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The mediating role of interpersonal conflict at work in the relationship between negative affectivity and biomarkers of stress

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Abstract This study examined the association between interpersonal conflict at work (ICW) and serum levels of three possible biomarkers of stress, namely the pro-inflammatory cytokines Interleukin 1 beta (IL-1β), Interleukin 12 (IL-12), and Interleukin 17 (IL-17). Additionally, this study investigated the role of negative affectivity (NA) in the relationship between ICW and the pro-inflammatory cytokines. Data from 121 employees in an Italian healthcare organization were analyzed using structural equation modeling. Results showed that ICW was positively associated with IL-1β, IL-12, and IL-17, after controlling for the effect of gender. Moreover, ICW completely mediated the relationship between NA and the pro-inflammatory cytokines IL-1β, IL-12, and IL-17. This mediating effect was significant after controlling for the effect of gender. Overall, this study suggests that work-related stress may be associated with biomarkers of inflammation, and that negative affectivity may influence the stress process affecting the exposure to psychosocial stressors.

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Introduction

Work-related stress may be defined as the process by which perceived characteristics of the work environment (i.e., job stressors) trigger psychological, physiological, physical and behavioral responses in the individual (i.e., psychophysical strain; Ganster & Rosen, 2013; Nixon et al., 2011). Individual characteristics, such as negative affectivity (NA), may influence the relationship between stressors and strain, affecting the way people expose themselves to stressors, appraise potentially threatening work characteristics, cope with stressful situations, and develop strain responses (Bolger & Zuckerman, 1995; Eaton & Bradley, 2008; Spector et al., 2000b).

According to some authors, inflammation and inflammatory mediators, such as pro-inflammatory cytokines, may be considered as biomarker of psychosocial stress (Hänsel et al., 2010). Increasing evidence implicates pro-inflammatory cytokines in neuropsychiatric illnesses that arise following prolonged stress and typically include symptoms such as anhedonia, anxiety-like behaviors, fatigue and somatic symptoms and mild cognitive impairment (Leonard & Maes, 2012). Pro-inflammatory cytokines are known to modulate neuronal plasticity and affect neurotransmission within the circuits of emotion in the central nervous system (Arnsten, 2009; Singhal et al., 2014). In particular, Interleukin 1 beta (IL-1β) has been proposed as a key mediator in a variety of behavioral actions of stress. It has been associated with depression, a disorder that has frequently been linked to work-related stress (see Ganster

& Rosen, 2013, for a review), and is considered a new drug target for treating stress-induced depression (Howren et al., 2009; Koo & Duman, 2009; Kubera et al., 2011). Previous studies found a positive association between IL-1β and both acute and chronic stress in humans, including work-related stress (Ramey et al., 2012; Steptoe et al., 2007; Yoon et al., 2014). Interestingly, IL-1β seems to play a central role in Th17 cell differentiation, a novel pathway associated with stress-related responses (Acosta-Rodriguez et al., 2007). Moreover, Interleukin 17 (IL-17) has recently attracted interest as a new modulator of Th17-mediated pro-inflammatory pathway that is also involved in stress-related behavior (Hong et al., 2013; Steinman, 2007). Additionally, both circulating levels of Th17 cells and serum levels of IL-17 were higher in depressed patients (Chen et al., 2011). Finally, IL-17 activity contributes to both acute and chronic inflammation (Miossec & Kolls, 2012). Interleukin 12 (IL-12) is a major pro-inflammatory cytokine that is involved in the differentiation of naive T cells into Th1 cells and in cell-mediated immune response (Hsieh et al., 1993). Higher levels of IL-12 were found in workers experiencing psychological stress and in patients with depression (Kim et al., 2002; Lee & Kim, 2006; Ricci et al., 2013). Additionally, decreased levels of IL-12 were observed in depressed patients treated with antidepressant drugs (Kim et al., 2002; Lee & Kim, 2006).

Other inflammatory factors have been proposed as serum biomarkers of various types of chronic stress, including psychosocial stress and burnout, in particular C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and Interleukin 6 (IL-6; Segerstrom & Miller, 2004; Hänsel et al., 2010; Johnson et al., 2013). CRP expression in peripheral monocytes and other cell types is induced by IL-1β and IL-6 and therefore the relative levels of these factors largely correlate (Haider et al., 2006). On the other hand, the data concerning the association of IL-6 and TNF-α serum levels with chronic job stress are mixed (Segerstrom & Miller, 2004; Copertaro et al., 2011). Accordingly, we decided to omit CRP, TNF-α and IL-6 from our study.

Therefore, the aims of the present study are twofold. The first is to examine whether interpersonal conflict at work (ICW) is associated with higher serum levels of three possible biomarkers of stress, namely the pro-inflammatory cytokines IL-1β, IL-12, and IL-17. The second aim is to investigate the role of negative affectivity in the relationship between interpersonal conflict at work and the strain response. Given the results of previous studies, we propose a theoretical model in which negative affectivity affects exposure to interpersonal conflict at work, which, in turn, is associated with biomarkers of stress (i.e., ICW mediates the relationship between NA and biomarkers of stress; Falco et al., 2013b; Girardi et al., 2011).

The Allostatic Load (AL) model (Juster et al., 2010; Ganster & Rosen, 2013) provides theoretical support for a possible role of pro-inflammatory cytokines (i.e., IL-1β, IL-12, and IL-17) as three biomarkers of work-related stress. According to the AL model, actual or anticipated exposure to a job stressor (e.g., a dispute with a colleague) elicits physiological reactions, such as the activation of the sympathetic-adrenal-medullary (SAM) system, and hypothalamic–pituitary–adrenal (HPA) axis. This adaptation process involves stimulation of primary mediators, which are stress hormones and their antagonists (e.g., epinephrine, norepinephrine, and cortisol) in conjunction with pro/anti-inflammatory cytokines (e.g., IL-1β, TNFα; Ganster & Rosen, 2013; Juster et al., 2010; Slavich & Irwin, 2014). These physiological reactions are usually short-lived, that is, when exposure to job stressor decreases, acute physiological reactions decrease within a certain period of time. However, when an individual faces chronic or repeated job stressors, primary mediators are activated chronically or repeatedly. At this stage, secondary mediators, which involve metabolic (e.g., insulin, glucose), cardiovascular (e.g., blood pressure), and immune systems (e.g., CRP), may reach sub-clinical perturbation. If this dysregulation persists over time, allostatic overload may occur, which is characterized by physical (e.g., cardiovascular disease) or psychological (e.g., depression) diseases (Ganster & Rosen, 2013; Juster et al., 2010).

Recovery (i.e., a process of psychophysiological unwinding through which the activation associated with the experience of stressor at work is restored to its baseline level) may play a central role in the transition from acute, short-lived physiological reactions associated with the exposure to job stressors to chronic physiological activation (Geurts & Sonnentag, 2006).

According to some authors, the association between stressors and biomarkers of stress related to inflammation seems to be stronger for stressors which involve social conflict, rejection, or exclusion, such as interpersonal conflict at work (Slavich & Irwin, 2014). ICW is a form of social stressor that refers to negative interactions with others in the workplace. These negative interactions can range from minor disagreements between coworkers and supervisors to heated arguments or assaults on others (Meier et al., 2014; Nixon et al., 2011; Spector & Jex, 1998). Several studies showed an association between interpersonal conflict at work and both psychological (e.g., depression, anxiety, emotional exhaustion) and physical strain (e.g., somatic complaints such as backache, headache and gastrointestinal problems; Meier et al., 2014; Nixon et al., 2011; Spector & Bruk-Lee, 2008; Spector & Jex, 1998).

From a theoretical point of view, this relationship may be explained in the light of the "need to belong" theory

(Baumeister & Leary, 1995), according to which individuals have a pervasive drive to create and maintain a minimum number of lasting, positive, and significant interpersonal relationships. The experience of interpersonal conflict at work may threaten the fundamental need of belonging to significant groups, thus triggering negative emotions (e.g., anger, anxiety, irritation, fear, and frustration; Ilies et al., 2011; Meier et al., 2013; Spector & Bruk-Lee, 2008), and perseverative cognitions (i.e., repeated or chronic activation of the cognitive representation of a psychological stressor, Brosschot et al., 2006), such as worry and rumination. Negative emotions and perseverative cognitions may spill over into the private life of the worker and impair the recovery process (Ilies et al., 2011; Geurts & Sonnentag, 2006; Sonnentag et al., 2008). This may in turn lead to a state of sustained psychophysiological activation, which, according to the AL model, is considered an important factor in the development of future diseases (Geurts & Sonnentag, 2006; Juster et al., 2010). Therefore, we hypothesize a positive association between interpersonal conflict at work and biomarkers of stress (Hypothesis 1).

H1a interpersonal conflict at work is positively associated with IL-1β;

H1b interpersonal conflict at work is positively associated with IL-12;

H1c interpersonal conflict at work is positively associated with IL-17.

Negative affectivity is conceptualized as a stable personality trait that reflects pervasive individual differences in the conception of the self and the tendency to experience aversive emotional states (Watson & Clark, 1984; Watson & Pennebaker, 1989). Individuals high in NA tend to experience subjective feelings of nervousness, tension, worry, fear, anxiety, and guilt. They also tend to be distressed, self-dissatisfied, and to have a negative self-concept, focusing on their failure and shortcomings. High-NA individuals are also inclined to concentrate on the negative aspects of others and of the world in general, perceiving their surrounding environment as hostile and threatening (Spector et al., 2000b; Watson & Clark, 1984; Watson & Pennebaker, 1989). NA may influence in several ways the relationship between psychosocial stressors, such as ICW, and psychophysical strain. According to some previous studies, high-NA individuals may report higher levels of both interpersonal conflict at work and psychophysical strain, such as, for example, psychosomatic complaints (i.e., NA may act as a confounding variable in the relationship between ICW and strain; Brief et al., 1988; Burke et al., 1993). Therefore, NA accounts for the relationship between ICW and strain, and this relationship should disappear (or, at least, substantially decrease) when the effect of NA is controlled for (Burke et al., 1993; Watson & Pennebaker, 1989).

However, according to more recent studies, negative affectivity may positively affect exposure to interpersonal conflict at work, which, in turn, may lead to psychophysical strain (i.e., NA may substantively influence the relationship between ICW and strain; see the differential exposure model, Bolger & Zuckerman, 1995, or the stressor creation mechanism, Spector et al., 2000b). For example, high-NA individuals may be involved in conflicts with others more often, since they are nervous, irritable and inclined to see the world negatively (Spector et al., 2000b). Additionally, high-NA individuals may perceive ambiguous social interactions with others as threatening (i.e., hyper vigilance; Aquino et al., 1999), and they may also have worse overall job performance because of affect regulation (Beal et al., 2005). Overall, this may lead to negative reactions from supervisors and colleagues and, consequently, to higher ICW. Therefore, negative affectivity may have a positive indirect effect on psychophysical strain through interpersonal conflict at work (i.e., ICW mediates the relationship between NA and psychophysical strain; Falco et al., 2013b; Girardi et al., 2011). Accordingly, we hypothesize that negative affectivity has a positive indirect effect on biomarkers of stress (Hypothesis 2).

H2a NA has a positive indirect effect on IL-1β through ICW;

H2b NA has a positive indirect effect on IL-12 through ICW;

H2c NA has a positive indirect effect on IL-17 through ICW.

Finally, previous studies suggest that the relationship between NA, psychosocial stressors and psychophysical strain may be confounded, at least partly, by gender (Jex et al., 2002). Indeed, some studies showed an association between gender and negative affectivity, with females reporting higher levels of NA and experiencing more negative emotions (Jex et al., 2002; Parkes, 1990). Additionally, compared to men, women may experience higher levels of psychosocial stressors, such as interpersonal conflict, engage more frequently in emotion-focused coping strategies, and also experience higher levels of strain (Eaton & Bradley, 2008; Parkes, 1990, Spector & Bruk-Lee, 2008; Spector & Jex, 1998). Furthermore, some studies showed gender differences in the production of pro-inflammatory cytokines in response to stressful events and also in glucorticoid sensitivity (Prather et al., 2009; Rohleder et al., 2001). Therefore, in order to rule out the possibility that the relationship between NA, interpersonal

conflict at work and pro-inflammatory cytokines is confounded by gender, we controlled for the effect of gender in all the models tested (Jex et al., 2002).

Methods

Participants and procedure

The study was performed examining a sample of workers in an Italian healthcare organization. Workers were informed beforehand by the management and participated voluntarily in the investigation of work-related stress. Recruitment was carried out by research team members, who also performed the clinical interview using a health questionnaire. Workers completed a self-report questionnaire aimed at determining negative affectivity and interpersonal conflict at work. The questionnaire was completed by 121 subjects who agreed to a clinical interview followed by a blood test. Blood samples were collected in the morning, between 9:00 a.m. and 11:30 a.m. and were associated to the identification code attributed to each subject who carried out the self-report questionnaire and the clinical interview.

Subjects reporting mood or anxiety disorders, neuroendocrine diseases, drug abuse or dependence, according to DSM-IV-TR criteria, were excluded from the investigation. Therefore, the final study sample comprised 121 workers, of whom 71.9 % were women, with a mean age of 45.21 years ($SD = 9.11$). For the work position, 16.7 % were managers-doctors, 63.3 % were doctors or head nurses, 20 % were nurses. Most respondents had a permanent contract (95.9 %). All participants gave their written, informed consent, and the study was approved by the local ethics committee according to the recommendations of the declaration of Helsinki.

Measures

Interpersonal conflict at work

Interpersonal conflict at work was determined using three items taken from the Q-Bo test, an instrument standardized for the Italian context (De Carlo et al., 2008). The six point response scale ranged from 1 (*strongly disagree*) to 6 (*strongly agree*). Cronbach's alpha in our study was .81.

Negative affectivity

Negative affectivity was determined using the Italian version of the Strain-Free Negative Affectivity Scale (Fortunato et al., 1999; see also Falco et al., 2013b), a 9-item scale with responses ranging from 1 (*strongly disagree*) to 6 (*strongly agree*). Cronbach's alpha in our study was .74.

Biochemical assessments

Blood samples were collected using standard venipuncture technique. In brief, five milliliters of anticoagulant-free blood were drawn between 9:00 a.m. and 11:30 a.m. by venipuncture from each subject on the day of the clinical interview (Carlino et al., 2011). Serum was obtained by centrifugation at $3000 \times g$ for 5 min and then kept frozen at −80 °C until the assay (i.e., 6 months later). Serum cytokines, IL-1β, IL-12 and IL-17 levels were measured using the Bio-Plex Pro Human xMAP Assay (Bio-Rad Laboratories Srl, Milan, Italy) and read on a Bio-Plex 200 instrument, as previously described (Comar et al., 2014).

Data analysis

The hypothesized relationships were tested using structural equation modeling with latent variables. We used the software LISREL 8.8 (Jöreskog & Sörbom, 2006). Overall, nine different models were estimated. These models are presented graphically in Fig. 1. In order to test Hypothesis 1a, a baseline model was estimated (Model 1a), in which IL-1β was regressed on interpersonal conflict at work. Moreover, in order to investigate the role of negative affectivity in the relationship between ICW and IL-1β (Hypothesis 2a), a partial mediation model was estimated (Model 2a). In this model, the direct effects of NA on both ICW and IL-1β, as well as the direct effect of ICW on IL-1β, were freely estimated. Furthermore, a complete mediation model (Model 3a) was also estimated, in which the direct effect of NA on IL-1β, controlling for the effect of ICW, was fixed to zero. The same models were also estimated considering IL-12 (Model 1b, 2b, 3b) and IL-17 (Model 1c, 2c, 3c) as the dependent variable. Finally, in our models we also controlled for the effect of gender, which was modeled as an additional exogenous variable.

With regard to the measurement component of the structural regression models, the three items of the interpersonal conflict at work scale were used as indicators of ICW, while for NA, parcels of scale items were created (Little et al., 2013). IL-1β (for Model 1a to Model 3a), IL-12 (for Model 1b to 3b), IL-17 (for Model 1c to 3c) and gender were measured by a single indicator. Factor loading was fixed at one, while error variance was fixed at zero (Brown, 2006). Since most of the variables were not normally distributed, the robust maximum likelihood method was used as the estimation method. In order to evaluate model fit, the scaled Satorra–Bentler Chi square test ($SB\chi^2$) was used. A model shows a good fit to data if the Chi

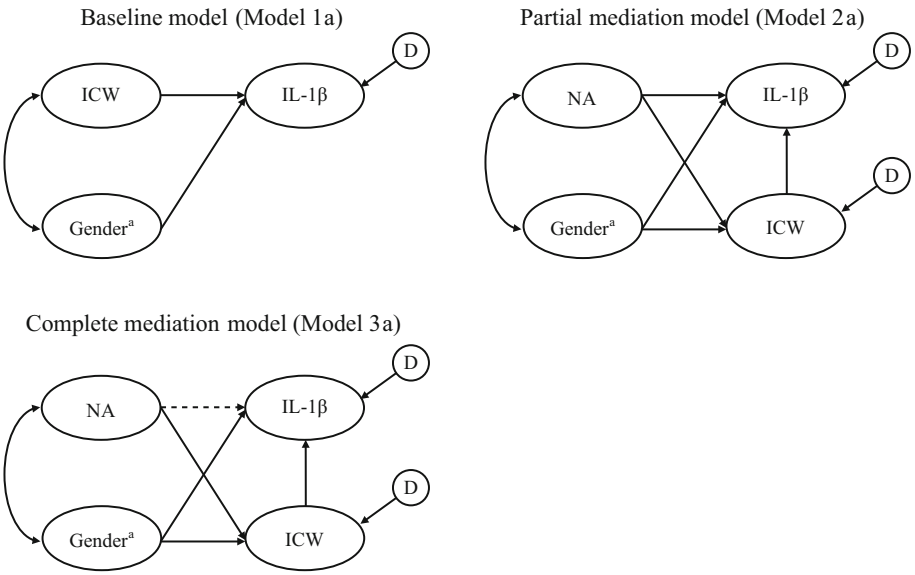

Fig. 1 The three structural models tested in the study. *Note* Measurement model was omitted for clarity. *Dashed lines* represent paths fixed to zero. *D* represents the disturbance variance for each endogenous variable. The same models are also estimated with IL-12 and IL-17 as the dependent variable. Those are Model 1b, 2b, and 3b for IL-12, and Model 1c, 2c, and 3c for IL-17. [a]0 = female; 1 = male

square test is non-significant. Three additional fit indices were used: the root-mean-square error of approximation (RMSEA), the comparative fit index (CFI), and the standardized root mean square residual (SRMR). For RMSEA and SRMR, values close to or smaller than .08 indicate an acceptable fit. For CFI, values close to or greater than .95 indicate an acceptable fit (Brown, 2006). In order to test the significance of the indirect effect of NA on the pro-inflammatory cytokines (i.e., mediation), we computed 95 % asymmetric confidence intervals for the indirect effect based on the distribution of product method using the RMediation package (Tofighi & MacKinnon, 2011). Before analysing data, missing values were estimated using the Expectation–Maximization algorithm (LISREL 8.8; Jöreskog and Sörbom, 2006). The null hypothesis was rejected when $p < .05$.

Results

Descriptive statistics and correlations between latent variables are reported in Table 1. First, in order to test Hypothesis 1, three structural regression models (Model 1a, 1b, and 1c) with latent variables were estimated. The fit indices (Table 2) showed an acceptable fit to the data for Model 1a, $SB\chi^2_{M1a}(4) = 2.649$, $p = .618$, Model 1b, $SB\chi^2_{M1b}(4) = 7.407$, $p = .116$, and Model 1c, $SB\chi^2_{M1c}(4) = 1.881$, $p = .758$. In Model 1a, interpersonal conflict at work was positively associated with IL-1β ($\gamma = .170$, $p = .017$). Additionally, ICW was positively associated with IL-12 in Model 1b ($\gamma = .247$, $p = .031$), as well as with IL-17 in Model 1c ($\gamma = .224$, $p = .027$). These associations were significant, after controlling for the effect of gender. Overall, Hypothesis 1 was supported.

In order to investigate the role of negative affectivity in the relationship between ICW and pro-inflammatory cytokines (Hypothesis 2), three partial mediation models were estimated. The fit indices (Table 2) showed an acceptable fit to the data for Model 2a, $SB\chi^2_{M2a}(16) = 14.943$, $p = .529$, Model 2b, $SB\chi^2_{M2b}(16) = 19.933$, $p = .223$, and Model 2c, $SB\chi^2_{M2c}(16) = 16.804$, $p = .398$. In Model 2a, negative affectivity was positively associated with interpersonal conflict at work ($\gamma = .337$, $p = .017$), which, in turn, was positively associated with IL-1β, controlling for both NA and gender ($\beta = .218$, $p = .004$). Moreover, in Model 2b, NA was positively associated with ICW ($\gamma = .341$, $p = .018$). Additionally, ICW was positively associated with IL-12, controlling for both NA and gender ($\beta = .310$, $p = .024$). Finally, in Model 2c, NA was positively associated with ICW ($\gamma = .342$, $p = .017$), which, in turn, was positively associated with IL-17, controlling for both NA and gender ($\beta = .256$, $p = .023$). Since the 95 % asymmetric confidence intervals for IL-1β (95 % CI .011–.268), IL-12 (95 % CI .304–35.685), and IL-17 (95 % CI .218–18.506) do not contain zero, the indirect effect of NA on the pro-inflammatory cytokines through ICW was significant. Overall, Hypothesis 2 was supported.

Finally, three complete mediation models were estimated (Model 3a, 3b, and 3c). Since the complete mediation model is nested within the partial mediation model, the relative fit of each of the complete mediation models (Model 3a/3b/3c) was compared to that of its respective partial mediation model (Model 2a/2b/2c) using the Satorra–Bentler scaled difference Chi square (Bryant & Satorra, 2012). If the difference Chi square is non-significant, the complete mediation model is supported, since it fits the data as well as the partial mediation model. For IL-

Table 1 Means, standard deviations, and correlations between variables

	M	*SD*	1	2	3	4	5
1. IL-1β (pg/ml)	1.503	1.033	–				
2. IL-12 (pg/ml)	50.429	87.323	.191**	–			
3. IL-17 (pg/ml)	58.875	55.540	.037	.061	–		
4. Interpersonal conflict	2.984	1.177	.159*	.252*	.230*	–	
5. Negative affectivity	3.808	.613	−.133	−.157	−.041	.327**	–

$N = 121$

* $p < .05$; ** $p < .01$

1β, the complete mediation model (Model 3a) showed a fit which is not different from that of the partial mediation model (Model 2a): $\Delta SB\chi^2(1) = 2.893$, $p = .089$. Therefore, the complete mediation model (Model 3a) is supported. Similar results occurred for both IL-12, $\Delta SB\chi^2(1) = 2.879$, $p = .090$, and IL-17, $\Delta SB\chi^2(1) = 1.164$, $p = .281$. Therefore, the complete mediation model is supported for both IL-12 (Model 3b), and IL-17 (Model 3c). Overall, these results suggest that interpersonal conflict at work completely mediates the relationship between NA and the pro-inflammatory cytokines, after controlling for the effect of gender.

Discussion

The present study provides initial support for the hypothesis that interpersonal conflict at work is associated with three possible biomarkers of stress, namely the pro-inflammatory cytokines Interleukin 1 beta, Interleukin 12, and Interleukin 17. Indeed, results showed a positive association between interpersonal conflict at work and IL-1β, IL-12, and IL-17, after controlling for the effect of gender. Additionally, results from this study suggest that negative affectivity may affect exposure to interpersonal conflict at work, which, in turn, is associated with biomarkers of stress. Indeed, results showed that interpersonal conflict at work completely mediates the relationship between negative affectivity and IL-1β, IL-12, and IL-17, after controlling for the effect of gender.

Our study makes several contributions to the literature. First of all, our study highlights the fact that exposure to stressful situations at work (i.e., job stressors) is associated with three possible biomarkers of stress in the individual (i.e., the pro-inflammatory cytokines IL-1β, IL-12, and IL-17). These results are in line with what was hypothesized by the Allostatic Load model and provide initial empirical support for the role of inflammation in the strain response and in the transition between acute strain response and chronic ill health (Ganster & Rosen, 2013; Hänsel et al., 2010; Hickman et al., 2014; Juster et al., 2010). Moreover, although several previous studies highlighted the role of IL-1β in the stress process (Steptoe et al., 2007; Yoon et al., 2014), results concerning the relationship between

Table 2 Comparison of relative fit for the models tested

	$SB\chi^2$	*df*	*p*	RMSEA	CFI	SRMR
Interleukin 1β						
Model 1a (baseline)	2.649	4	.62	0	1	.023
Model 2a (partial mediation)	14.943	16	.53	0	1	.055
Model 3a (complete mediation)	17.192	17	.44	.010	.999	.060
Interleukin 12						
Model 1b (baseline)	7.407	4	.12	.084	.974	.042
Model 2b (partial mediation)	19.933	16	.22	.045	.986	.060
Model 3b (complete mediation)	22.594	17	.16	.052	.980	.068
Interleukin 17						
Model 1c (baseline)	1.881	4	.76	0	1	.019
Model 2c (partial mediation)	16.804	16	.40	.021	.997	.060
Model 3c (complete mediation)	17.758	17	.40	.019	.997	.064

SBχ^2 Satorra–Bentler χ^2, *df* degrees of freedom, *RMSEA* root mean square error of approximation, *CFI* comparative fit index, *SRMR* standardized root mean square residual

interpersonal conflict at work and pro-inflammatory cytokines such as IL-12 and IL-17 are new and also worthy of further investigation.

Additionally, our findings suggest that negative affectivity may play a substantive role (rather than a confounding one) in the stress process. Indeed, negative affectivity seems to affect only indirectly, i.e., through interpersonal conflict at work, the pro-inflammatory cytokines IL-1β, IL-12, and IL-17. These results are in line with the differential exposure model (Bolger & Zuckerman, 1995; see also the stressor creation mechanism, Spector et al., 2000b), according to which individual differences influence the exposure to job stressors that, in turn, lead to psychophysical strain. Interestingly, in the present study stressor and the strain response were measured using different measurement methods, namely a self-report questionnaire for ICW and physiological measures (i.e., biomarkers) for the strain response. Therefore, we expect that the observed association between stressor and strain is not affected by common method bias (i.e., the inflation or deflation of observed relationship due to shared method variance; Podsakoff et al., 2012). This may occur when both stressors and strain are determined using the same measurement method (e.g., self-report).

Finally, the present study shows that the relationship between negative affectivity, interpersonal conflict at work and pro-inflammatory cytokines does not depend on gender. This is an interesting finding, since gender has mostly been ignored in studies on the relationship between negative affectivity and occupational stress (with some exceptions, see for example Parkes, 1990), although some evidence exists for gender differences in the stress process (Eaton & Bradley, 2008; Jex et al., 2002; Prather et al., 2009).

Our study has some limitations. Firstly, negative affectivity, interpersonal conflict at work and strain response are measured at the same time in our study. Therefore, our research design did not allow for causal inferences. Although we assumed that NA influences interpersonal conflict which, in turn, is related to strain response (i.e., pro-inflammatory cytokines), it is also possible that people in poor health (i.e., with high levels of pro-inflammatory cytokines) tend to assess their work environment and their interpersonal relationship more negatively (i.e., higher levels of ICW) which, in turn, increases NA in individuals (i.e., causality mechanism; see Spector et al., 2000b). Although these two models are equivalent from a statistical standpoint (Brown, 2006), the directionality of the model proposed in this study seems consistent with previous research, from both a theoretical and empirical point of view. First, negative affectivity is defined as a stable personality trait that is only weakly affected by environmental variables, such as job stressors (Oliver et al., 2010; Spector et al., 2000a). Additionally, Oliver et al. (2010) found in a longitudinal study that NA predicts work stressors over time, but work stressors do not predict NA over time. Finally, interpersonal conflict at work has been associated with both negative affective reactions in diary studies (Ilies et al., 2011; Meier et al., 2013) and with psychophysical strain in longitudinal studies (Falco et al., 2013b; Nixon et al., 2011). Overall, although more research is needed in order to examine the relationship between NA, ICW, and pro-inflammatory cytokines, the complete mediation model seems therefore consistent with current theories and evidence.

A second limitation concerns the role of possible confounders in the relationship between NA, ICW, and the strain response. Although structural equation models were estimated controlling for the effect of a possible confounder such as gender (Jex et al., 2002), it is also possible that the transitory mood of the respondents (i.e., the mood mechanism; Spector et al., 2000b) or other individual characteristics, such as workaholism (i.e., the tendency to work beyond what is reasonably expected because of internal pressures and to have persistent thoughts about work when not working, Clark et al., 2014), may confound the relationship between NA, stressors and pro-inflammatory cytokines (Clark et al., 2014; Falco et al., 2013a; Falvo et al., 2013; Kravina et al., 2010, 2014). A future diary study could clarify the unique contribution of NA, transitory mood and workaholism in the relationship between stressors and the strain response.

Moreover, our study was conducted in a single healthcare organization and the sample was relatively small. This may pose problems for the generalization of the results, in particular with regard to the physiological measures. Indeed, some previous studies showed that plasma levels of IL-12 are down-regulated in response to acute and chronic behavioral stress in rats (Shaashua et al., 2012). Additionally, confidence intervals for the indirect effects of negative affectivity on pro-inflammatory cytokines were wide, suggesting that these effects might not be easily replicated (MacKinnon, 2008). Therefore, caution is warranted in drawing conclusions about the mediating role of ICW in the relationship between NA and biomarkers of stress. However, it must be noted that although the small sample size may have led to a somewhat reduced statistical power, all the hypothesized relationships were significant and in the expected direction. Overall, further research is recommended to replicate and extend the results presented in this study.

Furthermore, although immune factors have diurnal rhythms, we neither measured nor controlled for the effect of time of waking. However, time of waking should not be a concern in our study, since participants were all medical staff working during the same day shift.

Finally, although NA may influence the exposure to ICW, it is also possible that high-NA individuals perceive interpersonal events as conflictual more often (i.e., perception mechanism; Spector et al., 2000b). Even though previous studies suggest that self-reported conflicts substantially reflect the actual occurrence of conflicts for both low- and high-NA individuals (Bolger & Schilling, 1991), a future study could address this possible issue, combining for example both self- and supervisor-rating of ICW.

The present study also has several practical implications. Managers and supervisors should prevent ICW by creating a climate of trust and cooperation, in which employees can disagree about the content of the task being performed (i.e., task conflict) without disagreement over personal issues that are not task-related (i.e., relationship conflict; Meier et al., 2013). Indeed, task conflict may have less negative consequences on a worker's well-being than relationship conflict (Meier et al., 2013). In this perspective, once people disagree, supervisors may promote confrontation aimed at resolving a specific problem and discourage attacks related to the person. Additionally, occupational psychologists or psychotherapists could implement cognitive-behavioral interventions (CBI), in order to give employees the opportunity to recognize (e.g., through teaching or case studies) that negative emotions and irrational beliefs at work may elicit interpersonal conflict. Moreover, employees could learn (e.g., through group discussion or role playing) how to cope with their negative emotions (e.g., avoid rumination), and how to generate positive interpretations (e.g., reappraisal) of social interactions (Aldao & Nolen-Hoeksema, 2010; Dal Corso et al., 2013).

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Compliance with Ethical Standards

Conflict of interest Damiano Girardi, Alessandra Falco, Alessandro De Carlo, Paula Benevene, Manola Comar, Enrico Tongiorgi and Giovanni Battista Bartolucci declare that they have no conflict of interest.

Human and animal rights and Informed consent All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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