persons (Kitzbichler et al., 2021), and another is the exploration of the two isoforms of CRP, only one of which has inflammatory effects (Del Giudice and Gangestad, 2018).

4.4. Limitations

Like all research, the results of this study have some methodological limitations upon their generalizability. The sample was confined to a specific geographical and social subset of the population; participants were volunteers, suggestive of some degree of self-selection, and arguing for more comprehensive collection of data from depressed patients (although the focus of the study was on community members); and a single observation of participants' CRP and depressive symptomatology was collected, preventing any conclusions to be drawn regarding differences found over time. Self-reported SDS data have been found to agree with clinician diagnosis (see Methods), but data based on both sources would give more confidence in the findings, and this must be acknowledged as a limitation when considering the clinical implications of these findings because the self-report on the SDS does not necessarily equate to a formal diagnosis of MDD. CRP is well-established in the research literature on depression and inflammation, but is a single cytokine: others may have different associations with MEL across males and females. There was no significant correlation between age and CRP, arguing against the presence of a possible confound due to age-related illness. Similarly, the highest CRP value was 26.40 mg/L, which represents only mild-moderate elevation of this cytokine (Reeves, 2007). This study purposely defined sex according to self-reported biological status, and the investigation of wider gender-based categories of sexual identification is always relevant to future research. The measure used here to detect Melancholia was based upon that reported by Parker and colleagues (1994; 2019), but was not completely congruent with that scale (or any other measures of Melancholia), although the combination of the SDS item "I still enjoy sex" and the SMPI item "I do not feel better even when good things happen", argues for the comprehensiveness of this aspect of the MEL. Nevertheless, some caution must be used when considering the MEL scale as an index of Melancholia, simply because of the previously-mentioned lack of universal agreement as to the precise definition of Melancholia (Tondo et al., 2020). Although that uncertainty regarding the precise content of Melancholia remains (Martino et al., 2019; Sani et al., 2020), a recent machine learning study provided some extra confirmation of the measure applied in this study (Parker and Spoelma, 2021). Finally, although *a priori* power analysis supported the current sample sizes, replication in larger and different samples always has the potential to add further detail to research findings. The wide CI ranges may be a consequence of the sample sizes and the lack of variability given that single items were used, which would be clarified by replication.

4.5. Conclusion

These data extend the previous literature regarding the association between peripheral inflammation and Melancholia by examining sex differences within an adequately powered study, by applying a well-validated measure of Melancholia, doing so via the whole range of scores rather than a simple dichotomy, and by examining the Melancholia construct at the individual symptom level rather than as a simple total score. The results provide some basis for considering the inflammation-Melancholia relationship to be tempered by the sex of respondent.

CRediT authorship contribution statement

Christopher F. Sharpley: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Vicki Bitsika:** Writing – review & editing, Methodology, Conceptualization. **Wayne M. Arnold:** Writing – review & editing, Formal analysis, Data curation. **Ian D. Evans:** Writing – review & editing, Methodology, Formal analysis. **Emmanuel Jesulola:** Writing – original draft, Resources, Methodology. **Linda L. Agnew:** Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

None of the authors has any conflict of interest to declare.

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