Within subject rise in serum TNFα to IL-10 ratio is associated with poorer attention, decision-making and working memory in jockeys

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A B S T R A C T

Jockeys work in high-risk environments that rely heavily on attention- and decision-making to perform well and safely. Workplace stress literature has often overlooked the impact of stress on cognition, and designs that include physiological measures are rare. This study assessed the prospective concurrent relationships between workplace stress, depression symptoms and low-grade inflammation with cognitive performance among professional jockeys. Professional jockeys ($N = 35$, $M_{age} = 32.29$) provided information on workplace stress and depression symptoms, with serum levels of inflammatory cytokines (IL-6, IL-10, TNFα) and cytokine balance (IL-6: IL-10, TNFα: IL-10) quantified with SIMOA, and cognitive performance with CogSport computer-based testing battery. These measures were repeated after a twelve-month interval. Increased workplace stress between testing intervals was associated to an increased cytokine imbalance ($\beta = 0.447$, $p = .015$) after controlling for age and gender. Increases in cytokine imbalance occurred in unison with decreases in attention ($\beta = 0.516$, $p = .002$), decision-making ($\beta = 0.452$, $p = .009$) and working memory ($\beta = 0.492$, $p = .004$). These preliminary findings suggest the underlying mechanisms linking workplace stress and reduced cognitive performance may be influenced by measures of low-grade inflammation and specifically a cytokine imbalance. Our findings suggest a measure of cytokine balance may explain the heterogenous findings in previous studies that have focussed solely on the association of workplace stress with pro-inflammatory cytokines. Future work is needed however, to provide a broader evidence-base for our claims to better inform designs to intervene in the higher workplace stress-poorer cognition relationship.

1. Introduction

Professional jockeys have consistently reported high levels of workplace stress [19,21,22] and negative affect (e.g., depressive symptoms, anxiety) [19,22,25] and based on fatality rates at work, behind off-shore fisherman, they have the second most dangerous jobs in the world [4]. Prospective research with jockeys has shown that increases in workplace stress are associated with decreases in visual attention (specifically simple and choice reaction time) [21]; this is unwelcome news for a highly stressful occupation where deficits in attention can have dire consequences. Our review of depression

literature focussed on non-clinical samples with several reviews revealing that workplace stress [33,48] and depression symptoms [6,14] are associated with low-grade inflammation, and these three constructs have been associated with poorer cognition [31]. Despite evidence of individual associations between workplace stress, depression symptoms, low-grade inflammation and cognition [31], these factors have not been assessed concurrently in a single study.

1.1. Workplace stress, depression, and low-grade inflammation

Low-grade inflammation is defined as inflammation that is not the

result of acute injury or infection [37]. It is generally measured with a focus on pro-inflammatory cytokines as reported in reviews and meta-analyses of both cross-sectional [9,33] and prospective [15] studies of workplace stress and inflammatory markers. The complex network of both pro- (e.g., interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α)) and anti-inflammatory (e.g., interleukin 4 (IL-4) and interleukin 10 (IL-10)) cytokines may explain the pathogenesis of depression and other disease states [5]. Despite this evidence, the consideration of anti-inflammatory cytokine concentrations (i.e., IL-4, IL-10) in this research remains sparse [7,13]. Recently, some studies have considered the effect of workplace stress on pro-to anti-inflammatory cytokine ratios (i.e., IL-6: IL-10, TNF-a: IL-10 ratio), with abnormally high or low ratios defined as a 'cytokine imbalance' [2,17, 46,48].

Pro-inflammatory dominance is linked to the development of psychiatric disorders [16,16], cardiovascular disease [10], and cancer [23]. Given the high individual variability in basal cytokine levels [14,45], a measure of cytokine balance is likely better equipped to assess between and within-subject comparisons [5]. A consideration of cytokine balance alongside individual pro-inflammatory marker concentrations provides a more comprehensive analysis of the stress-depression-inflammation pathway and enables a comparison of the sensitivity of the inflammatory outcome measures [5]. Despite this, very little empirical work has investigated relationships between workplace stress, depression symptoms, and low-grade inflammation when this is defined in terms of a pro-inflammatory dominance. Understanding the association of workplace stress and depression symptomology with low grade inflammation can also assist in understanding how these factors impact cognitive function.

1.2. Workplace stress, depression symptoms, low-grade inflammation, and cognition

Much work has shown that chronic stress and higher circulating glucocorticoids are associated with poorer memory [39,41], while decreased cognition is a common symptom of depression [35]. Chronic workplace stress is related to decreased attention and decision-making in jockeys [21]. In the [21] study, the magnitude of the deficits in cognition between stressed and non-stressed jockeys was greater than the difference between participants at 0.00% and 0.05% blood alcohol concentration in a separate study that assessed the same cognitive outcomes [29]. The impact of chronic stress on poorer attention [21] and memory [40,41] is likely driven by increased HPA axis activation as increases in HPA-axis activation precipitate a pro-inflammatory response [3]. To date however, the role of low-grade inflammation in the association between workplace stress and depression symptoms with cognition has largely been overlooked.

1.3. Present investigation

This study concurrently assessed workplace stress, depression symptoms, blood markers of inflammation (IL-6, TNF-α, IL-10) and a cytokine balance (IL-6: Il-10, TNFα: IL-10) with cognition in a prospective sample of professional jockeys. The aim of the study was to (i), measure the strength of associations between stress and depression symptoms and low-grade inflammation and (ii), determine which measure of low-grade inflammation was associated most strongly with stress and depression symptoms, and (iii), determine the extent to which indices of mood or low-grade inflammation were associated with visual attention and working memory. The hypothesis was that depressive symptoms would be associated most strongly with markers of low-grade inflammation and that dysregulation of inflammatory function would be related with poorer cognition. The study also aimed to explore if changes in workplace stress or depressive symptoms or changes in low-grade inflammation would also be associated with changes in cognition. Finally, a non-directional hypothesis explored if low-grade

inflammation moderated the relationship between psychological factors (i.e., depression, workplace stress) and poorer cognitive performance.

2. Method

2.1. Participants & procedures

Full-time professional, currently licensed Australian jockeys were recruited for this study at timepoint 1 (T1) (N = 81) and approximately twelve months ($M = 373$, $SD = 24$ days) later at timepoint 2 (T2) (N = 79). All jockeys are required to undergo and pass a cognitive assessment annually in order to maintain their riding licence. Immediately after this assessment, jockeys were verbally invited by an investigator to participate in the study. Prior to testing, participants received an information sheet and provided written consent. Self-reported information on workplace stress and depressive symptom levels and blood samples were then collected in a quiet indoor location at the industry facility. Only jockeys who completed all measures at both timepoints were included in this study ($N = 35$, $M_{age} = 32.29$).

Participants were also excluded if they reported a concussion, or had sustained a medically diagnosed concussion (taken from medical records) in the 6-months preceding testing periods.

(See McCrory et al. [32]) for criteria and definition used to diagnose concussion). Jockeys with CRP concentrations >20 mg/L were also removed, as levels at and above this threshold are typically associated with acute inflammatory responses that may confound interpretation of low-grade inflammation [11]. CRP values < 3 are considered normal and those between 3 and 10 mg/L reflect low grade inflammation. At both T1 and T2, 57% of jockeys had normal levels and 43% had low-grade inflammation. Participants received a $50 voucher at each testing occasion. La Trobe University Human ethics committee granted approval for the study procedures (HEC17-041).

2.2. Blood collection and quantification

2.2.1. Blood collection

Using standard phlebotomy procedures, 8.5 mL of whole blood was collected into a BD Vacutainer® SST™ II advance tube for serum preparation. The tube was gently inverted several times and blood allowed to clot at room temperature for 30 min. Samples were then centrifuged at 1500 g for 10 min. Serum was then transferred to 500 μl aliquots and flash frozen on dry ice and later stored at −80 °C until required for analysis.

2.2.2. Inflammatory marker quantification

Assays were performed in a temperature-controlled laboratory by an experimenter blinded to clinical information of the samples. Quantification of pro-inflammatory (IL-6, TNFα) and anti-inflammatory (IL-10) cytokines in serum was conducted using 'Cytokine 3-plex A assay' on the SIMOA HD-X analyser (Quanterix, Billierica, MA, USA). Each sample was tested in duplicate, with a total volume of 100 μl for each sample. To minimise potential batch effects, prospective samples from the same individual were run on the same plate. All samples measured above their lower limit of quantification for each inflammatory marker (IL-6: 0.011 pg/mL, TNFα: 0.051 pg/mL, and IL-10: 0.007 pg/mL). The average coefficient of variation (CV) for duplicate samples was within an acceptable range, with values of 4.9%, 4.0% and 3.3% for IL-6, TNFα, and IL-10 respectively. The average interplate CV of samples repeated across each plate was as expected, with values of 7.7%, 8.5% and 8.4% respectively. Within-subjects inflammatory indices were measured individually for each cytokine across time-points and ratios of these (IL-6: Il-10, TNFα: IL-10) were also computed to assess inflammatory balance – higher scores reflect pro-inflammatory dominance.

2.3. Psychological measures

2.3.1. Workplace stress

The effort-reward imbalance (ERI [42]; model is a well-validated model of workplace stress used in large prospective studies relating high stress to increased health risk [9,38]. The ERI questionnaire is used to assess the components of the ERI model (ERI, overcommitment, efforts, rewards). The model focuses on social reciprocity in the workplace whereby stress ensues when high efforts are not reciprocated by rewards of the job (e.g., money, esteem, job security) [43]. The questionnaire consists of 16-items with 6-items measuring effort (e.g., "My job is physically demanding" or "I am often pressured to work long hours") and 10-items measuring rewards (e.g., "My job security is poor" or "Considering all my efforts and achievements, I receive the respect and prestige I deserve at work"). Scores for each item are assessed on a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). The predominant hypothesis of the ERI model is that stress and poor health ensures when efforts are not reciprocated by rewards. As such, the ERI ratio is used to quantify the experience of workplace stress. ERI ratios are calculated using a formula to evenly weight the constructs given the uneven number of items for each construct (efforts/rewards*.6). ERI ratios greater than 1 have been associated to an increased risk of ill health [43]. High internal consistencies (Cronbach α) were demonstrated at both timepoints for the effort (T1: $\alpha = 0.86$, T2: $\alpha = 0.78$) and rewards (T1: $\alpha = 0.84$, T2: $\alpha = 0.85$) scales.

2.3.2. Depressive symptoms

Depression symptoms were measured using the 7-item depression subscale (e.g. "I felt downhearted and blue" or "I felt I wasn't worth much as a person") from the 21-item Depression, Anxiety and Stress scale (DASS-21; [27]). Items were scored on a 4-point Likert scale ranging from 0 (Never) to 3 (Almost Always) where cut-off scores determining depression symptom severity were: 0–9 (normal), 10–13 (mild), 14–20 (moderate), 21–27 (severe) and 28+ (extremely severe). High reliability of this scale was demonstrated at both timepoints (T1: $\alpha = 0.75$, T2: $\alpha = 0.95$).

2.4. Cognitive measures

The CogSport computerized test battery (Cogstate Ltd, New Haven, Connecticut, USA) is a computerised battery that measures key cognitive domains of simple and choice reaction time (detection and identification tasks respectively), visual learning (one card learning task) and working memory (one-back task). The CogSport battery is well validated and has been able to sensitively predict cognitive impairment in various neuropsychiatric and neurodegenerative disorders [28,30]. The battery was completed on a 14-inch laptop computer and tasks were based on simple card game simulation requiring a yes/no response using the 'K/D' keyboard keys, respectively. Prior to the commencement of each test, a description of that test and the test instructions were presented on the computer display which was followed by a brief interactive demonstration. The tests in the CogSport battery were as follows.

Attention. The detection test (DET) is a simple reaction time paradigm used to measure attention. The task involved responding as quickly as possible with the 'K' (yes) key when a playing card, placed face down in the centre of the screen flips to face up. The DET task has shown good test-retest reliability, at 1 week, $r = 0.85$ [26]. Performance on the DET task was assessed using speed in milliseconds.

Decision-making. The identification test (IDN) is a choice reaction time paradigm used to measure decision-making. Similar to the DET task, a card is placed in the centre of the screen but when it flips the participant must indicate whether the card in question is red or black. At 1 week, the IDN task has shown good test-retest reliability, $r = 0.86$ [26]. Performance on the IDN task was assessed using speed in milliseconds.

Visual learning. The one card learning test (OCL) is a pattern separation paradigm used to assess visual learning. On the OCL participants

were asked, "Have you seen this card before in this task?" where the participant was required to respond as quickly as possible using the appropriate key. At 1 week, the OCL has shown good test-retest reliability, $r = 0.83$ [26]. Performance for the OCL task was based on accuracy as determined by the proportion of correct responses.

Working memory. The one-back test (ONB) is a n-back paradigm used to assessment working memory. On the ONB test, participants were asked, "Is the card in view the same as the previous card shown?" again; the response required the participant to press the appropriate key. The ONB has shown good test-retest reliability at 1 week, $r = 0.93$ [26]. Performance for the ONB task was assessed using speed in milliseconds. The CogSport software scores the tests and automatically transforms speed and accuracy for each test to a normalised distribution (log10 and arcsine transformations, respectively).

2.5. Statistical analysis

Within subjects inflammatory indices were measured individually for each cytokine across timepoints and ratios of these (IL-6: IL-10, TNFα: Il-10) were also computed as a means to assess inflammatory balance, higher scores reflect pro-inflammatory dominance. Prior to conducting parametric analyses, variables were assessed for normality with several positively skewed (depressive symptoms IL-6, TNFα, IL-10, $z > 3.29$) that were transformed using a natural logarithm. Other assumptions for the regression analyses were confirmed, linearity and homoscedasticity identified from scatterplots and normal probability plots respectively, and multicollinearity assessed with tolerance values (all >0.10) [44].

All statistical analysis was conducted using SPSS statistics version 25 (IBM SPSS Inc., Chicago, Il, USA). Pearson correlation analyses assessed the relationships between the change scores of the measures of psychological distress, inflammation, and cognition. Hierarchical regressions with age and gender entered in the first step, followed by the entry of both ERI and depression symptom changes in the second step were conducted to determine their relationships with the change scores of the inflammatory markers (IL-6, TNFα, IL-10, IL-6:IL-10 and, TNFα: IL-10). To preserve statistical power while also identifying the strongest psychological and inflammation predictors of cognitive change, a hierarchical regression with age and gender at step 1 and a stepwise solution at step 2 (variables entered from a pool of all psychological and inflammation measures) was conducted. Finally, using the PROCESS Macro version 3.5.3 for SPSS [12] a moderation analysis (Model 1) using $N = 5000$ resamples was conducted to assess if inflammation (moderating variable) attenuated the relationship between workplace stress (independent variable) and cognition (dependent variable). The PROCESS software uses observed variables and an ordinary least squares approach to conduct path analyses [12]. The G*Power package was used to determine the sample size required for our largest regression model with 4 predictors and assumed a moderate effect size ($f^2 = 0.30$, taken from a related study [20]. This analysis indicated that 36 participants was necessary to retain power at .80 with alpha set at $p < .05$.

3. Results

The group of unavailable or excluded jockeys (n = 46 see Fig. 1), did not differ from the included sample ($n = 35$) in age, gender or any of the measures in Table 1 (p range .108–.985). Jockeys reported high workplace stress at both timepoints (Table 1), with average levels equivalent between the timepoints, $t(34) = 1.57$, $p = .125$. Depressive symptoms, however, were low at both timepoints. Individual cytokine levels, as well as cytokine ratios, did not differ between the timepoints (Table 1). A statistically significant decline in cognitive performance from T1 to T2 was observed for the DET, $t(34) = -2.42$, $p = .021$, and IDN, $t(34) = -2.05$, $p = .049$ tasks (Table 1). With the exception of higher depression symptoms, $t(34) = -2.406$, $p = .011$ at T2 and lower IL-6, $t(34) = 2.163$, $p = .009$ and IL-6:IL10, $t(34) = 1.773$, $p = .043$ at T1 for women,
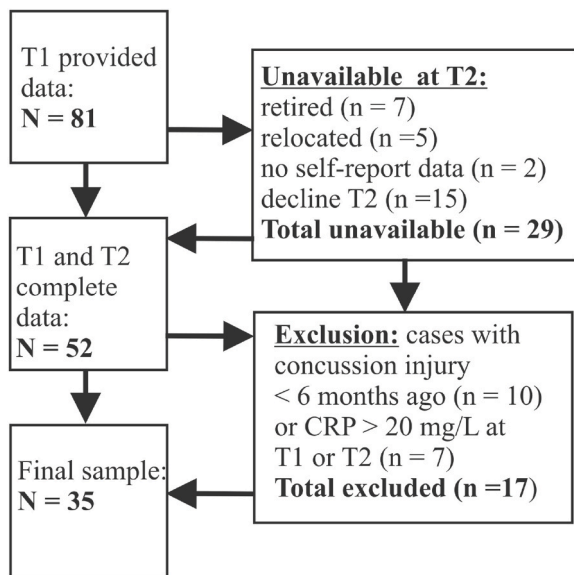
Fig. 1. Flow chart outlining data selection.

associated with increased TNFα: IL-10. For the cognitive measures, increased TNFα: IL-10 scores, which may indicate pro-inflammatory dominance, were associated with poorer performance on the IDN, DET and ONB tests (Table 2).

A series of hierarchical regressions were used to assess if changes in ERI or depression symptoms were most associated with changes in inflammation. Neither ERI or depression symptoms were associated with IL-6, TNFα, or IL10 after controlling for age and gender (see Supplementary Table 2). The bivariate association of ERI with TNFα: IL-10 persisted after controlling for age, gender, and depression symptoms (Table 3) whereas changes in IL-6:IL-10 was not predicted by any of the entered variables (Supplementary Table 3).

A series of hierarchical regressions assessed if changes in depression symptoms, ERI or inflammation was associated with changes in cognition. Specifically, a hierarchical regression with a stepwise solution at Step 2 (Table 4) identified that increases in the TNFα: IL-10 ratio was associated to poorer scores on the DET, IDN and ONB tests. Given the findings, we assessed if TNFα:IL-10 imbalance attenuated the association between ERI and cognition. A moderation analysis with $N = 5000$ re-samples revealed that ERI and TNFα: IL-10 did not influence the association between ERI and performance on the DET ($\beta = 0.005$, CI [$-0.047, 0.057$], $p = .849$), IDN ($\beta = -0.037$, CI [$-0.082, 0.007$], $p = .098$), OCL ($\beta = 0.002$, CI [$-0.084, 0.089$], $p = .954$) or ONB ($\beta = -0.029$, CI [$-0.084, 0.026$], $p = .291$) tests.

genders were equivalent on all other measures (see Supplementary Table 1).

The correlation matrix (Table 2) shows that higher ERI was

Table 1

Descriptive statistics of workplace stress, depression symptoms, inflammatory markers, and CogSport measures in jockeys (N = 35).

Measure	Variable	T1		T2			
		M	SD	M	SD	p	d
Workplace stress	Efforts	17.49	3.79	15.97	3.20	.023	.433
	Rewards	30.03	4.32	29.40	4.67	.339	.140
	ERI	1.00	0.32	0.93	0.25	.125	.244
Depression Symptoms	Depression symptoms	2.28	3.25	3.97	3.37	.189	.185
Inflammatory markers	IL-6, pg/mL	1.13	0.95	1.19	0.89	.417	.178
	TNFα, pg/mL	2.92	0.97	3.02	1.23	.669	.090
	IL-10, pg/mL	1.41	1.21	1.29	0.77	.806	.044
	IL-6: IL-10	0.95	0.68	1.02	0.67	.285	.217
	TNFα: IL-10	2.63	1.10	2.72	1.00	.621	.086
Cognitive tasks	DET	2.48	0.07	2.52	0.09	.021	.399
	IDN	2.64	0.06	2.67	0.06	.049	.421
	OCL	1.09	0.11	1.10	0.10	.570	.095
	ONB	2.82	0.08	2.81	0.08	.849	-.125

Note. pg/mL: picograms per millilitre; ERI = effort reward imbalance, IL-6 = interleukin 6, TNFα = tumour necrosis factor alpha, IL-10 = interleukin 10, DET = detection task, IDN = identification task, OCL = one card learning task, ONB = one-back task; Raw means and standard deviations are presented but transformed values were used for all analyses. p-values were derived from a paired samples t-test based on the change score for each variable between T1 and T2, d = Cohen's d. Higher OCL denotes better performance, but for all other cognitive measures lower scores (time in milliseconds) denote better performance.

Table 2

Correlation matrix depicting associations between change scores on key variables after controlling for age and gender (N = 35).

	Age	Gender	ERIΔ	Depression symptomsΔ	IL6Δ	TNFαΔ	IL10Δ	IL6:IL10Δ	TNFα:IL10Δ	DETΔ	IDNΔ	ONBΔ
Gender	.149											
ERIΔ	.176	-.015										
Depression symptomsΔ	-.203	.313	.209									
IL6Δ	.254	.149	.316	-.087								
TNFαΔ	.006	-.134	.026	-.161	.484**							
IL10Δ	-.015	.180	-.203	.172	-.471**	.683**						
IL6:IL10Δ	.260	.308	.173	.048	.688**	-.040	.316					
TNFα:IL10Δ	-.088	-.139	.402*	.023	.350*	.114	-.747**	-.238				
DETΔ	-.164	.028	.075	-.030	.071	.060	-.353*	-.214	.512**			
IDNΔ	.084	-.088	.212	-.073	.082	-.062	-.300	-.158	.447**	.478**		
OCLΔ	.092	-.192	.062	-.010	-.026	-.029	-.036	-.058	.048	.219	-.070	
ONBΔ	-.002	-.001	.286	-.076	.267	.077	-.401*	-.043	.481**	.372*	.640**	-.314

Note. *$p < .05$, **$p < .01$; ERI = effort reward imbalance, IL6 = interleukin 6, TNFα = tumour necrosis factor alpha, IL10 = interleukin 10, DET = detection task, IDN = identification task, OCL = one card learning task, ONB = one-back task; Δ = change score; Δ was calculated by subtracting T2 values from T1 values. Higher scores on the OCL denote improved performance and higher change scores for DET, IDN and ONB denote poorer performance.

Table 3
Hierarchical Regression of Age, Gender, and Changes in ERI and Depression Symptoms Predicting Changes in TNFα: IL-10 ratios (N = 35).

Predictor	TNFα: IL-10 Step Summary		
	Beta	$R^2\Delta$	p
Step 1		.024	.678
Age	- .170		
Gender	- .083		
Step 2		.180	.047*
ERI	.447*		
Depression symptoms	-.079		

Note. *$p < .05$, The full model (Step 1 + Step 2 variables) for TNFα: IL-10 was $R^2 = 0.204$, $F(4, 30) = 1.926$, $p = .132$; ERI = effort reward imbalance, IL-6 = interleukin 6, IL-10 = interleukin 10, TNFα = tumour necrosis factor alpha.

4. Discussion

This study investigated the concurrent relationship between workplace stress, depression symptoms, low-grade inflammation, and cognition across two timepoints in a sample of professional jockeys. The primary findings were that increased workplace stress was associated with a strongly positive serum TNFα:IL-10 ratio, which is an index of serum cytokine imbalance. Furthermore, this relationship extended to a decrease in attention and working memory. The relationships between increased workplace stress and an increased TNFα: IL-10 ratio with cognition do not appear to overlap however, as increases in the TNFα: IL-10 ratio across time did not attenuate the association between changes in workplace stress with any of the cognitive measures. In summary, the findings suggest that increased ERI predicts increased TNFα: IL-10 and that increased TNFα: IL-10 is associated with poorer attention, decision-making and working memory (Fig. 2).

The findings of increased workplace stress with an increased TNFα: IL-10 ratio aligns with cross-sectional findings of increased ERI with TNFα: IL-10 [2], but is inconsistent with observations from a cross-sectional study which observed no association between burnout and TNFα: IL-10 [46]. It is worth noting however, that von Kanel and colleagues (2008) do report that burnout, as a consequence of high workplace stress, was associated with higher ratios on their other measure of cytokine imbalance (i.e., TNFα: IL-4). The current study found no association between workplace stress and pro-inflammatory cytokine concentrations, which opposes a large body of literature highlighting the positive relationship between increased workplace stress and pro-inflammatory mediators (e.g., Refs. [1,37]. The lack of association of workplace stress with any of the individual pro-inflammatory markers may be due to the low levels of depression symptoms reported by the sample at both timepoints (Table 1).

Consistent with our previous observations [21] and that of others [19], the professional jockeys studied here showed very high levels of workplace stress, with 43% of the sample exhibiting ERI scores greater than 1 at the first timepoint and 31% showing elevated scores at timepoint 2 one year later. Such scores have been classified as 'at risk' for

future ill-health [43]. While there was a direct relationship in jockeys with high workplace stress and TNFα: IL-10 concentrations, depressive symptoms were not associated with any of the inflammatory cytokines or their ratios. Depression symptoms remained stable and low across the study period, with a majority (97.3%) of the sample reporting depression symptoms in the 'normal' range [27] and only one jockey reporting moderate depression symptoms across timepoints. The low levels of depression symptoms observed are inconsistent with observations from previous studies suggesting professional athletes experience greater depression symptomology than the general population (e.g., Refs. [19, 25]. This may help explain why the findings differ from many studies that have shown that higher levels of depression symptoms are related with higher levels of pro-inflammatory cytokines, specifically, IL-6 and TNFα concentrations [8,14,24]. It is possible that in-person completion of questionnaires may have led to socially desirable answers and this approach differs from other studies where jockeys sent back responses anonymously [19,25].

Potentially, our findings suggest that in samples with low depression symptoms, workplace stress may not be a sensitive predictor of IL-6 concentrations, and that measures of cytokine imbalance may be more sensitive physiological indicators of increased workplace stress when depression symptoms are low. Despite the absence of any association between work stress and the inflammatory cytokines individually, the association of increased workplace stress with an increased TNFα: IL10 ratio builds on previous literature that has shown increases in TNFα and decreased IL-10 concentrations are individually associated with higher workplace stress [36,43].

Our findings indicate that an increased TNFα:IL-10 ratio was associated with poorer attention, decision-making, and working memory.
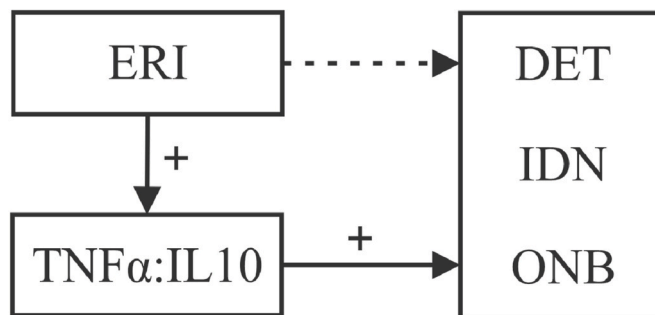

Fig. 2. Path Diagram summarising Key Findings.
Note. Increased workplace stress (ERI) is associated with an increased cytokine imbalance (TNFα:IL-10), and increased cytokine imbalance is associated with poorer cognition (IDN, DET and ONB). Solid lines refer to significant associations and dotted lines refer to non-significant associations. ERI = effort reward imbalance, TNFα = tumour necrosis factor alpha, IL-10 = interleukin 10, DET = detection task, IDN = identification task, ONB = one-back task. The one card learning (OCL) task was not included in the path diagram as it contained no significant associations with the variables of interest.

Table 4
Hierarchical regression of age, gender and changes in TNFα: IL-10 predicting changes in DET, IDN and ONB (N = 35).

Predictor	DET Step Summary			IDN Step Summary			ONB Step Summary		
	Beta	$R^2\Delta$	p	Beta	$R^2\Delta$	p	Beta	$R^2\Delta$	p
Step 1		.030	.616		.017	.755		.000	.999
Age	-.137			.130			.031		
Gender	-.120			- .045			.063		
Step 2		.260	.002*		.199	.009**		.236	.004**
TNFα: IL-10	.516*			.452**			.492**		

Note: *$p < .05$, **$p < .01$; TNFα = tumour necrosis factor alpha, IL-10 = interleukin 10, DET = detection task, IDN = identification task, ONB = one-back task; Full model (Step 1 + Step 2 variables) for DET was $R^2 = 0.260$, $F(3, 31) = 4.223$, $p = .013$, Full model for IDN was $R^2 = 0.217$, $F(3, 31) = 2.859$, $p = .053$, Full model for ONB was $R^2 = 0.236$, $F(3, 31) = 3.199$, $p = .037$. The regression did not include any variables at Step 2 for the OCL variable.

This finding is supported by earlier work with jockeys where high workplace stress interacted with dysregulated autonomic activity (i.e., decreased vagal tone) and was associated with substantial deficits in attention and decision-making on CogSport tests [21]. Similar findings of an interaction between chronic stress and autonomic arousal were reported in a sample of university students where an inability to cope with academic stress was associated with poorer decision-making measured using the same cognitive tests as that used here [20]. The present study therefore extends findings of high stress associated with poorer working memory and visual learning (see Ref. [39] for a review) by also considering the impact of inflammation on these outcomes.

While the current findings are important and build on previous literature, some caveats are important to consider with generalization of its findings. Although the sample is drawn from a high-risk occupation, and reported significant moderate associations, the study was not powered to detect smaller effects and although we measured psychological factors that may be related to fall-risk, we did not assess if stress or cognition were related with falls. Additionally, although the biomarkers of inflammation were appropriate, concurrent measurement of the autonomic nervous system and the HPA-axis may better expose the pathways that lead from work stress to poor cognition. Although we controlled for age and gender in our regressions, we did not control for BMI. As the BMI of professional jockeys is very stable and homogenous (see Ref. [47] for a review) and approached a constant score for the sample, to maintain statistical power, this variable was not included as a covariate. For similar reasons, we did not control for other covariates such as poor health or unhealthy behaviours (e.g., smoking, alcohol consumption) given the sample of elite athletes. We do acknowledge however, that statistical control for these covariates may have enhanced the rigour of our findings. Although most of our findings were p < .01, we acknowledge that we conducted several regression analyses and did not correct the alpha rate to allow for multiple testing. Finally, there are conflicting views on the direction of association between workplace stress, depression symptoms, and inflammation [34] and it is also possible that the direction between psychological measure such as depression symptoms and workplace stress with inflammation is bi-directional. Unfortunately, our sample size was under powered to assess these more complex relationships.

These limitations were balanced by several strengths including a consideration of cytokine imbalance in a prospective design and access to medical data to systematically exclude participants with a recent concussion (<6 months, $N = 10$). Finally, individuals with CRP levels >20 mg/mL ($N = 7$), were excluded as this may suggest acute injury or illness which confounds interpretation of low-grade inflammation [11].

This was the first study to consider how changes in workplace stress and a cytokine imbalance are associated with poorer cognitive performance. In many occupations, including sport and emergency services for instance, reductions in attention, decision-making, and working memory can substantially impact performance and lead to dire outcomes for the employee and the wider community. A recent meta-analysis has shown that interventions such as physical exercise may reduce low-grade inflammation [15]. However, until the underlying mechanisms linking workplace stress to lowered cognition are better understood, more expansive empirical work is required to provide an evidence base for intervention. Our preliminary findings suggest utilisation of a measure of cytokine imbalance in such research may help to disentangle the associations between variables, and further, may explain the heterogenous findings in previous studies that have focussed solely on the association of workplace stress with pro-inflammatory cytokines.

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2022.100131.

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