

Full Length Article

Depression symptoms mediate the association between workplace stress and interleukin 6 in women, but not men: The Whitehall II study

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ABSTRACT

Workplace stress and depression are positively related with inflammation, and each other. Low-grade inflammation and concurrent high levels of workplace stress or depression has been related with future morbidity. The potential pathway between constructs however, remains elusive. For the first time, this study explored the concurrent relationship between workplace stress, depressive symptomology and low-grade inflammation, and considered the role of gender in these relationships. Data from the Whitehall II cohort study ($N = 2528$, $M_{age} = 57.01$, 23.7% females) provided measures of workplace stress (job demand-control; JDC), depressive symptomology (Centre for Epidemiological Studies Depression scale; CES-D) and circulating inflammatory markers, interleukin-6 (IL-6) and C-reactive protein (CRP) collected on the same day from a single time point. Females had higher workplace stress, depressive symptoms and lower serum IL-6 concentrations. For males, higher workplace stress was associated with higher depressive symptoms. For females, higher depressive symptoms were related with elevated IL-6 levels, and both higher workplace stress and IL-6 levels were associated with higher depressive symptoms. Higher depressive symptoms were related with higher CRP levels in men only. Higher depressive symptoms statistically mediated the relationship between higher workplace stress and IL-6 levels in females only, $b = 0.016$, CI [0.002, 0.039]. Females in this large cohort had higher levels of job strain, depression and lower IL-6 concentrations than males. In females, higher depressive symptoms were associated with higher serum IL-6 levels and workplace stress was not. Considered together, these findings suggest that low job control may be more apparent in females than males, but it is primarily negative affect that drives the positive relationship between work stress and serum IL-6 concentrations in females. Replicating the current design with a suitably proximal follow-up is required to determine if the associations identified are causal.

1. Introduction

There exists a growing body of literature investigating the association of workplace stress with depression (Dragano et al., 2008; Theorell et al., 2015) and inflammation (Eddy et al., 2016; Elovainio et al., 2010). Research suggests a bidirectional pathway between depression and inflammation (Messay et al., 2012). However, what is missing from the literature is what is touted by the transactional model of stress and coping (TMSC) (Folkman and Lazarus, 1984) – a consideration of whether it is stress exposure per se, or states of negative affect such as depression, that drive the association with low-grade inflammation. Understanding the

association between these constructs is required to assist with identifying those at risk for low-grade inflammation and diseases including diabetes (Van Greevenbroek, Schalkwijk and Stehouwer, 2013), cardiovascular disease (Wirtz and von Kanel, 2017), cancer (Lancellotti et al., 2019), dementia (Tao et al., 2018), and arthritis (Robinson et al., 2016). Some research suggests that the relationships between psychological factors and low-grade inflammation may differ by gender (Elovainio et al., 2010), but to our knowledge no study has assessed the concurrent association of workplace stress and depression with markers of inflammation using gender-specific analyses.

Abbreviations: CES-D, Centre for Epidemiological Studies Depression scale; CESgrp, CES-D group; CRP, C-reactive protein; ERI, Effort-reward imbalance; IL-6, interleukin-6; JC, Job control; JD, Job demand; JDC, Job demand control ratio; JDR, Job demand-resources; JSgrp, Job strain group; OJ, Organisational Justice; TMSC, Transactional model of stress and coping.

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1.1. Workplace stress and depression

A positive association between workplace stress and depressive symptomatology has been described in both meta-analyses (Netterstrom et al., 2008; Stansfeld and Candy, 2006; Theorell et al., 2015) and large prospective studies (Dragano et al., 2008; Lunau et al., 2018) using a variety of workplace stress models, including Siegrist's effort-reward imbalance (ERI; (Siegrist, 1996) (Bellingrath et al., 2010), Karasek's job demand-control (JDC; (Karasek Jr, 1979) (Dragano et al., 2008; Lunau et al., 2018), Demerouti & Bakker's (Demerouti et al., 2001) job demand-resources (JD-R), and Greenberg's (Greenberg, 1987) organisational justice (OJ) (Elovainio et al., 2010; Grynderup et al., 2013) models. While the direct relationship between workplace stress and the development of depressive symptomatology is well established, recent studies have also revealed that a direct relationship between workplace stress and elevated levels of circulating inflammatory markers is likely (Eddy et al., 2016; Wright et al., 2020) but whether these associations persist after controlling for negative affect is unknown.

1.2. Associations of workplace stress and depression with low-grade inflammation

Systemic, low-grade inflammation is distinguished from responses to infection or injury that are acute in nature or limited to a local site of injury or infection (Rohleder, 2019). In workplace stress literature, systemic inflammatory activity is most commonly assessed by measuring circulating markers of inflammation such as C-reactive protein (CRP) (Del Giudice and Gangestad, 2018; Rohleder, 2019; Slavich and Irwin, 2014; Tanaka et al., 2014). Although understanding of the workplace stress-inflammation pathway has progressed, the potential interactions of workplace stress, depression and inflammation remain unclear, largely due to a lack of concurrent assessment of these constructs.

The TMSC suggests that an inability to cope with stress precedes changes in negative affect, and that negative affect precedes physiological arousal. Although a bi-directional association likely exists between workplace stress and depressive symptoms, most researchers appear to endorse that the predominant pathway is workplace stress to depression, and only assess the association unidirectionally. It would appear logical that higher workplace stress is associated with greater depressive symptoms, but research linking workplace stress with increased inflammation (Del Giudice and Gangestad, 2018; Slavich and Irwin, 2014; Tanaka et al., 2014) may be tainted by a lack of concurrent examination of depressive affect. Specifically, the association between workplace stress and inflammation may be due to depressive symptoms that are unrelated to workplace stress. That is, persons with depressive symptoms may perceive and report higher work stress. This notion of reverse causation has largely been ignored but some research does show that negative affect impacts the experience of the work environment, but that the association of workplace stress with negative affect is stronger (De Jonge et al., 2001; Ibrahim et al., 2009; Shimazu and de Jonge, 2009). Despite strong evidence of the role of depression with stress and inflammation, recent studies have not considered the role of negative affect in studies that confirm relationships between workplace stress and inflammation with diabetes (Hanson et al., 2019) or coronary heart disease (Nabi et al., 2008).

Unlike the stress to depression pathway, the depression to low-grade inflammation pathway has been the subject of much research that assesses both unidirectional pathways. The depression to increased low-grade inflammation association has been supported by the findings from a large meta-analysis (Howren et al., 2009) and there is also a substantial body of evidence suggesting that inflammation may drive depressive symptoms in prospective studies (Au et al., 2015; Das, 2016; Fagundes et al., 2013; Gimeno et al., 2009; Hiles et al., 2015; Khandaker et al., 2014; Luukinen et al., 2010; Matthews et al., 2010; van den Biggelaar et al., 2007; Zalli et al., 2016).

1.3. Important covariates

Given that inflammatory markers differ by sex and body mass index (BMI) (Festa et al., 2001) it is surprising that these factors are often not incorporated as a covariate when assessing the relationship of workplace stress with inflammation. Research has shown that statistically controlling for gender (Gimeno et al., 2009) or BMI (Stewart et al., 2009) can alter the association between workplace stress and inflammation. This trend continues in studies that have controlled for both gender and BMI (Hiles et al., 2015; Niles, Smirnova, Lin and O'Donovan, 2018). Accordingly, gender-specific analyses may be most appropriate, with Elovainio and colleagues finding an association between workplace stress and low-grade inflammation in males but not females (Elovainio et al., 2010). However, despite the recognized strong association of workplace stress with depressive symptomatology and markers of inflammation in the literature, there remains a dearth of research concurrently assessing the impact and role of gender in the stress-depression-inflammation relationship. In fact, to our knowledge, no published literature has concurrently considered the association of self-reported measures of workplace stress and depressive symptomatology with circulating markers of inflammation.

1.4. Present investigation

The present investigation used data collected from the Whitehall II cohort study, that featured concurrent assessments of elements of workplace stress (items measuring JDC) (Karasek Jr, 1979), self-reported depressive symptomatology (Centre for Epidemiologic Studies Depression scale; CES-D) (Radloff, 1977) and circulating markers of inflammation (IL-6 and CRP). We anticipated a positive association between the workplace stress, depression and inflammation markers for both genders. Further, we hypothesised that as per the TMSC (Folkman and Lazarus, 1984), that self-reported depressive symptoms would mediate the association between workplace stress and low-grade inflammation. Finally, consistent with researchers who separated their analyses by gender (Elovainio et al., 2010), we predicted that the relationship between workplace stress, depression and inflammation would be stronger in males.

2. Methods

2.1. Participants

Participant data from phase 7 (2002–04) of the Whitehall II study, see (Marmot and Brunner, 2005) for full details, was used to identify cases with listwise completion for items on workplace stress (JDC) and depressive symptomatology (CES-D), BMI, and inflammatory markers IL-6 and CRP. The questionnaires and screening invitation letter were sent on average 14 days before the screening appointment. Participants were asked to complete the questionnaire prior to their appointment and submit it at their appointment. In line with other studies, high CRP values (>10 mg/L) and those reporting cold/'flu' symptoms in the 2 weeks prior to testing were excluded from analysis, as these conditions are typically associated with acute inflammatory processes that may confound interpretation of enduring conditions (Gimeno et al., 2009; Myers et al., 2004). This resulted in a total sample of 599 females and 1929 males ($n = 2528$, $M_{age} = 57.01$, $SD = 4.01$) who responded and met all requirements at phase 7 (Fig. 1).

2.2. Workplace stress measures

Workplace stress was assessed using measures of job demands (JD) and job control (JC) from the job content questionnaire (Karasek et al., 1998) associated with the JDC model (Karasek Jr, 1979). JD were assessed using 4-items ($\alpha = 0.73$, e.g. "Do you have to work very fast?" or "Do you have to work very intensively?"). JC was assessed using 15-items

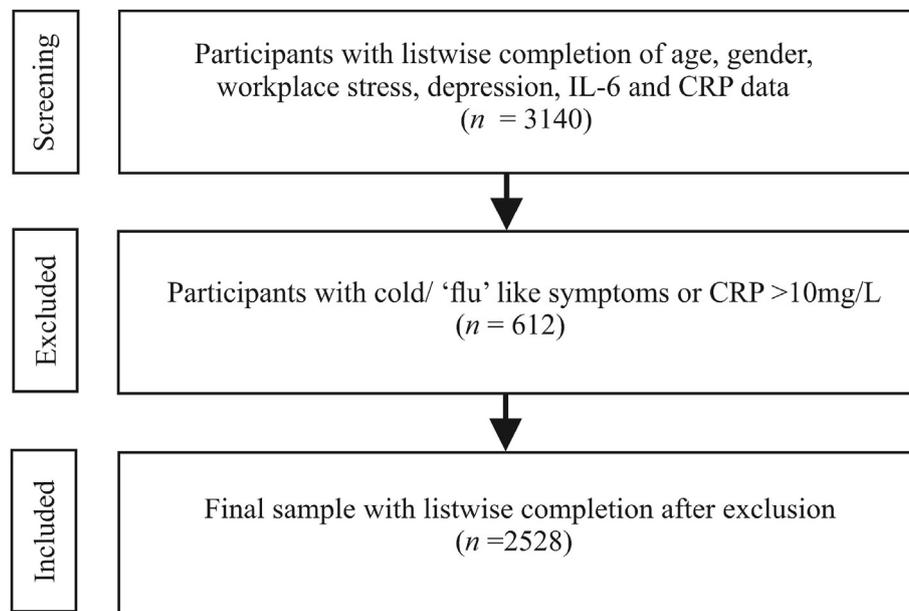


Fig. 1. Flow chart outlining data selection.

($\alpha = 0.86$) split into 6-items assessing skill discretion ($\alpha = 0.76$, e.g. “Does your job demand a high level of skill or expertise?” or “Is your job boring?”) and 9-items assessing decision authority ($\alpha = 0.83$, e.g. “Do you have a choice deciding what you do at work?” or “My working time can be flexible”). Possible answers to each item ranged from 1 (‘Almost never’) to 4 (‘Often’), and for each scale the score was calculated as the sum of item-scores with reverse scoring used for ‘negatively’ worded questions. We calculated two commonly used composite measures of job strain (Wright et al., 2020). Specifically, the job strain group measure (JSGrp) was calculated and interpreted in the conventional way (Landbergis et al., 1994) by dividing demand and control scores at the median to form quadrants, with those in the high demand/low control quadrant considered most at risk (score of 2) while the other 3 quadrants were considered less at risk (score of 1). Additionally, a job demand/control ratio (JDC) was also calculated. Given the difference in the number of items for each measure, the formula $JD \times 3.75/JC$ was used to evenly weight each measure. The binary JSGrp measure was calculated to provide context on the proportion of participants that reported strain using this standard formula. The continuous JDC measure was selected a priori as the workplace stress measure to be used in all parametric tests given its stronger statistical power.

2.3. Depressive symptoms

Depressive symptoms were assessed using the CES-D scale (Radloff, 1977). The scale aims to measure current levels of depressive symptomatology (i.e. within the last 7 days), with an emphasis on depressed mood (affective component) (Radloff, 1977). Although items are based on clinical symptoms of depression, the scale cannot be used to clinically diagnose depression. The scale consists of 20-items ($\alpha = 0.86$, e.g. “I was happy” or “I was bothered by things that usually don’t bother me”) matching depressive symptoms on a Likert scale ranging from ‘less than once a week’ to ‘5–7 days a week’. Depressive cases using this scale are defined as participants with a score of ≥ 16 (max 60). Using this cut-off score, participants are separated into two groups of depressive symptoms (CESGrp), those considered at risk of developing depression (CES-D ≥ 16) and those not at risk (CES-D < 16). The scale showed excellent inter-item reliability, Cronbach $\alpha = 0.89$.

2.4. Inflammatory markers

Fasting blood was collected, with serum separated and stored at -80°C until needed for analysis. CRP levels were measured using a high sensitivity immunonephelometric assay in a BN Prospec nephelometer (Dade Behring, Milton Keynes, Bucks, UK). IL-6 concentrations were measured using a high-sensitivity enzyme linked immunosorbent assay (R & D systems, Oxford, Oxon, UK). Values below the detection limit for each (0.154 mg/L for CRP and 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit for each assay respectively. To account for short-term biological variation and laboratory error, a repeated measure sample was taken from a subset of 533 participants for CRP and 329 for IL-6 at phase 7. The average elapsed time between the repeat tests was 24 days (SD = 11 days). Intra- and inter-assay coefficients of variation were 8.3% and 8.9% for CRP and IL-6 concentrations respectively. The test-retest reliability of the samples were $r = 0.72$ and $r = 0.63$ for CRP and IL-6 concentrations respectively.

2.5. Statistical analysis

All statistics were conducted using SPSS statistics version 26 (IBM SPSS Inc., Chicago, IL, USA). We assessed all variables for deviations from a normal distribution ($p = .001$). The CRP and IL-6 variables were positively skewed and corrected with a natural logarithm transformation. To assess gender differences across the key variables, independent samples t -tests were used for continuous outcomes and Chi square analyses for categorical outcome measures. To assess if workplace stress or depression was most associated with inflammation, multiple linear regression was used to identify the association of workplace stress and depression with measures of inflammation after controlling for age and BMI in a series of gender-specific analyses. Assumptions of linearity, independence and multicollinearity were satisfied (all Tolerance statistics ranged from 0.68 to 0.99). Finally, using the PROCESS Macro version 3.4.1 for SPSS (Hayes, 2017) a cross sectional mediation analysis using $N = 5000$ resamples was conducted to assess if depression mediated the relationship between work stress and IL-6 or CRP concentrations. We also assessed if IL-6 or CRP levels mediated the relationship between work stress and depression.

3. Results

Although the effect size was small, females had higher levels of depressive symptoms and reported higher levels of job strain when compared to males in this sample (Table 1). Higher levels of job strain in females can be attributed to a lower sense of job control, as differences were not observed in job demands between males and females. Females also had higher levels of CRP and lower levels of IL-6 compared to men. Violations in homogeneity were observed in all variables except age (years), JD and IL-6 levels, with the robust Brown-Forsythe test used for these variables (Table 1).

The multiple regression analyses (Tables 2 and 3) revealed that for males, only higher workplace stress was associated with higher depression symptoms. Whereas for females, higher depression symptoms were related with higher IL-6 concentrations, and both workplace stress and IL-6 concentrations were associated with higher depression symptoms. For both genders, CRP levels were not associated with workplace stress. Higher depressive symptoms were only related to higher CRP levels in men.

Higher age and BMI as a set in Step 1 was related with higher IL-6 and CRP concentrations for both men and women but younger age and higher BMI as a set was only associated with depression with men. As a set, at Step 2, higher JDC, IL-6 and CRP predicted higher depressive symptoms for both men and women. Higher JDC and depression scores as a set at Step 2, predicted higher IL-6 concentrations in women, but not men. When considered collectively, the regression findings revealed that higher depression scores were bi-directionally related with higher IL-6 concentrations among females while job strain and IL-6 levels were not associated with either gender. Among males, higher depression scores were associated with increased CRP concentrations (Fig. 2).

Given the regression findings, we assessed if depression acted as a mediator in the stress - IL-6 relationship. A mediation analysis with $N = 5000$ resamples revealed that depression mediated the link between workplace stress and IL-6 levels, $b = 0.016$, CI [0.002, 0.039] for females. The relationship between workplace stress and concentrations of IL-6 is diminished by 60% when depression is included in the regression model (Fig. 3). This suggests that the relationship between increased workplace stress with greater IL-6 expression is largely explained through concurrent levels of high depression. Depression did not mediate the relationship between stress and CRP levels for females, $b = 0.001002$, CI [-0.012, 0.013] nor did depression mediate the relationship between stress and IL-6 concentrations, $b = 0.00403$, CI [-0.006, 0.014] or CRP, $b = .003004$, CI [-0.007, 0.014] for males.

Table 1

A comparison of gender differences on the key variables ($n = 2528$).

Variables	Male ($n = 1929$)		Female ($n = 599$)		Hedges g	p
	M	SD	M	SD		
Age (years)	57.08	4.07	56.79	3.82	-.072	.12
BMI (kg/m^2)	26.65	3.83	26.56	5.12	-.022	.67
CES-D	7.74	7.34	9.76	8.39	.266	<.001
JDC	0.94	0.59	1.04	0.74	.163	<.001
JD	59.32	20.09	58.60	20.54	-.036	.45
JC	69.86	18.01	64.20	19.21	-.309	<.001
JSgrp (high/low)	625/1304	32.40%	231/599	38.60%	.055*	.006
CESgrp (high/low)	257/1304	13.30%	114/599	19.00%	.069*	.001
CRP (mg/L)	1.65	1.73	1.99	2.03	.189	.001
IL-6 (pg/mL)	2.07	1.76	1.91	1.67	-.232	.033

* = Phi effect size from Chi square analysis.

Note. CES-D = Centre for Epidemiological Depression scale; JD = Job demand; JC = Job control; JDC = Job demand control ratio; JSgrp = Job strain group; CESgrp = CES-D group; CRP = C-reactive protein; IL-6 = interleukin-6. Untransformed CRP and IL-6 concentrations are provided but all parametric tests used the log transformed version of these variables.

To assess the alternate pathway, a mediation analysis was conducted to assess if inflammatory concentrations (IL-6 and CRP) mediated the link between workplace stress and depression. IL-6 levels did not mediate the relationship between workplace stress for males, $b = 0.001-0.003$, CI [-0.003, 0.001] or females, $b = 0.003$, CI [-0.007, 0.0174] nor was there any evidence to suggest that CRP concentrations mediated this relationship in males, $b = -.001$, CI [-0.004, 0.002] or females, $b = 0.001$, CI [-0.006, 0.005].

4. Discussion

In this study, females presented with higher workplace stress, depressive symptoms and lower serum IL-6 concentrations. Further, an association between these variables was only present in females. Specifically, findings from the concurrent examination of stress and depression with serum IL-6 concentrations align with the tenets of the transactional model of stress and coping, with depressive symptoms more strongly associated with IL-6 levels than workplace stress.

A positive association between depressive symptoms and serum IL-6 concentrations is well supported (Duivis et al., 2011; Stewart et al., 2009); however, the role and impact of gender in this association has been largely unexplored, and even less research has considered the role of workplace stress in this relationship. In this study, females reported higher depression and CRP concentrations and lower IL-6 levels and the disparity between the inflammation markers may appear odd. However, pre-menopausal women (a substantive portion of our sample) have shown to have higher CRP levels than men (Rexrode et al., 2003; Ridker et al., 1999) possibly due to influence of estrogens on CRP levels. These same estrogens can have an inhibitory effect on IL-6 concentrations (Cartier et al., 2009) and this may explain findings of lower IL-6 levels in women (An et al., 1999; Ershler and Keller, 2000). Our findings also align with research that suggests females may be more frequently depressed than males, which may be a result of greater inflammation (Bekhat and Neigh, 2018; Derry et al., 2015). This assertion may be too simplistic however, as the physiological response to high-strain jobs might also depend on gender.

In the present study, females reported higher job strain, and this appeared to be due to lower perceptions of job control. Although we found that workplace stress was positively associated with depression and IL-6 levels, evidence from a systematic review (Van der Doef and Maes, 1999) suggested that males were more vulnerable to the negative consequences of high-strain occupations than females. Similarly, although females reported higher overall strain and negative psychosocial characteristics at work, males may be more likely to exhibit work-related psychological distress (Vermeulen and Mustard, 2000). However, others have suggested that the association between workplace stress and depression does not differ between genders (Theorell et al., 2014).

A prospective study by Theorell & colleagues (Theorell et al., 2014) found that despite females reporting higher levels of job strain than males, the association with increased depressive symptoms did not differ between genders at equivalent levels of job strain. This indicated that reduced affect might result from objective factors associated with an occupation (e.g. position, type of work, psychosocial working condition etc.). Specifically, females may report lower perceptions of job control due to unequal access to positions with high job control. Nonetheless, despite females reporting a lower sense of job control at work than males in this study, an adverse response to lower job control is seemingly more associated with a greater threat to self-worth for males than females (De Bruin and Taylor, 2006; Theorell et al., 2014). Considered collectively, our choice to separate analyses by gender appears justified, and highlights that entering gender as a covariate in statistical analyses, while better than not doing so, may limit the interpretation of findings.

While understanding the effect of gender on the observed associations helps explain the underlying mechanisms in the stress - ill health pathway, gender differences in depressive symptoms may be due to the

Table 2
Linear model of associations with IL-6, CRP and depression for females (n = 599)

Independent Variable	IL-6			CRP			CES-D		
	Final Summary	Step Summary	<i>p</i>	Final Summary	Step Summary	<i>p</i>	Final Summary	Step Summary	<i>p</i>
Step 1	Beta	<i>R</i> ² Δ	<i>p</i>	Beta	<i>R</i> ² Δ	<i>p</i>	Beta	<i>R</i> ² Δ	<i>p</i>
Age	.063	.181	<.001	.071	.246	<.001	-.040	.005	.26
BMI	.414**			.491**			.004		
Step 2		.011	.02		.001	.83		.036	<.001
CES-D	.104**			-.003			–		
JDC	.010			.021			.144**		
IL-6	–			–			.139**		
CRP	–			–			-.049		

Note. IL-6 Total model *R*² = 0.193, *F* (4, 594) = 35.459, *p* < .001, CRP Total model *R*² = 0.249, *F* (4, 594) = 49.192, *p* < .001, CES-D Total model *R*² = 0.041, *F* (5, 593) = 5.031, *p* < .001.

CES-D = Centre for Epidemiological Depression scale; JD = Job demand; JC = Job control; JDC = Job demand control ratio; CRP = C-reactive protein; IL-6 = interleukin-6, The ‘Step Summary’ denotes the variance explained (*R*²) by the addition of the set of variables within each step, ***p* < .01, **p* < .05.

Table 3
Linear model of associations with IL-6, CRP and depression for males (n = 1929)

Independent Variable	IL-6			CRP			CES-D		
	Final Summary	Step Summary	<i>p</i>	Final Summary	Step Summary	<i>p</i>	Final Summary	Step Summary	<i>p</i>
Step 1	Beta	<i>R</i> ² Δ	<i>p</i>	Beta	<i>R</i> ² Δ	<i>p</i>	Beta	<i>R</i> ² Δ	<i>p</i>
Age	.065*	.101	<.001	.025	.1685	<.001	-.101**	.020	<.001
BMI	.309**			.409**			.013		
Step 2		.001	.31		.002	.06		.049	<.001
CES-D	.016			.015*			–		
JDC	-.034			-.051			.225**		
IL-6	–			–			.012		
CRP	–			–			.013		

Note. IL-6 Total model *R*² = 0.102 *F* (4, 1924) = 54.637, *p* < .001, CRP Total model *R*² = 0.170, *F* (4, 1924) = 99.543, *p* < .001, CES-D Total model *R*² = 0.069, *F* (5, 1923) = 28.427, *p* < .001.

CES-D = Centre for Epidemiological Depression scale; JD = Job demand; JC = Job control; JDC = Job demand control ratio; CRP = C-reactive protein; IL-6 = interleukin-6, The ‘Step Summary’ denotes the variance explained (*R*²) by the addition of the set of variables within each step, ***p* < .01, **p* < .05.

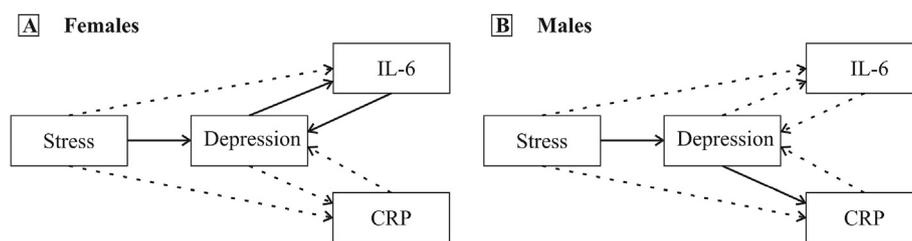


Fig. 2. A summary of regression findings for males and females after controlling for all listed variables and age and body mass index. Note. Solid lines signify significant associations, broken lines depict non-significant associations.

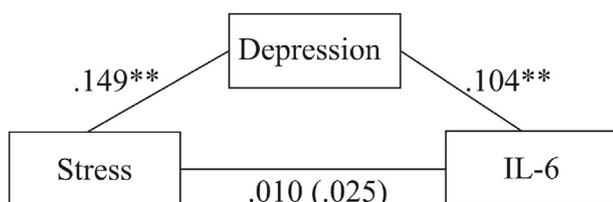


Fig. 3. Depression mediates the relationship between workplace stress and interleukin 6 for females.

Note. Numbers refer to the Beta statistic. Numbers in parentheses depict the Beta value when depression scores are not entered as a covariate and illustrates the 60% drop in association when depression is entered in the model.

CES-D measure. While the CES-D is a well-validated measure for depressive symptoms (Vilagut et al., 2016), it may better capture generalised depressive symptoms attributed to various social and cultural ‘norms’ in females but not males (Carleton et al., 2013; Cole et al., 2000; Stommel et al., 1993). As such, use of the CES-D may provide a biased assessment of depressive symptomatology in males and females, as certain affective responses may not be a viable indicator of depression severity whereas a lack thereof might not indicate an absence of depression (Carleton et al., 2013). In the present study, not only was the mean score on CES-D higher for females, but the proportion considered as ‘at risk for clinical depression’ (i.e., scores >16 (Radloff, 1977)); was also higher. The impact of gender bias of the CES-D is less of an issue in the current study however, as females in this sample were considered in separate regression analyses to males, but nevertheless, the lack of association between variables for males, may be due to poorer sensitivity of the

CES-D measure with men.

Although the mediation analysis was not a primary aim of this research, a two or three wave design would have been more appropriate to investigate the paths between workplace stress, depression, and inflammation. However, previous Whitehall II research has suggested that a lack of association between depressive symptoms and inflammation at follow-up may be due to the time between clinical phases (5-years) being too great to make causal connections between constructs (Gimeno et al., 2009). Nevertheless, while the cross-sectional mediation analysis showed that depressive symptoms mediate the link between workplace stress and IL-6 levels, it is not possible to infer causality between the three variables of interest due to the cross-sectional nature of the present study. A prospective design that uses a shorter follow-up time is required to better understand the direction of the relationship between variables.

Understanding the pathway from stress to ill health is complex. In this study, we focussed on the interplay of workplace stress with depressive symptomatology and inflammation. Our findings indicate that females appear to be more at risk of both depression and inflammation than males, and that it is high depressive symptomatology rather than high workplace stress exposure that is related to greater inflammation. The females in this cohort reported lower job control than males, but before interventions can be used to identify if increasing work control for females with high depressive symptomatology is appropriate, a replication of our work with a more proximal follow-up phase is required. To that end, we believe that the data captured from this large sample of concurrent measurements of workplace stress, depression and serum IL-6 concentrations for the first time, provides preliminary evidence for the theory posited by the transactional model of stress and coping (Folkman and Lazarus, 1984), with greater depression symptomatology more associated with high IL-6 levels than workplace stress.

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Declaration of competing interest

Declarations of interest: none.

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