

**From risk to resilience: How lifestyle factors interact with early-life trauma, genetic polymorphisms, and stress, in predicting risk for depression**

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## **Abstract**

Despite the link that risk factors, such as early-life stressors and genetic polymorphisms, have with the development of depressive symptoms, not every individual who is ‘at risk’ develops this disorder. It has been suggested that lifestyle factors, such as diet and exercise, may play a critical role in this regard. To date, there have been few reports examining the interactions between these lifestyle factors and other risk factors in promoting depressive features. The purpose of the present investigation was to assess the moderating effects of dietary pattern and exercise frequency, in the relations between stressors experienced early in life and psychological outcomes (depressive symptoms and creative problem solving), as well as current stressors and a biological outcome (cortisol response). In addition, the present investigation sought to examine whether these lifestyle variables might interact with immune related gene mutations, in predicting depressive symptoms and other related measures (executive functioning, coping flexibility, and coping endorsement), as both depression and these lifestyle factors are related to immune functioning.

In Study 1 ( $N=278$ ), physical trauma was negatively related to performance on the Remote Associates Test, a measure of creative problem solving, but this relation only existed for individuals who consumed smaller amounts of healthy foods. It was also found that sexual trauma was positively related to depressive symptoms, but this relation was stronger among participants who consumed greater amounts of unhealthy foods. Study 2 ( $N=163$ ) demonstrated that dietary patterns interact with immune related genetic polymorphisms and sex, in predicting depressive symptoms, coping flexibility, and coping strategy endorsement. Building upon the findings of the previous study, Study 3 ( $N=144$ ) indicated that diet and exercise interacted with immune related polymorphisms and sex, in predicting performance on the Iowa Gambling Task

(a measure of executive functioning). Finally, Study 4 ( $N=81$ ) showed that adherence to an unhealthy dietary pattern was associated with elevated levels of cortisol in response to the Trier Social Stress Test. Together, these studies suggest that dietary pattern and exercise habits, can interact with stressors (both current and past) and immune related polymorphisms, in predicting risk for depression.

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## Table of Contents

Title.....	i
Abstract.....	ii
Acknowledgements.....	iv
Table of Contents.....	v
List of Tables.....	vii
List of Figures.....	ix
List of Appendices.....	xi
List of Abbreviations.....	xii
General Introduction.....	1
Chapter 1: Study 1.....	19
Abstract.....	19
Introduction.....	20
Methods.....	23
Results.....	26
Discussion.....	38
Chapter 2: Study 2.....	44
Abstract.....	44
Introduction.....	45
Methods.....	49
Results.....	53
Discussion.....	75
Chapter 3: Study 3.....	81

Abstract.....	81
Introduction.....	82
Methods.....	85
Results.....	88
Discussion.....	96
Chapter 4: Study 4.....	102
Abstract.....	102
Introduction.....	103
Methods.....	105
Results.....	108
Discussion.....	112
General Discussion.....	118
Limitations and Conclusions.....	122
References.....	126
Appendix A: Measures.....	163

## List of Tables

### Chapter 1

Table 1. Means and standard errors of the mean by sex on trauma scores, diet, exercise, depressive symptoms, and Remote Associates Test scores.....	27
Table 2. Zero-order correlations between early-life trauma, exercise, dietary patterns, depression, and Remote Associates Test scores.....	28
Table 3. Zero-order correlations by situational control between early-life trauma, exercise, dietary patterns, and depression. ....	29

### Chapter 2

Table 1. Means and standard deviations by Sex on predictor and outcome variables.....	54
Table 2. Zero-order correlations between dietary patterns, cognitive flexibility, coping strategies, and depression.....	55
Table 3. TNF- $\alpha$ : Table 3a, b. Interaction R-square change, beta, and t-value, by outcome variable.....	57
Table 4. IL-1 $\beta$ : Table 4a, b. Interaction R-square change, beta, and t-value, by outcome variable.....	60
Table 5. IL-6: Table 5a, b. Interaction R-square change, beta, and t-value, by outcome variable.....	63
Table 6. IL-10: Table 6a, b. Interaction R-square change, beta, and t-value, by outcome variable.....	66
Table 7. IL-17A: Table 7a, b. Interaction R-square change, beta, and t-value, by outcome variable.....	70

Table 8. <i>IL-18: Table 8a, b. Interaction R-square change, beta, and t-value,</i> <i>by outcome variable.....</i>	73
--	----

### **Chapter 3**

Table 1. <i>Means and standard deviations by Sex on predictor</i> <i>and outcome variables.....</i>	89
--	----

Table 2. <i>Zero-order correlations between dietary patterns, exercise,</i> <i>and Iowa Gambling Task performance .....</i>	90
--	----

### **Chapter 4**

Table 1. <i>Zero-order correlations between dietary patterns and exercise .....</i>	109
Table 2. <i>Interaction R-square change, beta, t-value, and t-value, by moderator.....</i>	110



## List of Figures

### Chapter 1

- Figure 1.* The moderating role of dietary pattern and exercise in the relation between situational control and coping strategies. ....31
- Figure 2.* The moderating role of diet in the relation between trauma and Remote Associates Test performance. ....33
- Figure 3.* The moderating role of diet in the relation between trauma and depressive symptoms.....35
- Figure 4.* The moderating role of exercise in the relation between trauma, and depressive symptoms and performance on the Remote Associates Test .....37

### Chapter 2

- Figure 1.* The moderating role of the TNF- $\alpha$  polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....58
- Figure 2.* The moderating role of the IL-1 $\beta$  polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....61
- Figure 3.* The moderating role of the IL-6 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....64
- Figure 4.* The moderating role of the IL-10 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....67
- Figure 5.* The combined interaction between the IL-10 polymorphism, Sex, and prudent dietary pattern, in predicting emotion-focused coping.....68
- Figure 6.* The moderating role of the IL-17A polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....71

<i>Figure 7.</i> The moderating role of the IL-18 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.....	74
--	----

### **Chapter 3**

<i>Figure 1.</i> The moderating role of the TNF- $\alpha$ polymorphism in the relation between lifestyle factors and Iowa Gambling Task performance .....	91
---	----

<i>Figure 2.</i> The moderating role of the IL-1 $\beta$ polymorphism and Sex, in the relation between lifestyle factors and Iowa Gambling Task performance .....	93
---	----

<i>Figure 3.</i> The moderating role of the IL-6 polymorphism in the relation between lifestyle factors and Iowa Gambling Task performance. ....	95
--	----

### **Chapter 4**

<i>Figure 1.</i> Salivary cortisol levels as a function of stressor condition .....	108
---	-----

<i>Figure 2.</i> The moderating role of dietary pattern and exercise in the relation between stressor condition and cortisol AUC <sub>i</sub> . ....	111
--	-----

### **General Discussion**

<i>Figure 1.</i> The moderating role of dietary patterns and exercise in the relation between risk factors and depression .....	125
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### **List of Abbreviations**

ACTH	Adrenocorticotrophic Hormone
AUC <sub>i</sub>	Area Under the Curve Increase
BBB	Blood Brain Barrier
BDI	Beck Depression Inventory
BDNF	Brain Derived Neurotrophic Factor
CRH	Corticotropin Releasing Hormone
E Tr.	Emotional Trauma
G Tr.	General Trauma
HPA	Hypothalamic-Pituitary-Adrenal
IDO	Indoleamine 2, 3-dioxygenase
IFN- $\alpha$	Interferon Alpha
IGT	Iowa Gambling Task
IL-10	Interleukin 10
IL-17A	Interleukin 17A
IL-18	Interleukin 18
IL-1 $\beta$	Interleukin 1 Beta
IL-6	Interleukin 6
M Tr.	Maltreatment
NMDA	N-Methyl-D-aspartic Acid
NPD	Non-prudent Dietary Pattern
OFC	Orbital Frontal Cortex
P Tr.	Physical Trauma

PD	Prudent Dietary Pattern
PFC	Pre Frontal Cortex
RAT	Remote Associates Test
S Tr.	Sexual Trauma
SNP	Single Nucleotide Polymorphism
TNF- $\alpha$	Tumor Necrosis Factor Alpha
TSST	Trier Social Stress Test

## **General Introduction**

### **Introduction**

Currently, depression is the most common cause of disability, and has increased more than 18% between 2005 and 2015 (WHO, 2017). Many factors may increase the risk for developing the disorder, such as being female, negative early-life experiences, genetic factors, or an exaggerated stress response. As well, depressive illnesses are often marked by biological disturbances, such as variations in cortisol levels, monoamine production, GABA and glutamate functioning, levels of neurotrophins, and immune system alterations (Strawbridge et al., 2017).

It is generally thought that the neurobiological responses to stressors may be adaptive; however, when experienced at exceptionally high severity or encountered on a chronic basis, these stress responses may become excessive (allostatic overload), and lead to adverse health outcomes (McEwen & Rasgon, 2018). For instance, the response to a chronic stressor may result in persistent cortisol levels, which can, in turn, lead to hippocampal cell loss, and further heighten cortisol levels, thereby perpetuating this cycle, which encourages the emergence of depressive disorders (Olson, 2018).

Genetic factors have likewise been implicated the evolution of depressive disorders. Evidence in line with these views, which have come from human and animal studies, have been inconsistent, which is not altogether unexpected given that depressive disorders are often considered to be biologically heterogeneous. Several lines of evidence have focused on the identification of biological substrates of depression. These have included, postmortem neurochemical determinations, imaging studies, assessment of pharmacological treatment effects, and genetic analyses. In the latter regard, a number of studies assessed the links between depressive illness and a variety of single nucleotide polymorphisms (SNPs) on genes coding for

stress-related genetic factors. Indeed, the BDNF Val66Met single nucleotide polymorphism (SNP) was related to the risk of developing depression, but this was dependent upon sex, as only males seemed to show this association (Verhagen et al., 2010). Moreover, SNPs related to serotonin reuptake might also interact with environmental factors, such as stressor experiences, in predicting risk for depression (Caspi et al., 2003). Multiple SNPs associated with immune function were also implicated in this risk as well, although there was appreciative variability in the associations among different genes (Barnes et al., 2017).

These risk factors are not only linked to depression directly, but indirectly as well, by impairing cognitive flexibility, the extent to which an individual is able to shift attention from one cognitive set to another. For example, both early-life trauma (Pechtel & Pizzagalli, 2011), and the immune related IL-1  $\beta$ -1418 C/T polymorphism, were linked to an impairment in cognitive functioning (Trenova et al., 2018). Cognitive flexibility may be a component of coping flexibility, which might favor individuals' ability to adapt their coping strategies to potential stressors, and thereby limit the risk of developing depression.

However, not everyone who might be at risk actually develops depression, as lifestyle factors such as diet and exercise can play a role in limiting this risk. By example, a reduction in depressive symptoms was associated with aerobic exercise among individuals who were exposed to early-life trauma (Maniam & Morris, 2010). In addition, a diet high in fat can interact with immune related gene polymorphisms in predicting the risk of developing diseases with an inflammatory component (Zhang, Guo, & Qin, 2016).

Despite the evidence suggesting diet and exercise can interact with risk factors in predicting mental health related outcomes, the research is limited, and the results seem to be inconsistent (e.g., Nazki, Sameer, & Ganaie, 2014). The aim of this research is to examine how

prudent and non-prudent dietary patterns, might interact with gene variants and early-life trauma, in their relation to depressive symptoms. In the same regard, the buffering effects of aerobic and anaerobic, as well as their combined effect will be tested as well. Furthermore, this research will examine the independent and interactive effects that might be present in relation to particular gene polymorphisms and early-life trauma in predicting risk for depression, but also on the physiological stress response in response to a stressor.

## **Depression**

Depressive disorders are often marked by frequent low mood, anhedonia, and cognitive disturbances, although symptomatology can vary across individuals. Depression is not a unitary illness, and several subtypes of the disorder have been identified. Typical depressive symptoms comprise neurovegetative symptoms, such as a reduction in appetite, body weight, and sleep, whereas atypical depression, in contrast, is characterized by a reverse neurovegetative symptom profile (e.g., increased sleep, greater eating and carbohydrate craving) as well as elevated stress reactivity.

Although many factors may contribute to the risk of developing depressive symptoms, the present research will focus specifically on how an exaggerated stress response, negative early-life experiences, and genetic factors play a contributing role in this regard. In particular, it is hypothesized that lifestyle factors, comprising diet and exercise, will play a moderating role in the relation between (1) early-life trauma and creative problem solving, a risk factor for the emergence of depressive symptoms, (2) genetic polymorphisms related to immune function and depression (and measures related to depression), (3) genetic polymorphisms related to immune function and cognitive flexibility, and (4) cortisol response to a socio-evaluative stressor, which might serve as a biomarker that is commonly altered in depressed individuals.

## **Stress**

Stressful life events are ubiquitous, and can play a role in the development and emergence of depressive symptoms; however, there are multiple characteristics of a stressor that may affect the biological and psychological impact on an individual's mood and cognitive functioning. In this regard, not all stressors act in a comparable manner. Different types of stressors, such as neurogenic (physical stressors, such as a muscle tear), systemic (stressors we may not be consciously aware of, such as a viral infection), and psychogenic stressors (psychological stressors, such as the death of a loved one), may have varying impacts on neurobiological and immune processes (Anisman, Hayley, & Kusnecov, 2018). Pertinent to the present investigation, psychogenic stressors, such as the Trier Social Stress Test (TSST), which has a socio-evaluative component, can have a particularly dramatic effect on the physiological stress response, such as cortisol release (Goodman et al., 2017), and may be even more pronounced than seemingly more profound stressors, such as the anticipation of heart surgery (Michaud et al., 2008).

When a potential stressor is first encountered, evaluations of various aspects of the stressor are made to assess the threat it presents. The impact of the potential stressor is first evaluated and interpreted as being either benign or threatening (termed 'primary appraisal'). If the event is interpreted as being a threat, then further appraisals are made. These secondary appraisals are to determine whether the individual perceives them self as having the coping resources available to mitigate the negative effects of the potential stressor. Although there are many different coping strategies that individuals use, they generally fall into three broad categories comprising problem-focused, emotion-focused, and avoidant methods. Effective coping methods may limit the emergence of pathology, as problem-focused coping was



negatively related, and emotion-focused strategies were positively related, to indices of depression and suicidal ideation (Horwitz et al., 2018). This said, it is thought that the effectiveness of a given strategy is dependent on the nature of the stressor, the context in which it occurs, and may vary over time as the stressor plays out (Anisman et al., 2018).

### **Stress and the Hypothalamic-Pituitary-Adrenal (HPA) axis**

Multiple biological changes can occur when an individual encounters a stressor, most of which serve in an adaptive capacity. However, when the activation of this response is exaggerated out of proportion to the injury, and occurs on a chronic basis, it can lead to pathology (Bottaccioli et al., 2018). Of the many biological stress responses, particular interest has been paid to the production of the glucocorticoid cortisol, which has many adaptive consequences (e.g., increases blood sugar), and is often used as a biomarker of stress reactivity. The production of cortisol in response to a stressor, may first be initiated by the activation of neurons in the prefrontal cortex and amygdala, which play a crucial role in the appraisal process described earlier. Activation of these neurons can then stimulate neurons within the paraventricular nucleus (PVN) of the hypothalamus, resulting in the production and release of corticotropin releasing hormone (CRH), which then triggers the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland into the bloodstream, and then stimulates the release of cortisol from the adrenal glands. Cortisol eventually feeds back to the hypothalamus and hippocampus, which then ceases the production of CRH, and essentially shuts down this stress response (i.e., the ‘negative feedback loop’). As beneficial as the elevated cortisol might be, if the increase is sustained, damaging effects on the hippocampus may occur. This likely occurs owing to the high concentration of mineralocorticoid receptors in this region, as cortisol has a

higher affinity to binding to these receptors, compared to glucocorticoid receptors, which are widely distributed throughout the brain (Keller et al., 2017).

### **The HPA axis and depression**

Activity of the HPA axis is intimately involved in the pathophysiology of depression, as it seems to be overactive (e.g., hypercortisolemia) in individuals with major depression, although this may depend on the depressive subtype (Keller et al., 2017), and age of the individual (Murri et al., 2014). It was found that adolescents with a history of non-suicidal self-injury and major depressive disorder, had a higher cortisol awakening response (CAR) than their non-self-injury major depressive counterparts, although they did not display any differences in cortisol reactivity to the TSST (Klimes-Dougan et al., 2018). Also, in adolescents, depressive symptoms were associated with higher cortisol responses immediately after and during the recovery period from the Socially Evaluated Cold-Pressor Test, but this association was only found among boys (Lopez-Duran et al., 2015). In pregnant women, it was indicated that postpartum depression was associated with elevated cortisol levels during their first and third trimester (Caparros-Gonzalez et al., 2017). It was also found that both women and men who have anxious depression (a subtype of major depressive disorder), and who have experienced sexual trauma as a child, displayed a heightened HPA activity in response to a dexamethasone injection (Menke et al., 2018). In essence, the link between cortisol and depression has been observed across multiple situations and test populations.

## **Trauma and depression**

Traumatic early-life experiences, which can encompass a variety of strong negative events, such as parental divorce, death of caregiver, abuse, or witnessing a murder, seem to be dose-dependently related to adverse health outcomes, including depressive disorders in adulthood (Mandelli et al., 2015). These events can generally be classified as being general traumatic experiences (e.g., exposure to a life threatening disaster), physical punishment (e.g., being punched or kicked), emotional abuse (e.g., being put down or ridiculed), or sexual abuse (e.g., being forced to perform sexual acts). Generally, traumatic experiences of an emotional nature, seem to show the strongest association with depression, followed by neglect, and sexual abuse (Mandelli et al., 2015). It also seems that individuals who had experienced greater childhood adversities subsequently perceived recent stressful events as being more stressful than those who had experienced fewer childhood adversities, and are also at risk for developing mood disorders (McLaughlin et al., 2010).

## **Trauma and the HPA axis**

Traumatic early-life experiences are associated with altered HPA functioning, which may contribute to the risk of pathology. Indeed, adults who had experienced early-life stress displayed a blunted diurnal cortisol profile (Kumsta et al., 2017; Kuras et al., 2017). This blunted HPA response also seemed to be apparent among depressed women who have been abused as children, as diminished ACTH levels in response to an injection of CRH was observed. Interestingly, these women displayed a greater HPA response compared to depressed women who were not abused, when exposed to a socio-evaluative stressor (Heim et al., 2008). In addition, women who experienced abuse by a romantic partner and suffered symptoms of PTSD, displayed a heightened cortisol response to a video depicting abuse (Matheson & Anisman,

2012). Together, these studies suggest that context of the stressor is important in determining the biological response. Ordinarily, PTSD is accompanied by diminished cortisol release, but when a particularly meaningful stressor is present, then appraisal processes may give rise to the cortisol inhibition being over-ridden (Matheon & Anisman, 2012).

Besides the different types of early life stressors mentioned earlier, other forms of stress during childhood such as nutrient deficiency (Tamburini et al., 2016), are associated with alterations in the gut microbiome, which plays a crucial role in HPA axis formation in early-life, as well as stress reactivity in adulthood (Malan-Muller et al., 2018). The influence of the gut bacteria in this regard may be especially pertinent to the present investigation, given that exercise (Allen et al., 2018a; b), and diet (Seura et al., 2017) is associated with regulating gut microbiota.

### **Dietary patterns and depression**

The study of diet and its relation to depression is complex, not only because the human diet consists of many different components, but also because these are usually consumed in different combinations, some of which might interact with one another. While studying the effect of individual dietary components can offer a controlled assessment of the effect of specific nutrients, studying diet as a pattern (the quantity and combinations of different foods and nutrients) allows the examination of the interactive and additive effects among dietary factors that might be related to disease. Generally, two dietary patterns have emerged based on the available dietary research related to disease; one that was positively associated with inflammation and depression (dubbed a ‘non-prudent’ dietary pattern), and a second that was negatively associated with inflammation and depression (dubbed a ‘prudent’ dietary pattern).

A non-prudent dietary pattern is characterized by a high consumption of red and processed meats, refined carbohydrates, and other processed foods. There is an abundance of

evidence suggesting that this dietary pattern may play a critical role in the etiology and maintenance of depression (Li et al., 2017). By example, a greater consumption of fast food and commercial baked goods has been linked to elevated risk for developing depression (Sánchez-Villegas et al., 2012). Similarly, among college students, greater consumption of ‘ready-to-eat’ foods, such as potato chips, fast food, or ice cream, was positively associated with depressive symptoms (Zazpe et al., 2014), although this eating pattern may simply be a symptom of atypical depression. Interestingly, although red meat is often considered part of a non-prudent diet, in some cases it is considered part of a ‘traditional’ or prudent diet, and is associated with lower odds for major depression, dysthymia, and anxiety disorders (Jacka et al., 2010). Not all studies have revealed this fairly common profile, and there have been reports indicating no association between a non-prudent diet and depression incidence (Molendijk et al., 2018).

The prudent diet, in contrast to the non-prudent diet, consists of items such as non-refined grains, fruits and vegetables, olive oil, and lean meat. Considerable research was conducted indicating that the Mediterranean diet is associated with better health outcomes such as a reduced risk for cognitive decline (Shakersain et al., 2018) and colorectal cancer (Garcia-Larsen et al., 2018). In addition to these outcomes, the Mediterranean diet has been associated with decreased risk for developing depression. Although there have been reports of a weak association between a prudent dietary pattern and depression symptoms (Molendijk et al., 2018), there are other reports indicating a much stronger relation (Fresán et al., 2018; Saghafian et al., 2018). A three-year longitudinal study likewise indicated that the Mediterranean diet was associated with a decrease in the prevalence of depression in middle-aged women (Rienks, Dobson, & Mishra, 2013), and in older individuals (Skarupski et al., 2013).

## **Exercise and depression**

Similar to the relation between healthy dietary patterns and risk for depression, frequent physical activity is also negatively associated with depression. Indeed, in a recent review comprising over one million cases, exercise was associated with a lower mental health burden, although longer durations of exercise were not always associated with better outcomes (Chekroud et al., 2018). It has been suggested that as little as one hour per week may have a protective effect against the risk of developing depression (Harvey et al., 2017), and even a single exercise bout can have a profound positive effects on mood, and stressor reactivity (Basso & Suzuki, 2017). Furthermore, cessation of regular physical activity has been shown to induce depressive symptoms in healthy adults, especially among females (Morgan et al., 2018).

A recent meta-analysis revealed that exercise interventions with a neuromuscular training element (e.g., physical rehabilitation type exercises) might be more effective in reducing depressive symptoms than endurance exercise interventions (Nebiker et al., 2018). Expecting mothers may benefit as well, as exercising during pregnancy, can reduce the likelihood of developing depression during late pregnancy or during the postpartum period (Vargas-Terrones et al., 2018). Despite the beneficial effects exercise can have on depressive symptoms, adherence to exercise programs among depressed individuals is low, however, adherence may depend on factors such as tobacco use, excessive alcohol intake, and flexibility with work schedules (Helgadóttir et al., 2018). Unfortunately, exercise programs for depression may not be prescribed by physicians due to the inaccurate reporting of findings of these programs by media sources (Ekkekakis et al., 2018).

## **Diet and HPA functioning**

Dietary components may also play a role in regulating the HPA axis, which can, in turn, affect the risk of pathology. For example, a recent review suggested that dietary intake of zinc, magnesium, and selenium, play a crucial role in HPA functioning and the risk of developing a mood disorder (Wang et al., 2018). Numerous other vitamins and minerals, such as vitamins B, C, and D, have also been linked to cortisol levels to varying degrees (Stachowicz & Lebidzińska, 2016). Dietary intake notwithstanding, omitting nutrient intake, as is the case with female ‘breakfast skippers’, was associated with higher morning circulating cortisol, compared to females that did not skip breakfast (Witbracht et al., 2015). There is also evidence suggesting that chronically perceived stress may sensitize HPA response to future stressors, that, in turn, increase palatable food consumption following a stressor (Dallman et al., 2005; Klatzkin et al., 2018; Tomiyama et al., 2011). These findings aside, there is limited research regarding the association between dietary *patterns* and HPA activity.

## **Exercise and HPA functioning**

The HPA axis may be another key mediating factor in the relation between exercise and depression. In a recent review, it was suggested that exercise can play a role in the cortisol awakening response (CAR), however, it seems that this effect was only apparent with higher frequencies of exercise (Anderson & Wideman, 2017). This finding may be particularly relevant, as the CAR is often broader among individuals who chronically perceived distress (Kaspers & Scholz, 2004). Adding to this, laboratory research with animals has suggested that lifelong exercise was accompanied by a downregulation of HPA activity in response to a stressor (Pietrelli et al., 2018). Animal research has also suggested that along with changes in sensitivity in hypothalamic paraventricular nuclei, changes in sensitivity in the dorsal raphe, along with

increases in neurotrophic factors, contribute to the antidepressant effect of exercise as well (Nishii et al., 2017). There are numerous factors that affect the relation between physical activity and HPA regulation, such as exercise type, duration, and intensity and chronicity (Lopresti et al., 2013). For example, excessive exercise (overtraining syndrome) is linked to HPA dysregulation (Cadejani & Kater, 2017), which may in turn impact the response to future stressors.

### **Inflammation and depression**

There has been increasing consideration that inflammatory processes, a critical component of the body's defense mechanism against infection, can also promote damaging effects, thereby contributing to the development and maintenance of pathological conditions, including depression (Hodes et al., 2015). This is especially the case when the immunological response is out of proportion to the injury sustained or when immune activation occurs chronically. Indeed, elevated levels of inflammatory markers have been found among depressed individuals (Haapakoski et al., 2015), and among suicide attempters, that reported greater levels of perceived stress, and these individuals also displayed lower levels of neurotrophins (Priya et al., 2016). In addition, the induction of inflammatory states through the administration of an endotoxin may alter the recognition of mood related stimuli, which may contribute to the risk of depression (Benson et al., 2017). Furthermore, some antidepressant medications result in a reduction in markers of inflammation (Baune, 2018), and anti-inflammatory drugs, in particular cyclooxygenase-2 (COX-2) inhibitors, have been associated with a reduction in depressive symptoms in some individuals (Müller et al., 2018), although such findings have been inconsistent (Eyre et al., 2015). Findings such as these suggest a causal link between levels of inflammation and depression, although as indicated, the relationship might be bidirectional (Krishnadas & Cavanagh, 2012).



The inflammatory response to infectious agents is brought about by lymphocytes and monocytes (astrocytes and microglia in the brain also contribute to inflammation), although monocytes, once in the brain, tend to function in a similar fashion to microglia (Hodes et al., 2015). The communication between these cells, and other aspects of the immune response, occurs through signaling molecules, pro-inflammatory cytokines, released from immune cells (or microglia in brain). Among other things, these inflammatory cytokines foster immune cell replication and trigger cytotoxic immune cell activity, and are thus fundamental to a potent immune response being mounted. Once the threat has been neutralized, anti-inflammatory cytokines are activated that signal the inhibition of immune cells (Reiche, Nunes, & Morimoto, 2004), thereby limiting the possibility of the immune system attacking the self.

It is generally accepted that the immune system can directly or indirectly affect brain functioning and vice versa. Although cytokines are relatively large molecules that do not readily pass through the blood-brain barrier (BBB), there are several ways by which they can gain access to the brain or affect brain activity. Cytokines in the periphery, through stimulation of the vagus nerve, can activate brain microglia, which play a key role in neural inflammation, in that they recruit monocytes, in order to keep pro- and anti-inflammatory states in check (Chesnokova et al., 2016). Damage to the structure or function of microglia caused by excessive levels of inflammation, or due to age, may be associated with reductions in neuroplasticity and neurogenesis, and hence the emergence of depression (Yirmiya et al., 2015). However, in the medial prefrontal cortex, acute and chronic stressors are accompanied by a reduction in activation of microglia in females, but not in males, which may contribute to the sex differences frequently observed in depression (Bollinger et al., 2016). A second route by which cytokines in the periphery may innervate the brain, is by entry to the brain where the BBB is not full

developed, such as the circumventricular organs, the posterior pituitary, the median eminence, and the area postrema (Black et al., 2017). A third route cytokines may innervate the BBB and affect neuronal functioning, is via transporter proteins (Banks, 2016).

Once inside the brain, cytokines can disrupt neural systems associated with mood regulation and stress, thereby promoting the emergence of mood disorders. For instance, cytokines, such as interleukin 2 (IL-2) and interferon alpha (IFN- $\alpha$ ) are associated with an increase in the enzyme indoleamine 2, 3-dioxygenase (IDO), which increases the conversion of dietary tryptophan (a precursor to serotonin) to kynurenine, rather than to serotonin (Capuron & Miller, 2011). In addition, kynurenine is metabolized into compounds that become cytotoxic, which can also contribute to the depressant effects of pro-inflammatory cytokines. By example, 3-hydroxykynurenine, a metabolite of kynurenine can induce neuronal apoptosis, and produce quinolinic acid, a potent N-methyl-D-aspartate (NMDA) receptor agonist, which can cause over stimulation of NMDA receptors, potentially leading to cell death (Qin et al., 2018).

Cytokines present within the brain, irrespective of their origin, may also influence hypothalamic-pituitary-adrenal axis (HPA axis) activity. Indeed, pro-inflammatory cytokines, such as IL-1, can increase levels of hypothalamic corticotropin releasing hormone (CRH) and pituitary adrenocorticotrophic hormone (ACTH), leading to adrenal cortisol (or corticosterone in animals) release (Besedovsky, Del Rey, Sorkin, Dinarello, 1986). Other cytokines, such as IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ) might also have such action, although producing less consistent effects (Connor, Song, Leonard, Merali, & Anisman, 1998). As depressive illness has also been associated with elevated HPA functioning (Otte et al., 2004), it is possible that chronic pro-inflammatory cytokine activation may trigger an HPA response that places individuals at risk for depressive illness.

Microglial cells in the brain, like their peripheral cousins, monocytes (macrophages) (Rosenblat, Cha, Mansur, & McIntyre, 2014), may also promote neural damage leading to pathology, in addition to the adaptive functions discussed earlier. Once activated, microglia can cause synaptic pruning (Ekdahl, 2012; Kraft & Harry, 2011) and activate apoptosis, essentially limiting existing neuronal pathways and the growth of new neurons. Furthermore, excessive cytokine levels may directly destroy neurons, thereby leading to psychological disturbances. Taken together, it seems that increased levels of pro-inflammatory cytokines in the periphery or within the brain not only disrupt neural systems involved in mood regulation, but can also cause structural changes, resulting in a lasting impairment of cognitive functioning that can increase the risk for depressive pathology. Of particular interest to the present investigation, is the association between lifestyle factors and inflammation (Lopresti et al., 2013), and their potential role in depression via the immune system.

### **Dietary patterns and inflammation**

There is an abundance of evidence across both sexes and multiple ethnicities, suggesting that a diet comprised mostly of red and processed meats, and refined grains, is associated with chronic inflammation (Berk et al., 2013; Lopresti et al., 2013; Ozawa et al., 2017). Although, various foods appear in diets, it can be difficult to make specific attributions regarding specific foods in relation to inflammation (for example see Nettleton et al., 2006). For instance, in a recent review, high glycemic carbohydrates were not associated with markers of inflammation (Milajerdi et al., 2018). However, in an interventional study, it was found that levels of an inflammatory marker were higher for participants who were assigned to eat at least two fast food meals a day for four weeks as well as adopting a sedentary lifestyle compared to individuals who were assigned to eat a control diet (Åstrand et al., 2010). Thus, it seems that although dietary

patterns can be complex and may vary, a diet that mostly comprises ‘unhealthy’ food items that are consumed on a consistent basis, may promote inflammation.

In contrast, The Mediterranean dietary pattern has been associated with lower levels of inflammation, which might be a potential mechanism explaining the reduced risk for depression. In a large scale epidemiological study conducted among men and women, Mediterranean style dietary adherence was negatively related to CRP, IL-6 and leukocyte and platelet counts, and granulocyte : lymphocyte ratio (Bonaccio et al., 2017). Likewise, a prudent dietary pattern was negatively associated with plasma levels of pro-inflammatory markers CRP and E-selectin (Lopez-Garcia et al., 2004). In a study conducted among patients with the metabolic syndrome (which is frequently accompanied by chronic inflammation), patients randomly assigned to a Mediterranean-style diet versus a control diet for a period of two years, had reduced concentrations of CRP, IL-6, and IL-18 (Esposito et al., 2004). Similarly, among a Spanish population, CRP levels were negatively related to adherence to a Mediterranean style diet (Lahoz et al., 2018). There are reports however, that suggest body mass index (BMI) might be mediating the relation between certain diets and markers of inflammation (Jaceldo-Siegl et al., 2018).

### **Exercise and inflammation**

There are multiple pathways by which exercise might be linked to depression, however, there is reason to suspect that immune functioning may play a key role in this regard. Although aerobic exercise is associated with inflammation in the short term, levels of pro-inflammatory markers such as CRP, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, are diminished in the long term (Lopresti et al., 2013). Anaerobic forms of exercise, such as high-intensity interval training, are also associated with elevated levels of IL-6 in the short term (Ferrandi et al., 2018), however, much less is known regarding the long-term effects. Acute bouts of exercise seem to be associated with

decreased levels of TNF- $\alpha$ , and increases in catecholamine production, which may contribute to the anti-inflammatory effect (Dimitrov et al., 2017). Although it has commonly been accepted that vigorous bouts of exercise may suppress the immune system, recent research suggests otherwise, in that frequent vigorous exercise is related to enhanced immune functioning (Campbell & Turner, 2018).

It seems that this long term benefit of aerobic exercise on immune functioning is apparent across the lifespan, as regular exercise was associated with lower levels of pro-inflammatory cytokines among the elderly (Simpson et al., 2012). Likewise, elderly cyclists, displayed elevated levels of IL-7, and lower levels of IL-6, and higher T cell production, when compared to their inactive counterparts (Duggal et al., 2018). In aged mice, exercise was associated with altered microglia activation, and seemed to be protective against reductions in neurogenesis in the hippocampus (Littlefield et al., 2015).

Exercise may also ameliorate some of the negative immune related effects associated with disease, as lower levels of IL-6 were also associated with acute and chronic exercise, among children and adults with chronic inflammatory disease (Ploeger et al., 2009). In animal models, voluntary exercise was associated with suppressed tumor growth, owing in part to the effects IL-6 may have on natural killer cell redistribution (Pedersen et al., 2016). Moreover, it was found that six months of regular walking was associated with a reduction in the plasma ratio of IL-6 to IL-10 levels of patients with chronic kidney disease, which also has an inflammatory component (Viana et al., 2014). In an animal model of diabetes, it appeared that low-intensity exercise was associated with a reduction in IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-4, and reactive oxygen species, although high-intensity exercise reduced some inflammatory markers in tissue-specific muscles as well (Kim et al., 2014).

## **Trauma and inflammation**

Stress experienced in early-life is associated with changes in immune regulation, which can impact the immune response to stressors later in life. This altered immune response to stressors is associated with excitotoxicity, which ultimately can lead to pathology (Brenhouse et al., 2018). Indeed, among those who have experienced early-life trauma, increased levels of IL-6 and TNF- $\alpha$ , to an endotoxin were observed, compared to individuals who had not experienced trauma (Hohmann et al., 2017). It was also found that in response to a socio-evaluative stressor, healthy adults who had experienced maltreatment in early-life, displayed greater IL-6 following the TSST compared to controls who had not experienced this kind of trauma (Carpenter et al., 2010). However, this effect was not always evident, as adolescents that were exposed to trauma in early-life, displayed lower cortisol reactivity. In contrast, changes of IL-6 levels, in response to various stressors, including the TSST, were not detected (Chiang et al., 2018).

The present investigation set out to assess the moderating effects of dietary pattern and exercise frequency, in the relations between stressors experienced early in life and psychological outcomes (depressive symptoms and creative problem solving), and a current stressor and a biological outcome (cortisol response). In addition, the present investigation sought to examine whether these lifestyle variables might interact with immune related gene mutations, in predicting depressive symptoms and other related measures (executive functioning, coping flexibility, and coping endorsement), as both depression and these lifestyle factors are related to immune functioning.

## **CHAPTER 1**

### **The moderating role of lifestyle factors in the relation between stress, and creative problem solving, coping, and depressive symptoms**

#### **Abstract**

Early-life traumatic experiences have been linked to the risk of pathology, however, there is limited research examining how current lifestyle habits, such as dietary pattern and exercise frequency, might play a moderating role in this regard. The present investigation examined the relation traumatic early-life experiences had with depressive symptoms and creative problem solving, and the moderating role diet and exercise patterns may have played in this relation. Among male and female undergraduate students ( $N=278$ ), it was observed that physical trauma was negatively related to performance on the Remote Associates Test (a measures of creative problem solving), but this relation only existed for individuals who adhered less to a healthy dietary pattern. It was also found that sexual trauma was positively related to depressive symptoms, but this relation was stronger among participants who consumed greater amounts of unhealthy foods. Although speculative, the present findings suggest that diet and exercise, might be a moderating influence on the pro-inflammatory profile associated with early-life traumatic experiences, as diet and exercise can play a regulatory role in immune functioning. These immune changes might in turn affect executive functioning and depressive symptoms.

## **Introduction**

Trauma experienced during early-life has been associated with dysfunction of brain regions associated with the stress response, such as the hypothalamic-pituitary-adrenal (HPA) axis, and regions associated with executive functioning, including the prefrontal cortex (PFC). Ultimately, these disturbances may favor the development of disorders, including anxiety and depression (Danese & Baldwin, 2017; Heim et al., 2008). Although there are multiple pathways through which this damage can occur, increased inflammation during critical periods of brain development might be the driving force behind these impairments. Indeed, higher levels of inflammatory markers have been found among individuals who have experienced early-life traumatic events (Baumeister et al., 2016), and among depressed individuals (Haapakoski et al., 2015).

Despite the link between early-life stress and risk for depression, not every individual who experiences trauma during childhood develops a mental illness. In this regard, lifestyle alterations secondary to trauma, such as diet and exercise, can play a moderating role in this regard. Indeed, among adolescents who had previously experienced early-life trauma, anxiety and depressive symptoms were reduced following an aerobic exercise program (Newman & Motta, 2007). Likewise, among rats that were exposed to early-life stressors, voluntary exercise was associated with a reduction in depressive-like behaviors (Maniam & Morris, 2010). Although there are multiple pathways through which exercise can have an antidepressant effect, this effect may come about, in part, due to its anti-inflammatory actions (Lopresti et al., 2013).

Like exercise, dietary pattern can also influence the risk of developing depression (for example see Lucas et al., 2014). Although there is little data on how diet may interact with childhood trauma in predicting risk for developing depression, it is possible that increased levels



of inflammation from a non-prudent diet (a higher intake of *trans* fat, high glycemic carbohydrates, and processed meats; Barbaresco et al., 2013) may exacerbate the risk for depression in individuals who have experienced early life trauma. In contrast, individuals who subscribe to a prudent dietary pattern (characterized by a higher intake of healthy fats, lean proteins, and slow digesting carbohydrates), which promotes lower levels of inflammation (Schwingshackl & Hoffmann, 2014), might experience lower depressive symptoms, even if they have experienced early-life stress.

Coping ability, or the efforts of an individual to mitigate the potential negative effects of a stressor, is a critical factor in the emergence and maintenance of depression. Many different types of coping strategies are available, which can be classified as either problem-focused (e.g., problem solving, cognitive restructuring), emotion-focused coping (e.g., emotional expression, self-blame), or avoidant strategies (e.g., avoidance, denial). The process of coping with a stressor is complex, as coping strategies can vary across situations and time (DeLongis & Holtzman, 2005; Tennen et al., 2000), and multiple strategies can be used simultaneously. Further contributing to the complexity, the controllability of the potential stressor can also play a role in relation to the type of coping strategy that may be most effective. Generally, problem-focused coping strategies tend to be most effective in controllable situations, and emotion-focused strategies tend to be a better fit in uncontrollable situations, although this view may be overly simplistic. Emotion-focused coping strategies seem to be for the most part maladaptive, as affective disorders are associated with a greater use of these strategies (Matheson & Anisman, 2003). However, there are cases in which an individual may have no control over a stressor (e.g., breast cancer), and avoidant or emotion-focused coping strategies might be more effective strategies (Stanton et al., 2000).

As diet and exercise can influence depressive symptoms, these factors can also play a role in coping selection during stressful encounters. Indeed, individuals who exercised more frequently, tended to endorse problem-focused coping methods to a greater extent than individuals who didn't exercise as frequently (Azizi, 2011). Likewise, a higher intake of snack foods was associated with a greater use of emotion-focused strategies during stressful events, and a healthier dietary quality was associated with more support seeking strategies (Kuczmarski et al., 2017). Given the associations between these lifestyles factors and coping selection, and that coping selection can be influenced by the controllability of a stressor, the possibility that diet and exercise might interact with the controllability of a stressor in predicting coping use was entertained.

Trauma experienced in early-life may also influence coping selection, in that it seems to promote the use of emotion-focused coping strategies in response to stressful situations (Vaughn-Coaxum et al., 2018). Like the effect that early-life stress can have on depressive symptoms (e.g., via the inflammatory immune system, or those involving HPA or PFC functioning), such stressor experiences can influence coping selection through these same pathways (Compas, 2006; Danese & Baldwin, 2017). Given the immune connection between early-life stress and coping selection, and that exercise and diet can have immune regulating effects (Lopresti et al., 2013), it is possible that these lifestyle factors might influence the relation between early life-trauma and coping.

Creative problem solving, which involves generating novel solutions to adapt to changing environments, is associated with more adaptive forms of coping (Carson & Runco, 1999), which can, in turn, impact the risk of developing depression. There are many ways creative problem solving can be assessed, including the Remote Associates Test (Mednick, 1968), which prompts

participants to find a word that connects three stimulus words. Although there is limited research on the effects of early-life stress on creative problem solving, areas of the brain strongly associated with creative problem solving, such as the PFC (Dietrich, 2004), are impaired as a result of inflammation induced by early-life stress. Inasmuch as lifestyle factors might generate immune modulating effects (Lopresti et al., 2013), it is possible that these factors might moderate the relation between early-life trauma and creative problem solving.

In view of the connections that exist between early life trauma, lifestyle factors, coping, and risk of depression, it is hypothesized that the controllability of a stressor would be positively related to the use of problem-focused coping strategies, and negatively associated with emotion-focused coping strategies, and that these relations would be stronger at higher levels of adherence to dietary pattern and exercise. In addition, childhood trauma would be positively related to depressive symptoms and negatively related to Remote Associate Test performance, and that these relationships would be weaker at a higher intake of prudent dietary items and a higher frequency of physical activity.

## **Methods**

### **Participants**

The study included female ( $n = 198$ ) and male ( $n = 80$ ) undergraduate students ( $M_{age} = 19.19$ ,  $SD = 1.86$ ), attending Carleton University, recruited on-line using Carleton University's SONA system. Self-reported ethnicity included Caucasian (67.3%,  $n = 187$ ), Black (4.0%,  $n = 11$ ), Arab (9.0%,  $n = 25$ ), South Asian (6.5%,  $n = 18$ ), other (e.g., mixed ethnicity, 8.3%,  $n = 23$ ), Latin American (1.1%,  $n = 3$ ), and Asian (2.5%,  $n = 7$ ).

## Procedure

Once consent was received, participants were randomly assigned to either the controllable or uncontrollable stressor condition (see *Coping*, under the Measures section). Participants then responded to a series of questionnaires that assessed dietary pattern, exercise frequency, early-life trauma, depressive symptoms, coping strategy use, and creative problem solving ability, through the SONA system using the online survey tool Qualtrics. Upon completion of the questionnaires, participants were debriefed and compensated with research participation credit.

## Measures

*Depressive symptoms.* Depressive symptoms were assessed using the 21-item version of the Beck Depression Inventory (BDI) (Beck et al., 1961). Total scores were calculated by summing across all items ( $\alpha = .94$ ).

*Creative problem solving.* Creativity was assessed using a shortened version of the Remote Associates Test (RAT) (Mednick, 1968), a 10-item measure that instructed participants to identify associations among three words that are not normally associated with each other. For example, participants were presented with the words ‘envy, golf, beans’, and have to write a word which they think connects the three words (answer: ‘green’).

*Coping.* Coping was measured by using a modified 27-item version of the Survey of Coping Profiles Endorsed (Matheson & Anisman, 2003) which measured the extent to which participants endorsed 13 different coping strategies over a potentially stressful situation (controllable and uncontrollable outcome). Based on our earlier reports, the coping scale was assessed as comprising two factors, emotion-focused and problem-focused coping.

In the controllable situation (Problem-focused  $\alpha = .69$ , Emotion-focused  $\alpha = .79$ ), participants were instructed to read a vignette which asked them to imagine themselves in a situation in which a professor has given them a poor grade on an assignment, but they can improve this grade by completing an additional assignment. In the uncontrollable situation (Problem-focused  $\alpha = .75$ , Emotion-focused  $\alpha = .69$ ), participants were given the same scenario, however, in this condition, they were told that nothing could be done about the poor grade on the assignment.

*Physical Exercise.* Physical exercise was assessed using the Godin-Shepard Leisure-Time Activity Questionnaire (Godin, 2011; Modified), a 3-item measure that instructed participants to indicate the frequency in which they participate in mild, moderate, and strenuous exercise, for more than 15 minutes per week.

*Dietary Pattern.* Dietary pattern was assessed using a modified food frequency questionnaire (FFQ) (Hu et al., 1999), a 44-item measure that instructs participants to indicate the frequency they consumed various dietary items (e.g., lean proteins, dairy products, green leafy vegetables, etc.) per week on average over the past year. The food items were then grouped into either a prudent dietary pattern (leafy vegetables, other vegetables, tomatoes, fruits, cruciferous vegetables, salad dressing, and fish;  $\alpha = .81$ ) and a non-prudent dietary pattern (desserts, processed meats, fried food, sweets, refined grain, high-fat dairy, and condiments;  $\alpha = .80$ ) based on Akbaraly et al. (2009)

*Childhood Trauma.* Childhood trauma was measured by the Early Trauma Inventory Self Report-Short Form (Bremner, 2007), a 25-item measure assessing various types of early-life events including, general trauma ( $\alpha = .41$ ), physical abuse ( $\alpha = .81$ ), emotional abuse ( $\alpha = .69$ ), sexual abuse ( $\alpha = .54$ ), and maltreatment ( $\alpha = .59$ ).

## Statistical Analyses

The statistical analyses were performed using IBM SPSS Statistics 20 for Windows (Armonk, NY: IBM Corp.). Analyses assessing differences in trauma scores, dietary pattern, exercise, depressive symptoms, and Remote Associates Test scores, as a function of sex, were determined by independent samples *t*-tests. Correlational analysis was performed using Pearson product moment correlations. Interactions between stressor condition and sex on emotion-focused and problem focused coping scores were performed by separate ANOVAs. Finally, moderation and simple slope analyses were conducted using the PROCESS macro (Hayes, 2013) in SPSS.

## Results

### *Differences by sex on predictor, moderator, and outcome variables*

In the present sample, general or physical trauma scores did not vary by sex, however, emotional trauma  $F(1, 276) = 9.76, p < .01$ , sexual trauma  $F(1, 276) = 12.07, p < .001$ , and maltreatment  $F(1, 276) = 4.46, p < .05$ , occurred more frequently among females than males (see Table 1 for means and standard deviations). Relative to males, the females on average also tended to adhere more to a prudent dietary pattern,  $F(1, 273) = 3.83, p < .05$ , and less to a non-prudent dietary pattern  $F(1, 273) = 25.02, p < .0001$ . In addition, neither exercise nor scores on the Remote Associates Test varied by Sex,  $t(276) = 1.77, p > .05$ ;  $t(276) = -1.17, p > .05$  respectively. Finally, an independent samples *t*-test revealed that depressive symptoms were higher among females than males,  $t(276) = -2.73, p < .01$ .

Table 1. Means (*M*) and standard errors of the mean (*SD*) by sex on trauma scores, diet, exercise, depressive symptoms, and Remote Associates Test scores.

	Male		Female	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
1. General Trauma	2.49	2.03	2.53	1.99
2. Physical Trauma	1.88	1.82	1.47	1.60
3. Emotional Trauma	1.56	1.82	2.36**	1.96
4. Sexual Trauma	0.43	0.87	1.13***	1.73
5. Maltreatment	3.86	3.33	4.96*	4.16
6. Exercise	52.23	28.29	45.17	30.75
7. Prudent Diet	49.53	12.08	52.81*	12.86
8. Non-prudent Diet	44.98***	9.82	37.85	11.07
9. Depression	10.53	10.30	14.56**	11.45
10. Remote Associates Test	3.34	2.52	3.76	2.81

Note. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ,

*Zero-order correlations between trauma, exercise, dietary pattern, depressive symptoms, and Remote Associates Test scores*

As displayed in Table 2, all subtypes of trauma were positively related to each other as well as to depressive symptoms. In contrast, scores on the Remote Associates Test were not associated with any measure.

Table 2. Zero-order correlations between early-life trauma, exercise, dietary patterns, depression, and Remote Associates Test scores.

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. General Trauma	-	-	-	-	-	-	-	-	-
2. Physical Trauma	.38**	-	-	-	-	-	-	-	-
3. Emotional Trauma	.40**	.46**	-	-	-	-	-	-	-
4. Sexual Trauma	.21**	.31**	.33**	-	-	-	-	-	-
5. Maltreatment	.44**	.77**	.82**	.69**	-	-	-	-	-
6. Exercise	.08	.10	-.007	.01	.05	-	-	-	-
7. Prudent Diet	.02	.13	.08	.01	.10	.21**	-	-	-
8. Non-prudent Diet	.02	.09	-.01	-.12	-.02	-.02	.05	-	-
9. Depression	.24**	.17**	.36**	.34**	.39**	-.04	-.05	.01	-
10. Remote Associates Test	-.01	-.06	.03	-.11	-.05	-.05	-.001	-.009	-.04

Note. \*\* $p < 0.01$

#### *Effects of situational control and sex on coping (SCOPE) scores*

The ANOVA indicated that emotion-focused coping was greater in the uncontrollable condition ( $M = 3.38$ ,  $SD = .51$ ) than in the controllable condition ( $M = 3.01$ ,  $SD = .61$ ;  $F(1, 274) = 26.20$ ,  $p < .0001$ ). In contrast, no significant differences were found in problem-focused coping endorsement as a function of situational control,  $p > .10$ . There was no significant main effect of Sex, or Sex x Condition interaction in predicting emotion-focused coping,  $p > .05$ , or problem-focused coping,  $p > .10$ .



*Zero-order correlations between coping, and predictor, moderator, and outcome variables by condition*

It appeared that in the uncontrollable condition, problem focused coping was negatively correlated with both emotional trauma and depressive symptoms, and depressive symptoms were positively related to emotion-focused coping (see Table 3). In the controllable condition, it seems that depression was related to higher emotion-focused coping strategies.

Table 3. Zero-order correlations by situational control between early-life trauma, exercise, dietary patterns, and depression.

	Uncontrollable									
	Prob. Cope	Gen. Trauma	Phys. Trauma	Emo. Trauma	Sex. Trauma	Maltr.	Ex.	PD	NPD	Dep.
Emo Cope	.03	.02	.06	.10	.07	.10	.11	.07	.10	.31**
Prob Cope	-	.04	-.04	-.24**	-.03	-.14	.20	.07	.16	-.36**

	Controllable									
	Prob. Cope	Gen. Trauma	Phys. Trauma	Emo. Trauma	Sex. Trauma	Maltr.	Ex.	PD	NPD	Dep.
Emo Cope	.06	.07	-.08	.05	-.004	-.007	-.14	-.04	.09	.34**
Prob Cope	-	-.05	-.08	-.10	-.12	-.13	.09	.11	.04	-.17

Note. \*\* $p < 0.01$

*Interactive effects between situational control and lifestyle factors, in predicting coping scores*

The controllable situation was negatively associated with emotion-focused coping endorsement ( $b = -.36$ ,  $SE = .07$ ,  $t = -5.43$ ,  $p = .0000$ ), whereas exercise was positively related to problem-focused coping strategies ( $b = .003$ ,  $SE = .001$ ,  $t = 2.48$ ,  $p = .01$ ). As depicted in Figure 1, exercise moderated the relation between situational control and emotion-focused coping endorsement, such that the controllable condition was associated with lower endorsement of emotion-focused coping strategies, but this relation was stronger at higher levels of exercise frequency,  $\Delta R^2 = 0.01$ ,  $b = -.005$ ,  $t = -2.06$ ,  $p = 0.04$ . No significant interactions between the dietary patterns and situational control were found.

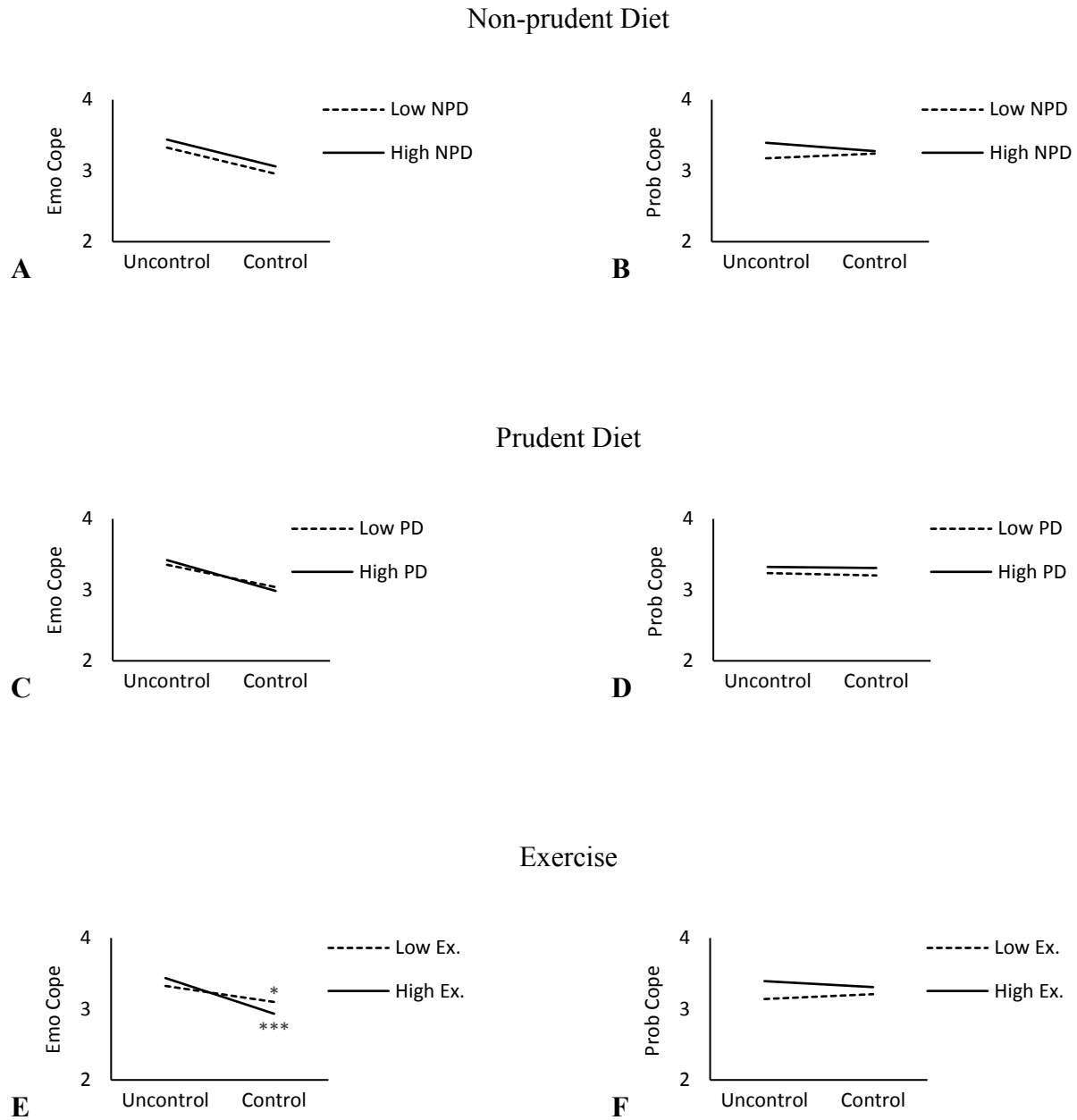


Figure 1. The moderating role of dietary pattern and exercise in the relation between situational control and coping strategies. Note: low levels of adherence to either dietary pattern or low frequency of exercise = 1 *SD* below the mean, high levels of adherence to either dietary pattern or high frequency of exercise = 1 *SD* above the mean. Note. \* $p < 0.05$ , \*\*\* $p < 0.001$

*Interactive effects between early-life trauma and dietary pattern, in predicting Remote Associates Test performance*

It was found that sexual trauma was negatively related to Remote Associates Test scores ( $b = -.22$ ,  $SE = .11$ ,  $t = -1.98$ ,  $p = .05$ ). As shown in Figure 2 panel C, the prudent dietary pattern moderated the relation between physical trauma and scores on the Remote Associates Test, such that physical trauma was negatively associated with scores on the Remote Associates Test, but this relation was significant only at lower levels of adherence to a prudent dietary pattern  $\Delta R^2 = 0.01$ ,  $b = .01$ ,  $t = 1.98$ ,  $p = 0.05$ .

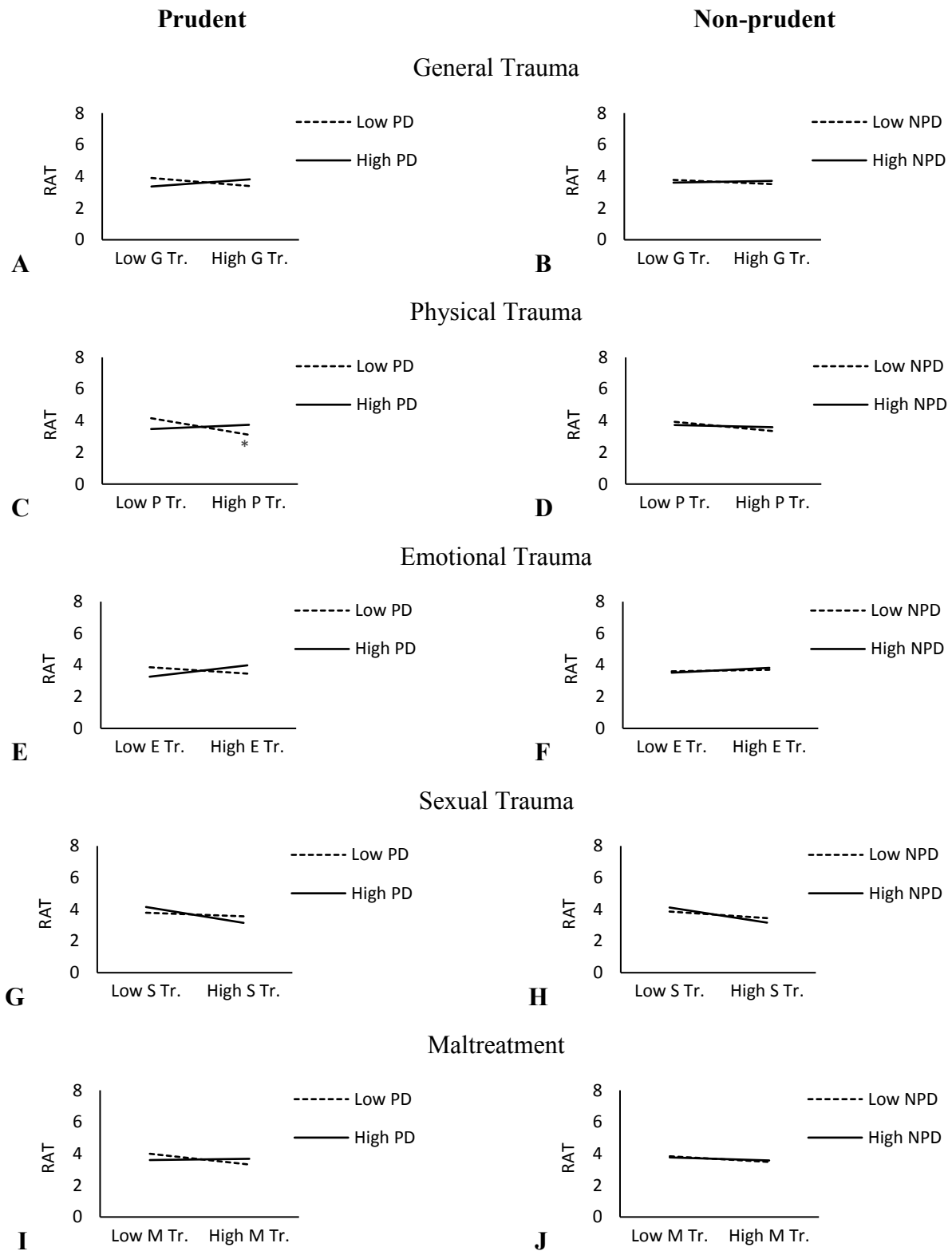


Figure 2. The moderating role of diet in the relation between trauma and Remote Associates Test (RAT) performance. Note:  $*p < .05$

*Interactive effects between early-life trauma and dietary pattern, in predicting Depressive Symptoms*

It was found that depressive symptoms were positively related to general trauma ( $b = 1.39, SE = .33, t = 4.21, p = .0000$ ), physical trauma ( $b = 1.20, SE = .40, t = 2.97, p = .003$ ), emotional trauma ( $b = 2.08, SE = .32, t = 6.41, p = .0000$ ), sexual trauma ( $b = 2.48, SE = .41, t = 6.05, p = .0000$ ), and maltreatment ( $b = 1.11, SE = .16, t = 6.99, p = .0000$ ). As depicted in Figure 3 panel H, the non-prudent dietary pattern moderated the relation between sexual trauma and depressive symptoms, in that sexual trauma was positively associated with depressive symptoms, but this relation was stronger at a higher intake of a non-prudent dietary pattern  $\Delta R^2 = 0.03, b = .08, t = 2.89, p = 0.004$ .

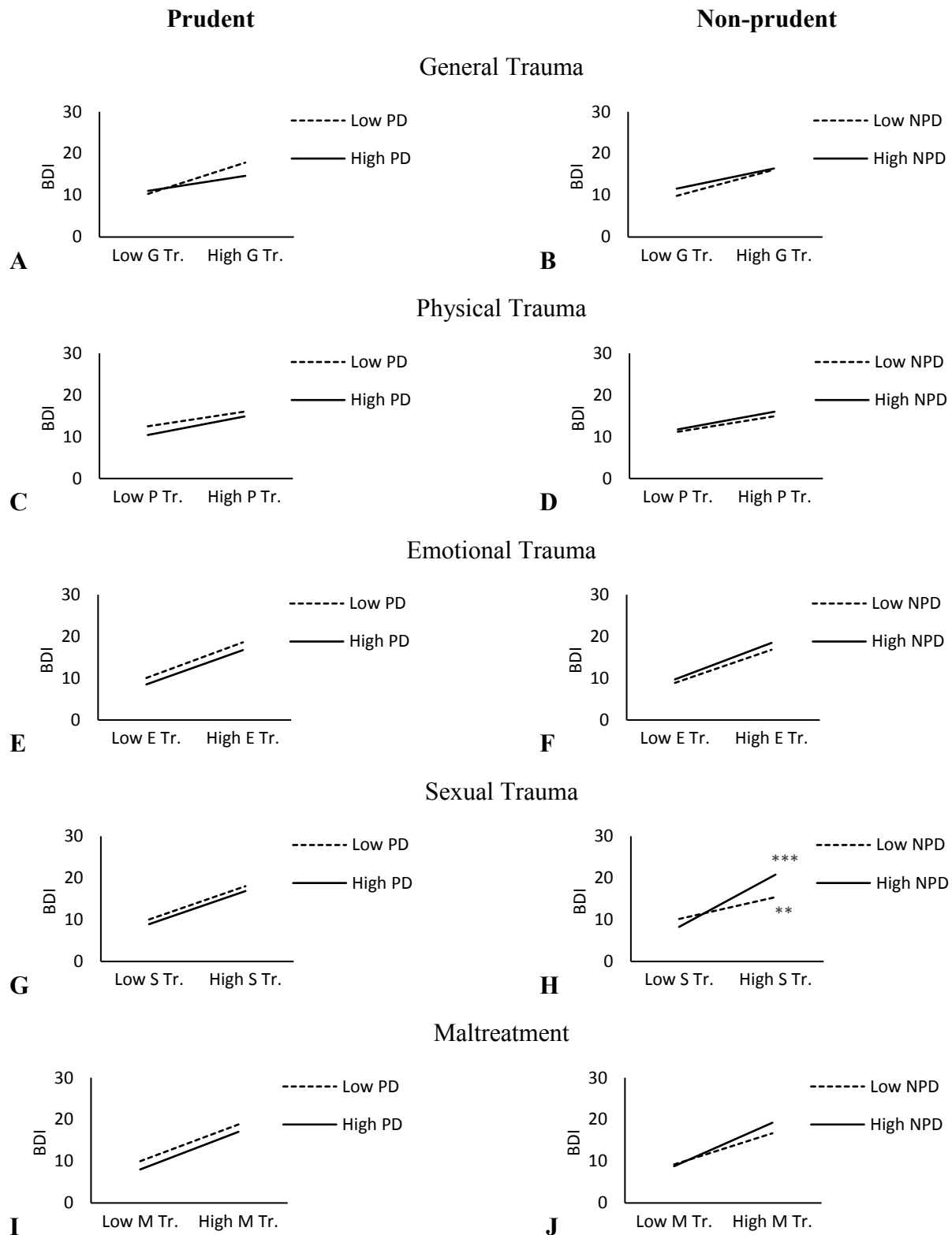


Figure 3. The moderating role of diet in the relation between trauma and depressive symptoms.  
Note: \*\* $p < .01$ , \*\*\* $p < .001$

*Interactive effects between early-life trauma and exercise, in predicting Remote Associates Test performance and Depressive Symptoms*

Moderation analyses revealed that exercise did not interact with any type of trauma in predicting either Remote Associates Test performance or depressive symptoms (Figure 4 panels A-J). There were also no main effects present.



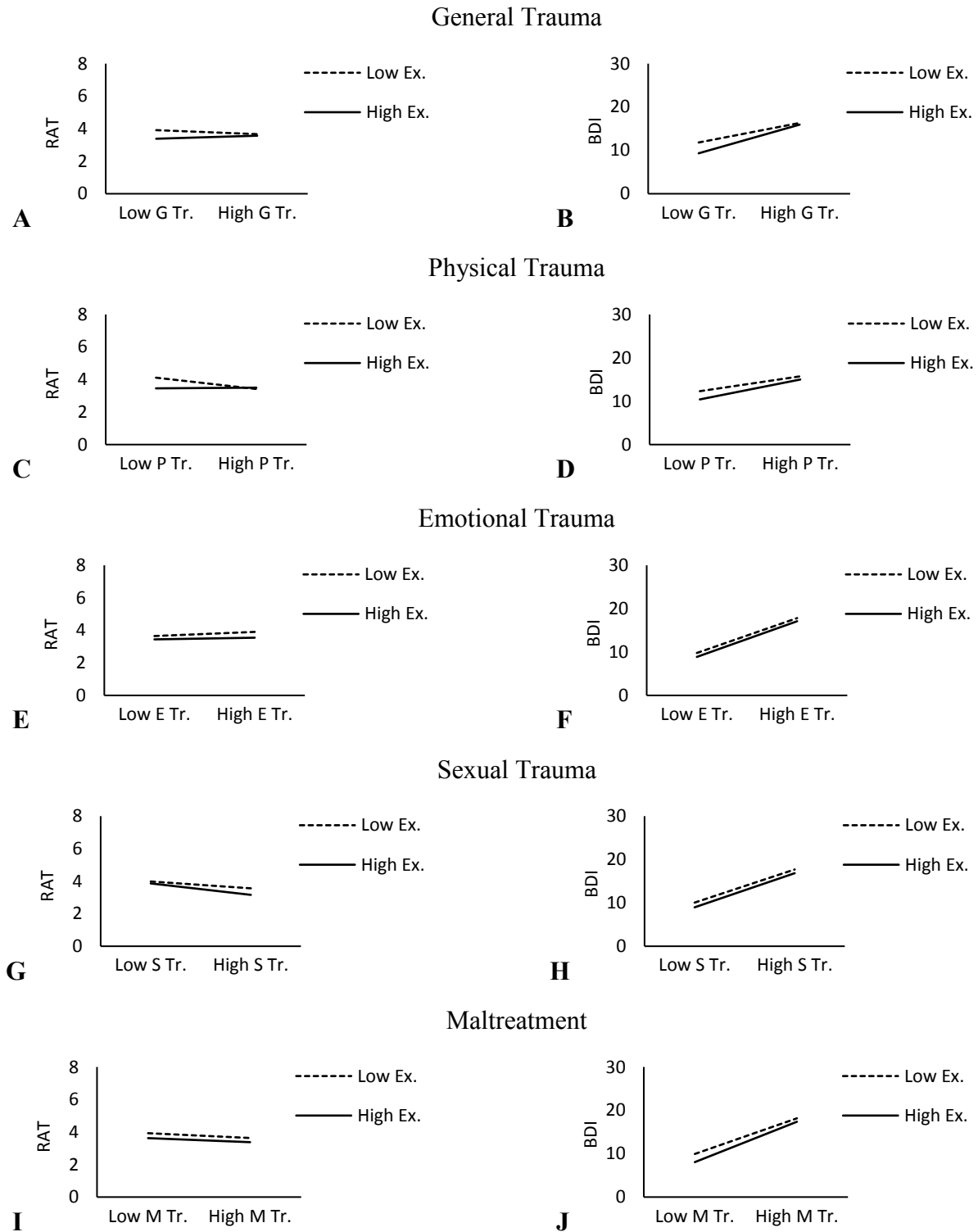


Figure 4. The moderating role of exercise in the relation between trauma, and depressive symptoms and performance on the Remote Associates Test (RAT).

## Discussion

### *Differences by sex on predictor, moderator, and outcome variables*

As frequently observed, the present investigation revealed that females reported higher levels of depressive symptoms than did males, and, as will be discussed shortly, several predictors of this dimorphism were detected, which is in line with past research (Altemus, Sarvaiya, & Epperson, 2014; Halbreich & Kahn, 2007). Consistent with earlier reports, sexual trauma was more prevalent among females than males (Briere & Elliott, 2003; Maikovich-Fong & Jaffee, 2010; Meng & D'Arcy, 2016; Stoltenborgh, Van Ijzendoorn, Euser, & Bakermans-Kranenburg, 2011; Waal et al., 2017). Although there is limited research concerning sex differences regarding maltreatment and emotional trauma, in the present investigation, these forms of trauma occurred more among females than males. Significant sex differences in physical abuse was not observed, which is in line with earlier research (Briere & Elliott, 2003), although the majority of studies indicated that males experienced more physical abuse during childhood than did females (Meng & D'Arcy, 2016; Thompson, Kingree, & Desai, 2004).

Aside from differences related to early-life traumatic experiences, females generally reported a healthier dietary intake, in that they consumed more prudent dietary foods, and less non-prudent dietary items, which corresponds to previous research (Leblanc et al., 2015). Although the present study did not find any sex differences in frequency of exercise, earlier reports suggest that males engage in physical activity more than females (Bauman et al., 2012; Hallal et al., 2012).

Given the breadth of research on early-life trauma and the promotion of mental disturbances (for example see Negele et al., 2015), it is not surprising that a positive relation between early-life trauma and depression was observed. It had been suggested that trauma

incurred during critical periods of brain development are associated with neurobiological changes in regions associated with the stress response and executive functioning (Danese & Baldwin, 2017; Heim et al., 2008), which in turn, can increase the risk for pathology. Although performance on the Remote Associates Test was not linked to early-life trauma in the present study, several reports have indicated that such experiences are associated with dysfunction within brain regions such as the hippocampus and prefrontal cortex (e.g., Heim & Binder, 2012; Pechtel & Pizzagalli, 2010), which play a role in creative insight (Dietrich, 2004). This said, there is research suggesting that creativity is not localized in any one particular area of the brain, but rather it is diffused across multiple areas and behavioral/cognitive domains (Dietrich & Kanso, 2010). Although we did not find a relation between performance on the Remote Associates Test and depressive symptoms, it has been reported that a positive association exists between mental illness and some measures of creativity (Johnson et al., 2012), although this may be dependent on current mood state of the individual (Fodor, 1999).

The present finding that emotion-focused coping strategies were higher in the uncontrollable condition, is consistent with past research, as these types of coping strategies are generally endorsed to a greater degree in situations where the outcome has to be accepted (Folkman, 2013). In contrast, although we didn't find that problem-focused coping endorsement varied by the controllability of the stressor situation, in controllable situations, the use of problem-focused coping strategies is typically elevated (Folkman, 2013). Although there was no main effect of Sex, or any Sex x Condition interactions on coping endorsement, it was usually found that among college students, females tend to report a higher use of emotion-focused coping strategies than males, although the sexes may vary in coping strategy endorsement by situation (Brougham, Zail, Mendoza, & Miller, 2009; Matheson & Anisman, 2003).

It was observed that in the uncontrollable condition, a negative correlation existed between problem-focused coping use in relation to trauma experienced early in life, however, there is limited past research corroborating this relation. More often, early-life adverse events were positively linked to emotion-focused coping strategy endorsement (Vaughn-Coaxum et al., 2018), although we did not observe this relation. It was also found that emotion-focused coping strategies were positively associated with depressive symptoms, which seems to correspond with past research (Matheson & Anisman, 2003).

*Interactive effects between situational control and lifestyle factors, in predicting coping scores*

As expected, stressor controllability interacted with exercise in predicting use of emotion-focused coping strategies, in that a negative relation existed between controllability and emotion-focused coping use, being most prominent in the presence of higher levels of exercise. The inverse relation observed between the controllability of a stressor and emotion-focused coping endorsement is again, in line with previous research (Folkman, 2013); however, the stronger association at a higher frequency of physical activity might be due to the increased likelihood that exercise, instead of emotion-focused coping strategies, might be used in the face of a stressor, as regular physical activity and ‘exercise coping’ were positively associated (Harris, Cronkite, & Moos, 2006). Moreover, frequent exercise was also associated with lower perceived stress (Garber, 2017), and enhanced cognitive control (Olson et al., 2017), which may facilitate more adaptive, problem-focused methods of coping.

*Interactive effects between early-life trauma and dietary pattern, in predicting Remote*

*Associates Test performance and Depression*

A negative relation existed between trauma (both physical and sexual) and Remote Associates Test performance, which as mentioned previously, was not surprising given that

early-life adverse events can negatively impact regions of the brain involved in creative problem solving. It appeared that the relation between physical trauma and the Remote Associates Test performance was contingent upon a lower adherence to a prudent dietary pattern, which might be due to negative effects on cognition promoted by a lower intake of prudent dietary items (Hardman et al., 2016). Although speculative, it is possible that the pro-inflammatory environment created by the lack of sufficient ‘healthy’ dietary items (Chrysohoou et al., 2004), coupled with the increased levels of inflammation stemming from early-life trauma (Heim & Binder, 2012), might be synergistically impacting creative insight (as measured by performance on the Remote Associates Test), as increased levels of inflammation are associated with impairment in multiple domains of cognition (Teunissen et al., 2003).

The positive relation between the subsets of trauma and depression is again not surprising, being supported by past research (Heim & Binder, 2012). The stronger relation between these two variables at higher levels of adherence to a non-prudent dietary pattern might be due to the inflammation from non-prudent dietary items (Berk et al., 2013), adding to the already present pro-inflammatory profile from trauma experienced early in life.

#### *Interactive effects between early-life trauma and exercise, in predicting Remote Associates Test performance and Depression*

It is unclear why exercise did not moderate the relation between early-life trauma and either Remote Associates Test performance or depressive symptoms. Comparing our findings with past research is difficult due to the lack of research specifically examining this interaction. Nevertheless, it was reported that exercise can enhance cognitive performance, particularly in domains associated with the prefrontal cortex (Hillman, Erickson, & Kramer, 2008), which could in turn enhance creative problem solving. However, most of this research is limited to aerobic

exercise, whereas in the present investigation, both forms of exercise (aerobic and anaerobic) were considered as ‘exercise’. Although there are reports that suggests aerobic and anaerobic may not differ in their positive effects on some aspects cognition, these reports were limited to reaction time, impulse control, and visual motor speed (Brutvan, 2011). Comparing our non-significant interactions between early-life trauma and exercise in predicting depressive symptoms is also difficult, as past research is limited to animal research, and to the best of our knowledge, to only one study with humans, which involved aerobic exercise (Newman & Motta, 2007).

Taken together, it appears that exercise and dietary habits are associated with a reduction of negative effects from trauma incurred early in life or from a current potential threat. Specifically, the controllability of a stressor was associated with a reduction in the use of emotion-focused coping strategies, and that physical activity seemed to further facilitate this relationship. It also appeared that a lower intake of healthy foods was accompanied by the exacerbation of the detrimental effects of early-life trauma on creative problem solving. In addition, a diet higher in unhealthy foods was associated with greater depressive symptoms associated with trauma experienced in early-life. It is also important to note that the nature of the trauma seems to play an important role as well, as not all traumas interacted with dietary pattern and exercise habits. Despite the effects of diet in influencing the relation between early-life stress and measures of mental health, it doesn’t seem that exercise is associated with a protective effect in this regard.

Several limitations of the present study need to be addressed, as it has been suggested that nutritional research, particularly correlational studies utilizing dietary questionnaire methods, may be inaccurate (Ioannidis, 2013). For example, dietary pattern was assessed using a food

frequency questionnaire, which although easily administered and cost efficient, might be prone to error owing to the time that elapsed between consumption and recording. It also appears that food consumption may be underestimated (Gemming, Jiang, Swinburn, & Mhurchu, 2014), although some studies have found it may vary depending on the type of macronutrient consumed (Schaefer et al, 2000). However, plasma levels of omega-3 fatty acids were comparable to that observed using a food frequency questionnaire in other research (Garneau et al., 2012). Similar to the limitations associated with dietary questionnaires, self-report measures of exercise, and early-life trauma, although cost effective and convenient, can be susceptible to memory biases.

## **CHAPTER 2**

### **The moderating role of immune related genetic polymorphisms in the relation between dietary pattern and cognitive flexibility, coping strategy endorsement, and depressive symptoms**

#### **Abstract**

Both lifestyle factors and immune related genetic polymorphisms have been linked to the risk of developing depression, but less is known about how these factors might interact in predicting this risk. The present study examined the potential interaction between dietary pattern and various immune related polymorphisms in predicting depressive symptoms, coping flexibility, and coping selection. Among male and female students ( $N=163$ ), adherence to a non-prudent dietary pattern was negatively related to coping flexibility, and positively related to emotion-focused coping strategy endorsement, although these relations only existed among participants with the GG genotype of the IL-6 polymorphism. It was also found, that a negative relation existed between prudent dietary pattern adherence and emotion-focused coping endorsement, but this relation was stronger among males with the CC genotype of the IL-10 polymorphism. Finally, it was observed that a non-prudent dietary pattern adherence was negatively related to coping flexibility, but only for the GG genotype of the IL-17A polymorphism. Moreover, this dietary pattern was also positively related to typical depressive symptoms, but again, this relation only existed for individuals with the GG genotype. Taken together, it seems that the immune regulating effects of dietary patterns and immune related polymorphisms, might be synergistically linked to immune functioning, and could thereby be tied to factors related to mental health.



## **Introduction**

It has been maintained that dietary pattern may contribute to the emergence and maintenance of depressive disorders (Khalid, Williams, & Reynolds, 2016). A subtype of this disorder, atypical depression, is of particular interest to the present investigation as it is marked by changes in food intake (as well as increased weight and sleep) together with the more common features of depression, such as anhedonia and poor mood. In addition to depressive symptoms, dietary pattern was also related to coping selection and cognitive processes that underlie coping flexibility, which are often impaired among individuals who are depressed (Gabrys, Tabri, Anisman, & Matheson, 2018).

Coping, or the efforts of an individual to mitigate the potential negative effects of a stressor, comprises many different types of strategies (or styles), which generally can be classified as either problem-focused (e.g., problem solving, cognitive restructuring), emotion-focused (e.g., emotional expression, self-blame), or avoidant methods (e.g., denial, active distraction). In general, emotion-focused coping strategies are often considered to be maladaptive, as affective disorders are associated with a greater use of these strategies (Matheson & Anisman, 2003). However, this view may be overly simplistic, as there are cases in which avoidant or emotion-focused coping strategies might be particularly effective (Stanton et al., 2000). Just as dietary patterns are related to depressive symptoms, they have also been associated with coping selection during stressful encounters. Indeed, elevated intake of snack foods was associated with a greater use of emotion-focused strategies during stressful events, whereas healthier dietary quality was associated with more support seeking strategies (Kuczmarski et al., 2017).

Cognitive flexibility, or the extent to which an individual is able to shift attention from one cognitive set to another while inhibiting habitual modes of thinking, has been implicated as playing a role in limiting depression (Fresco et al., 2006; Hou et al., 2016). Essentially, cognitive flexibility may be a component of coping flexibility, which might favor individuals' ability to adapt their coping strategies to potential stressors. As dietary intake is linked to depression, it might also be linked to coping flexibility, as intake of cholesterol (Kalmijn et al., 2004), and sucrose (Magnusson et al., 2015), are both related to tasks that assess cognitive flexibility.

Although there are multiple pathways through which diet might be linked to depressive symptoms and cognitive processes that underlie coping selection and coping flexibility, there is reason to suspect that immune system functioning can play a role in mediating this relation. To be sure, a prudent dietary pattern, which is characterized by a higher intake of vegetables, fruits, and fish, is associated with a reduction in C-reactive protein (CRP) and pro-inflammatory cytokines, IL-6, IL-18, and TNF- $\alpha$  (Lopresti, Hood, & Drummond, 2013). In contrast, a non-prudent dietary pattern, which is characterized by a higher consumption of processed meats, high glycemic carbohydrates, and unhealthy fats, was associated with increased production of inflammatory markers, such as CRP (Barbaresco et al., 2013).

Inflammation is also associated with both typical (Haapakoski et al., 2015) and atypical depression (Łojko & Rybakowski, 2017; Yoon et al., 2012), although markers of inflammation may vary between these two depressive subtypes (Dunjic-Kostic et al., 2013; Rudolf et al., 2014). Despite the link between inflammation and depression, limited research has been reported examining the association between inflammation and neuronal activity within brain regions that may play a role in coping selection and coping flexibility. Executive functions, such as inhibitory control and working memory, mediated in part by the prefrontal cortex (PFC), might underlie

coping selection, as problem-focused coping endorsement was positively related to inhibitory control, whereas avoidant strategies were negatively related to inhibitory control (Compas, 2006). As well, among individuals with typical depression, symptom severity was positively related to an emotion-oriented coping style. Moreover among these individuals, lower neural activity (as measured by hemodynamic response) was observed in the ventrolateral and dorsolateral prefrontal cortex, and midline fronto-polar and bilateral orbitofrontal cortex (OFC), during a cognitive task, compared to healthy controls (Pu et al., 2012). It has also been suggested that the mesocorticolimbic pathway, which comprises dopaminergic neurons projecting to the PFC, among other areas such as the nucleus accumbens and amygdala, may also play a role in coping processes (Bai et al., 2017). As cognitive flexibility may be fundamental in coping selection, it is not surprising that there is increased neural activity in the PFC during a cognitive set shifting task (Braver et al., 2003), although there is reason to believe that the parietal cortex (Fox et al., 2003) and striatum (Robbins, 2007) play a significant role in cognitive flexibility as well.

Despite the research linking specific brain regions to coping selection and cognitive flexibility, there are limited data tying inflammation with these brain regions or to executive functioning. However, it has been reported that elevating IL-6 levels in the OFC, is associated with enhanced cognitive flexibility, although excessive levels of IL-6 may have negative consequences (Donegan et al., 2014). The majority of the research has examined the relation between cytokines and other cognitive functions, particularly such as learning and memory. For example, IL-6 and TNF- $\alpha$ , which are typically considered to be pro-inflammatory cytokines, are associated with both positive and negative effects on learning and memory, but the association may depend on the age of the individual, and/or the magnitude and duration of the elevation

(acute vs. chronic), whereas it is clear that elevated levels of IL-1 $\beta$  seems to have negative effects on learning and memory (Yirmiya & Goshen, 2011). However, when the immune system is chronically activated, and excessive levels of pro-inflammatory cytokines are produced (e.g., in the case of an unhealthy dietary pattern), increased excitotoxicity, apoptosis, and neurodegeneration may result, which may impair a variety of cognitive processes (Yirmiya & Goshen, 2011). Other cytokines, such as IL-10 (Mesquita et al., 2008), IL-17 (Liu et al., 2012), and IL-18 (Merendino et al., 2002), have been associated with depression; however, their effects on cognition, coping selection and coping flexibility, is less well known.

In addition to dietary pattern, cytokine production may also be influenced by single nucleotide polymorphisms (SNPs), and their resulting changes in cytokine levels are also associated with depression. Indeed, multiple reports linked depression to immune related SNPs, such as IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ , although the effects of IL-17A and IL-18 seem to be less replicable (Barnes et al., 2017). Several reports have also linked cytokine-related SNPs to cognitive functioning. By example, the mutant allele of the IL-1 $\beta$  SNP (rs16944) was associated with poorer memory performance, and the mutant allele of the TNF- $\alpha$  polymorphism (rs1800629), was related to neuroprotective effects and increased processing speed (Baune et al., 2008). However, less is known concerning the links between IL-6, IL-10, IL-17A, and IL-18 and cognition, executive functioning, and the potential impact on coping selection and coping flexibility.

As dietary pattern and immune related SNPs are related to cognitive processes that underlie coping flexibility and coping selection, as well as depressive symptoms, it is possible that dietary pattern and these SNPs may interact in predicting these cognitive, behavioral and mood processes. Specifically, it is expected that prudent dietary adherence would be positively

related to measures of coping flexibility and problem-focused coping selection, and negatively related to emotion-focused coping endorsement and depressive symptoms, but these relations would be stronger for individuals with allele(s) associated with lower levels of inflammation. In contrast, it is expected that the non-prudent dietary pattern would negatively relate to measures of coping flexibility and problem-focused coping endorsement, and would positively relate to depressive symptoms and emotion-focused coping adherence, however, these relations would be stronger for individuals carrying allele(s) associated with higher levels of inflammation.

## **Methods**

### **Participants**

The study comprised female ( $n = 119$ ) and male ( $n = 44$ ) undergraduate students ( $M_{age} = 20.66$ ,  $SD = 4.63$ ) attending Carleton University, that were recruited on-line using Carleton University's SONA system (although  $N$  did vary slightly across genes). Due to the variability in frequencies of polymorphisms across ethnicities, all participants were of self-reported Euro-Caucasian decent.

### **Procedure**

Once informed consent was received, participants provided a saliva sample for genotyping, and then completed a series of questionnaires pertaining to demographic variables (e.g., ethnicity, age), dietary pattern, exercise frequency, coping endorsement, coping flexibility, and depression. All procedures were approved by the Carleton University Ethics Committee for Psychological Research.

## Genotyping

Samples for genotyping were collected using Norgen collection kits (Norgen Biotek Corp., Thorold, Ontario Canada). Genomic DNA was extracted from the sample collection kits according to the manufacturer's instructions, and diluted to approximately equal concentration (30 ng/ $\mu$ L). The samples were sent to McGill University and G  nome Qu  bec Innovation Center (Montreal, Canada) for genotyping. A multiplex PCR was performed on 20ng of template genomic DNA in a 5uL reaction mixture. Some PCR reactions were ran on QIAxcel (QIAGEN) to assess the amplification. A shrimp-alkaline-phosphatase (SAP) treatment was done to remove the unused nucleotides, followed by a primer extension reaction (iPLEX Gold) in multiplex. The products were then desalted with 6mg of resin (Agena Bioscience) and spotted on a 384-point SpectroCHIP (Agena Bioscience) using a nanodispenser (Agena Bioscience). The distinct masses were detected by MALDI-TOF mass-spectrometry and the data was analyzed using MassARRAY Typer Analyser software. Primer sequences were as follows:

TNF- $\alpha$  forward: ACGTTGGATGTTCTGGGCCACTGACTGATT  
TNF- $\alpha$  reverse: ACGTTGGATGAAGGAAACAGACCACAGACC  
TNF- $\alpha$  probe: ctAGGCTGAACCCCGTCC

IL-1 $\beta$  forward: ACGTTGGATGCTGTCTGTATTGAGGGTGTG  
IL-1 $\beta$  reverse: ACGTTGGATGATTTTCTCCTCAGAGGCTCC  
IL-1 $\beta$  probe: tCCTTGGGTGCTGTTCTCTGCCTC

IL-6 forward: ACGTTGGATGGATTGTGCAATGTGACGTCC  
IL-6 reverse: ACGTTGGATGAGTGGTTCTGCTTCTTAGCG  
IL-6 probe: cccaacGTGACGTCCTTTAGCAT

IL-10 forward: ACGTTGGATGGGTGAGGAAACCAAATTCTC  
IL-10 reverse: ACGTTGGATGAGTGGGTAAGAGTAGTCTGC  
IL-10 probe: GGTGTACCCTTGTACAGGTGATGTAA

IL-17A forward: ACGTTGGATGCCCCAATGAGGTCATAGAAG  
IL-17A reverse: ACGTTGGATGAGCTCTGCTCAGCTTCTAAC  
IL-17A probe: GAGGTCATAGAAGAATCTCT

IL-18 forward: ACGTTGGATGCTCTCCCCAAGCTTACTTTC  
IL-18 reverse: ACGTTGGATGTGCTGTATCAGATGCAAGCC  
IL-18 probe: TCTGTTGCAGAAAGTGTAATAATTATTA

The distributions of each gene were as follows:

TNF- $\alpha$ : 106 GG (36 male, 70 female), 32 GA (12 male, 20 female), and 6 AA (3 male, 3 female)

IL-1 $\beta$ : 56 GG (21 male, 35 female), 68 GA (23 male, 45 female), and 19 AA (7 male, 12 female)

IL-6: 55 GG (19 male, 36 female), 59 GC (22 male, 37 female), and 27 CC (8 male, 19 female)

IL-10: 116 CC (26 male, 90 female), 70 CT (19 male, 51 female), and 10 TT (5 male, 5 female)

IL-17A: 84 GG (16 male, 68 female), 64 GA (20 male, 44 female), and 15 AA (8 male, 7 female)

IL-18: 76 GG (17 male, 59 female), 95 GT (23 male, 72 female), and 28 TT (11 male, 17 female)

Note: in each distribution, alleles did not violate Hardy-Weinberg Equilibrium expectations, and due to the infrequency of the minor alleles, we collapsed all across mutant allele carriers for further analyses.

## Measures

*Physical Exercise.* Physical exercise was assessed using the Godin-Shepard Leisure-Time Activity Questionnaire (Godin, 2011; Modified), a 3-item measure that instructed participants to indicate the frequency in which they participate in mild, moderate, and strenuous exercise, for more than 15 minutes per week.

*Dietary Pattern.* Dietary pattern was assessed using a modified food frequency questionnaire (FFQ) (Hu et al., 1999), a 44-item measure that instructs participants to indicate the frequency they consumer various dietary items (e.g., lean proteins, dairy products, green leafy vegetables, etc.) per week on average over the past year. The food items were then grouped into either a prudent dietary pattern (leafy vegetables, other vegetables, tomatoes, fruits, cruciferous

vegetables, salad dressing, and fish;  $\alpha = .88$ ) and a non-prudent dietary pattern (desserts, processed meats, fried food, sweets, refined grain, high-fat dairy, and condiments;  $\alpha = .86$ ) based on Akbaraly et al. (2009).

*Coping.* Coping was assessed using the Survey of Coping Profiles Endorsed (Matheson & Anisman, 2003), a 50-item scale which measured the degree to which participants endorsed 13 coping strategies to cope with stressors in general. Based on our earlier reports, the coping scale was assessed as comprising two factors, emotion-focused and problem-focused coping. Emotion-focused coping comprised: rumination, emotional expression, other-blame, self-blame, passive resignation, and wishful thinking (Cronbach's  $\alpha = .78$ ). Problem-focused coping comprised: problem solving, cognitive restructuring, active distraction, avoidance, humor, and social support seeking (Cronbach's  $\alpha = .66$ ).

*Depressive symptoms.* Depressive symptoms were assessed using the 21-item version of the Beck Depression Inventory (BDI) (Beck et al., 1961). Total scores were calculated by summing across all items ( $\alpha = .91$ ). In addition, 6 further items were added to assess atypical depressive symptoms, as shown in Appendix A ( $\alpha = .67$ ).

*Cognitive Flexibility.* Cognitive flexibility was assessed using a modified 28-item version of the Cognitive Control and Flexibility Questionnaire (CCFQ) (Gabrys, Tabri, Anisman, & Matheson, 2018), which assesses an individual's capability of exerting control over unwanted (negative) thoughts and emotions, when these are counterproductive to resolving a stressful situation. The items comprise two factors, *cognitive control* (the extent to which an individual can control intrusive thoughts and emotions;  $\alpha = .92$ ) and *cognitive resources* (an individual's ability to engage in a set of deliberate effortful behaviors that can facilitate a comprehensive and favorable



appraisal of a stressful situation as well as the selection of a broad range of coping strategies;  $\alpha = .89$ ).

### Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics 20 for Windows (Armonk, NY: IBM Corp.). Analyses assessing differences in dietary pattern, coping selection, cognitive flexibility, and depression, as a function of Sex and Genotype, were determined by separate MANOVA. Correlational analysis was performed using Pearson product moment correlations. Interactions between Genotype and lifestyle factors on coping selection, cognitive flexibility, and depression, were conducted separately using the PROCESS macro (Hayes, 2013) in SPSS.

### Results

#### *TNF- $\alpha$ polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

Separate MANOVAs of depression, cognitive flexibility, coping, and dietary scores revealed main effects of Genotype on cognitive control,  $F(1, 218) = 5.62, p = .02$ , in that individuals with the GG Genotype had higher scores ( $M = 3.77, SD = 1.27$ ) of cognitive control than A carriers ( $M = 3.44, SD = 1.20$ ), and that carriers of the A allele adhered more to a non-prudent diet ( $M = 43.82, SD = 10.87$ ) than individuals who were heterozygous for the G allele ( $M = 40.94, SD = 10.02; F(1, 196) = 6.09, p = .01$ ), irrespective of Sex. As depicted in Table 1, it appeared that males had higher non-prudent dietary scores than females,  $F(1, 196) = 9.96, p = .002$ , and that females had elevated atypical depressive symptoms compared to males ( $F(1, 219) = 5.17, p = .02$ ), irrespective of Genotype. The analysis also revealed no significant Genotype x Sex interactions on any of the predictor or outcome variables. Interactions between Sex and

dietary patterns in predicting depression, cognitive flexibility, and coping, using the PROCESS macro (Hayes, 2013), were not significant.

Table 1. Means (*M*) and standard deviations (*SD*) by Sex on predictor and outcome variables.

	Male		Female	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
1. Prudent diet pattern	38.27	10.71	36.23	10.39
2. Non-prudent diet pattern	45.97**	10.97	40.64	9.89
3. Cognitive control	3.98	1.26	3.57	1.24
4. Cognitive resources	4.86	1.05	4.53	1.04
5. Emotion focused coping	1.99	.69	2.13	.64
6. Problem focused coping	2.51	.50	2.54	.55
7. Typical depression	8.39	7.51	11.24	9.19
8. Atypical depression	2.63	2.75	4.03*	2.79

Note: \* $p < .05$ , \*\*  $p < .01$

*Zero-order correlations between dietary pattern, cognitive flexibility, coping strategies, and depression*

Table 2 shows the intercorrelations between dietary patterns, cognitive flexibility, coping strategies, and depression. Owing to the multiple correlations conducted, coupled with the large *N* within this sample, only correlations that yielded *p* values beyond 0.01 were considered to be statistically meaningful. As seen in this table, both cognitive control and cognitive resources were negatively associated with emotion-focused coping and both typical and atypical depression, while only cognitive resources was positively associated with problem-focused coping. It was also apparent that emotion focused coping was positively associated with both typical and atypical depression. In contrast, problem focused coping was negatively associated with typical depressive symptoms.

Table 2. Zero-order correlations between dietary patterns, cognitive flexibility, coping strategies, and depression.

	1.	2.	3.	4.	5.	6.	7.
1. Prudent diet pattern	-	-	-	-	-	-	-
2. Non-prudent diet pattern	.01	-	-	-	-	-	-
3. Cognitive control	.10	-.12	-	-	-	-	-
4. Cognitive resources	.17	-.00	.52**	-	-	-	-
5. Emotion focused coping	-.14	.12	-.62**	-.27**	-	-	-
6. Problem focused coping	.12	-.05	.14	.36**	.14	-	-
7. Typical depression	-.09	.12	-.60**	-.30**	.54**	-.23**	-
8. Atypical depression	-.13	.04	-.44**	-.22**	.43**	-.15	.67**

Note. \*\**p* < 0.01

### *Moderating effects of the TNF- $\alpha$ polymorphism*

As shown in Figure 1 (panels A-L), the TNF- $\alpha$  polymorphism did not significantly moderate the relation between the dietary patterns and any of the outcome variables (see Table 3a for prudent dietary pattern coefficients, and 3b for non-prudent dietary pattern coefficients). Likewise, there were no interactions with Sex present. However, prudent dietary pattern adherence was positively associated with cognitive resources ( $b = .02$ ,  $SE = .007$ ,  $t = 2.57$ ,  $p = .01$ ), and atypical depressive symptoms appeared to higher among females ( $b = -1.49$ ,  $SE = .44$ ,  $t = -3.40$ ,  $p = .0008$ ), irrespective of Genotype and dietary pattern.

Table 3a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.01	.03	1.51
Cognitive resources	.0003	.004	.25
Emotion-focused coping	.006	-.01	-1.05
Problem-focused coping	.0000	-.0007	-.08
Typical depression	.0006	-.05	-.35
Atypical depression	.001	.02	.50

Table 3b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.002	.01	.63
Cognitive resources	.01	.03	1.64
Emotion-focused coping	.02	-.02	-1.85
Problem-focused coping	.009	.01	1.33
Typical depression	.001	-.07	-.53
Atypical depression	.006	-.04	-1.15

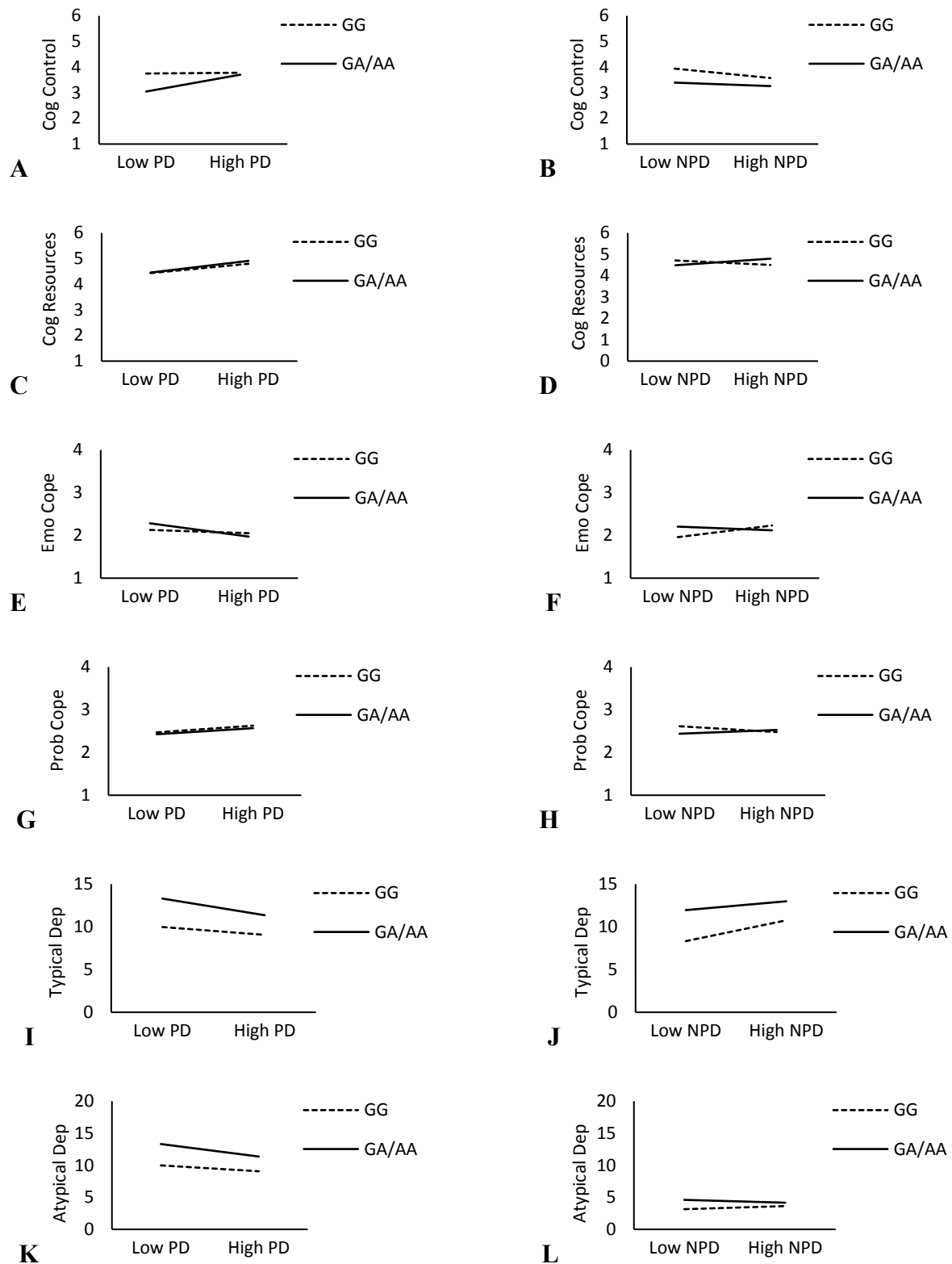


Figure 1. The moderating role of the TNF- $\alpha$  polymorphism in the relation between dietary pattern (PD and NPD), and cognitive flexibility, coping, and depression.

*IL-1 $\beta$  polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

MANOVAs conducted on depression, cognitive flexibility, coping, and dietary scores revealed no significant main effects of Genotype, or Gene x Sex interactions.

*Moderating effects of the IL-1 $\beta$  polymorphism*

As shown in Figure 2 (panels A-L), the IL-1 $\beta$  polymorphism did not significantly moderate the relation between either dietary pattern on any of the outcome variables (see Table 4a for prudent dietary pattern coefficients, and 4b for non-prudent dietary pattern coefficients). In addition, Sex did not interact with Genotype and either dietary pattern in predicting any of the outcome variables. However, prudent dietary pattern adherence was positively associated with cognitive resources ( $b=.02$ ,  $t = 2.55$ ,  $p=.01$ ,  $SE=.007$ ), irrespective of Genotype.

Table 4a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.008	.02	1.28
Cognitive resources	.009	.02	1.35
Emotion-focused coping	.02	-.02	-1.76
Problem-focused coping	.002	-.004	-.55
Typical depression	.0001	-.02	-.16
Atypical depression	.0007	.01	.37

Table 4b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.0000	-.0002	-.01
Cognitive resources	.002	.01	.70
Emotion-focused coping	.003	.006	.70
Problem-focused coping	.0004	-.002	-.28
Typical depression	.0003	.03	.23
Atypical depression	.007	.04	1.14



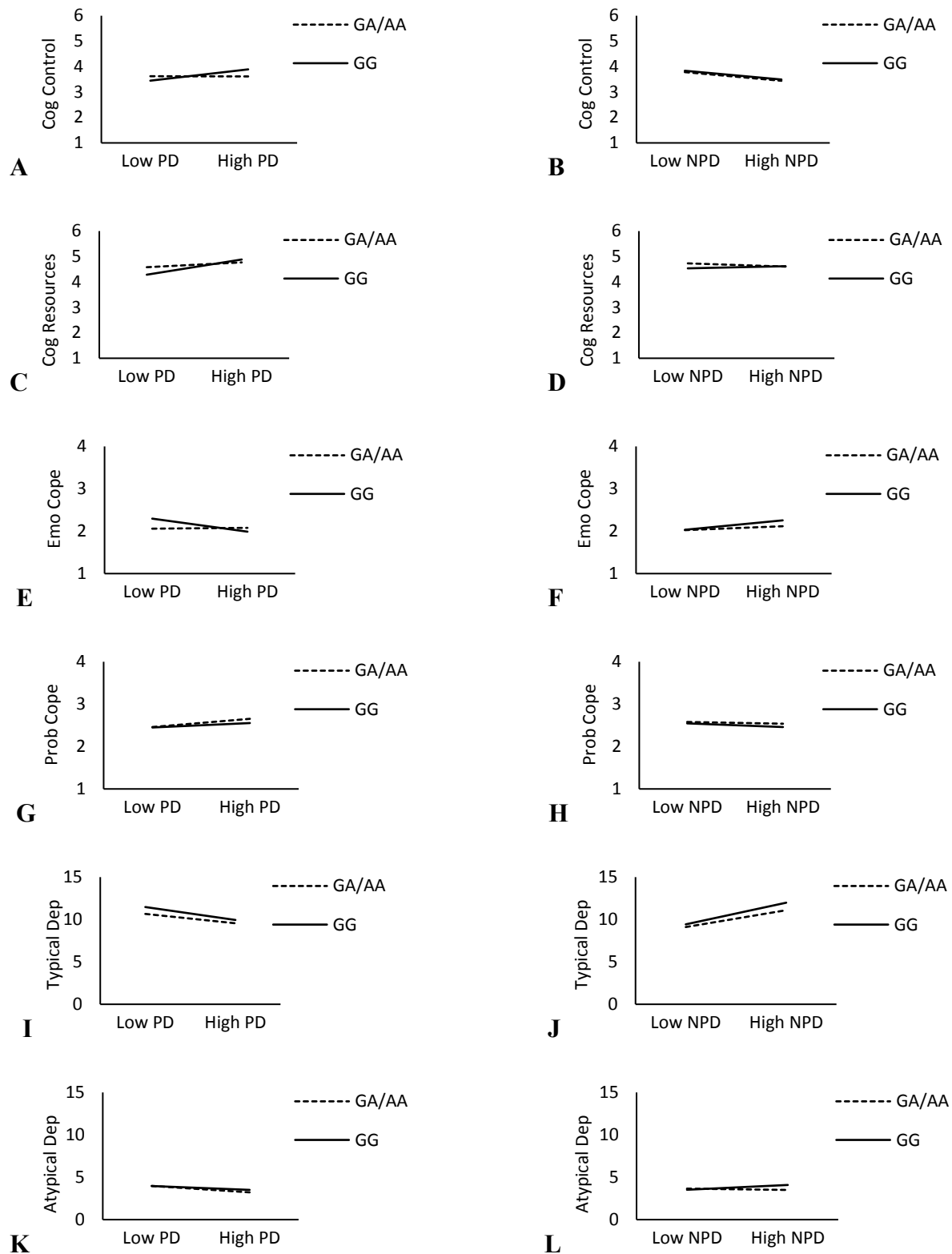


Figure 2. The moderating role of the IL-1 $\beta$  polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression.

*IL-6 polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

MANOVAs conducted on depression, cognitive flexibility, coping, and dietary adherence, revealed that C carriers ( $M = 4.74$ ,  $SD = 1.02$ ) had higher levels of cognitive resources than those with the GG Genotype ( $M = 4.48$ ,  $SD = 1.05$ ;  $F(1, 203) = 4.25$ ,  $p = .04$ ), and that Genotype and Sex did not interact.

*Moderating effects of the IL-6 polymorphism*

As depicted in Figure 3, the IL-6 polymorphism moderated the relation between non-prudent dietary adherence scores and cognitive control (see Table 5b for coefficients), such that non-prudent dietary adherence was negatively related to cognitive control, but only for the GG Genotype. As well, the IL-6 polymorphism moderated the relation between non-prudent dietary pattern adherence and emotion-focused coping (see Table 5b for coefficients), such that non-prudent dietary adherence was positively associated with emotion-focused coping, but this was only apparent among those with the GG Genotype. There were no interactions with Sex present (both interactions remained significant with Sex entered as a second moderator).

Table 5a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.02	.03	1.95
Cognitive resources	.01	.02	1.57
Emotion-focused coping	.0001	-.001	-.13
Problem-focused coping	.004	.006	.81
Typical depression	.004	-.11	-.88
Atypical depression	.006	-.04	-1.02

Table 5b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

Note: \*\**p* < .01, \*\*\* *p* < .001

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.04	.05	2.86***
Cognitive resources	.01	.02	1.53
Emotion-focused coping	.05	-.03	-2.93**
Problem-focused coping	.006	.009	1.09
Typical depression	.009	-.17	-1.25
Atypical depression	.0001	-.007	-.15

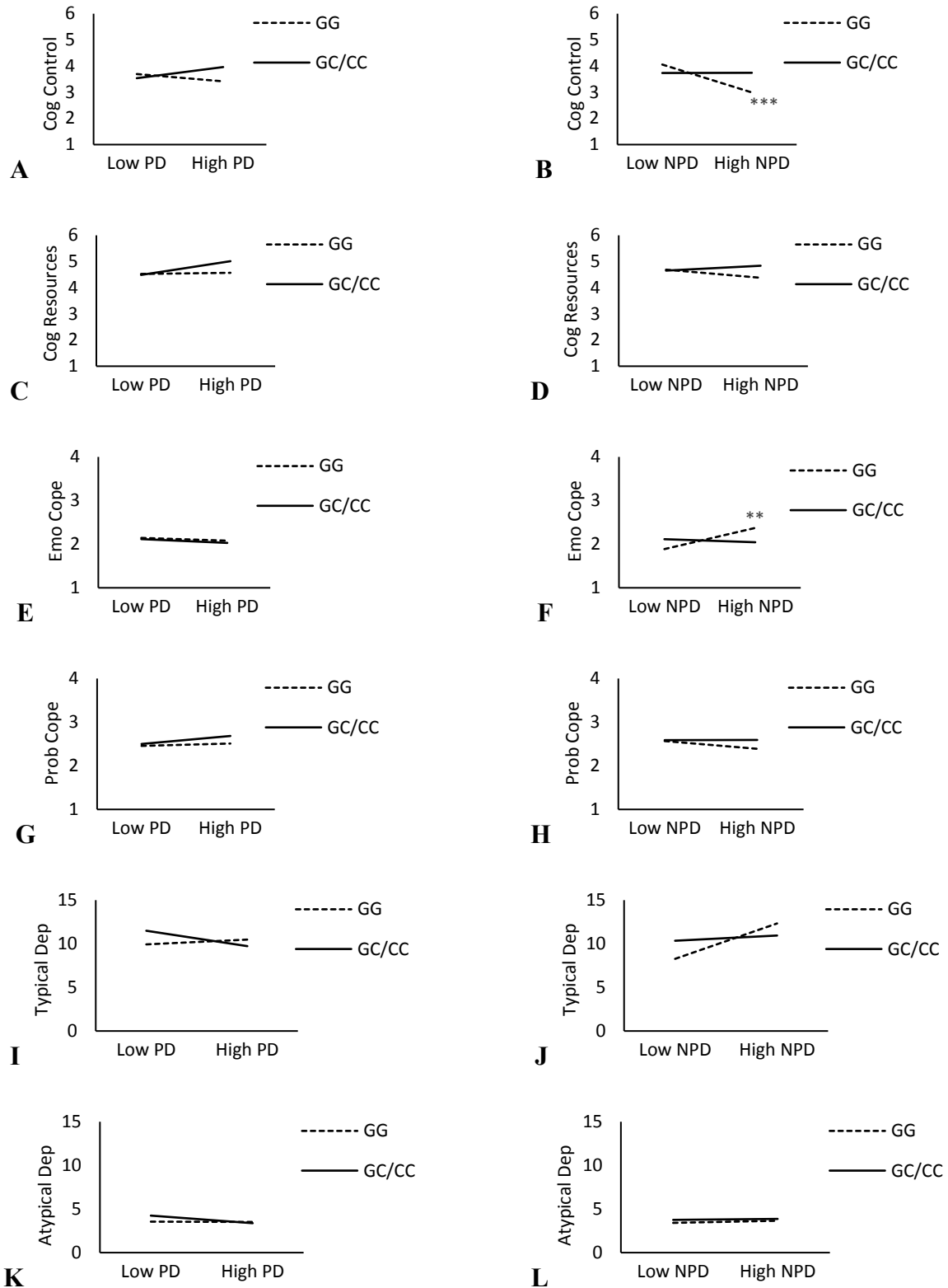


Figure 3. The moderating role of the IL-6 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression. Note: \*\* $p < .01$ , \*\*\* $p < .001$

*IL-10 polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

Separate MANOVAs that included depression, cognitive flexibility, coping, and dietary adherence, revealed no significant main effects of Genotype, or any Genotype x Sex interactions.

*Moderating effects of the IL-10 polymorphism*

As depicted in Figure 4, the IL-10 polymorphism moderated the relation between prudent dietary adherence scores and emotion focused coping, in that there was an inverse relation between prudent dietary scores and emotion-focused coping endorsement, but this was only true for the CC Genotype (see Table 6a for coefficients). Further moderation analyses revealed a 3-way interaction (see Figure 5) between prudent dietary adherence scores, Genotype, and Sex, in that there was a negative relation between prudent dietary adherence and emotion-focused coping only for the CC Genotype, but this interaction was only significant among males ( $\Delta R^2 = .04$ ,  $b = .06$ ,  $t = 2.76$ ,  $SE = .02$ ,  $p = .006$ ).

Table 6a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.  
 Note: \*\**p* < .01

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.007	-.02	-1.12
Cognitive resources	.002	.009	.62
Emotion-focused coping	.04	.02	2.69**
Problem-focused coping	.005	.008	.96
Typical depression	.003	.09	.75
Atypical depression	.009	.05	1.27

Table 6b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.0001	.003	.14
Cognitive resources	.009	.02	1.23
Emotion-focused coping	.0001	-.0009	-.10
Problem-focused coping	.02	.01	1.80
Typical depression	.0000	-.004	-.03
Atypical depression	.001	.02	.43

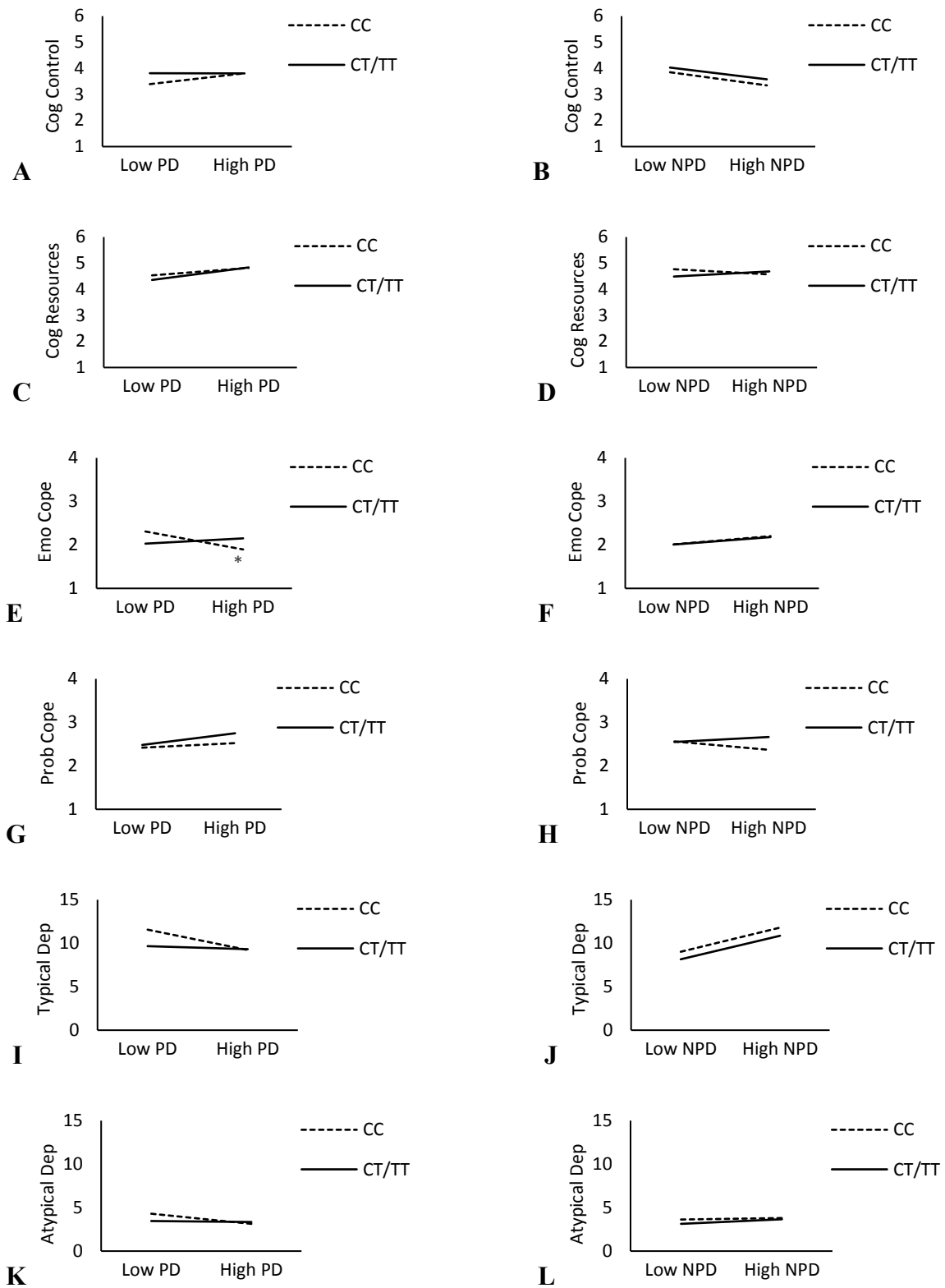


Figure 4. The moderating role of the IL-10 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression. Note: \*\* $p < .01$

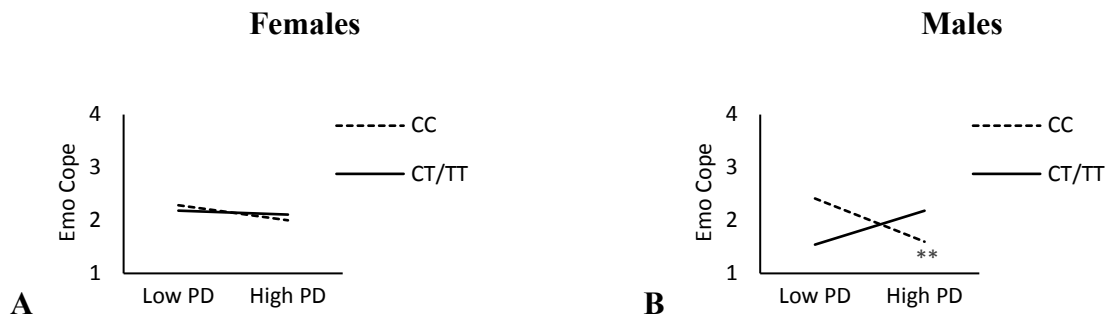


Figure 5. The combined interaction between the IL-10 polymorphism, Sex, and prudent dietary pattern, in predicting emotion-focused coping. Note: \*\* $p < .01$



*IL-17A polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

MANOVA revealed that prudent dietary scores were higher among males with the GG Genotype ( $M = 43.93$ ,  $SD = 9.75$ ) than females with the GG Genotype ( $M = 34.95$ ,  $SD = 10.14$ ;  $F(1, 140) = 7.26$ ,  $p = .008$ ). In addition, it appeared that male A carriers ( $M = 4.24$ ,  $SD = 1.27$ ) had higher levels of cognitive control than female A carriers ( $M = 3.33$ ,  $SD = 1.21$ ), however this effect only approached significance,  $F(1, 159) = 5.56$ ,  $p = .02$ . Likewise, it was found that female A carriers ( $M = 2.27$ ,  $SD = .66$ ) endorsed emotion-focused coping strategies more than male A carriers ( $M = 1.85$ ,  $SD = .73$ ), but again, this effect only approached significance,  $F(1, 159) = 4.37$ ,  $p = .04$ .

*Moderating effects of the IL-17A polymorphism*

As depicted in Figure 6B and 6D, the IL-17A polymorphism moderated the relation between non-prudent dietary adherence and both cognitive control and cognitive resources, such that non-prudent dietary adherence was negatively related to cognitive control (and cognitive resources), but only for the GG Genotype (see Table 7b for coefficients). It was also revealed that a positive relation existed between non-prudent dietary adherence and depressive symptoms, but only for the GG Genotype (as depicted in Figure 6J; see Table 7b for coefficients). There were no interactions present between dietary pattern, Sex, and Genotype in predicting any outcome variable.

Table 7a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.0007	-.006	-.33
Cognitive resources	.0001	.002	.13
Emotion-focused coping	.002	.006	.56
Problem-focused coping	.01	-.01	-1.34
Typical depression	.02	.25	1.89
Atypical depression	.02	.07	1.65

Table 7b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.  
Note: \*\**p* < .01, \*\*\**p* < .001

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.05	.06	2.69***
Cognitive resources	.04	.04	2.54**
Emotion-focused coping	.02	-.02	-1.66
Problem-focused coping	.02	.01	1.52
Typical depression	.05	-.40	-2.75***
Atypical depression	.01	-.06	-1.27

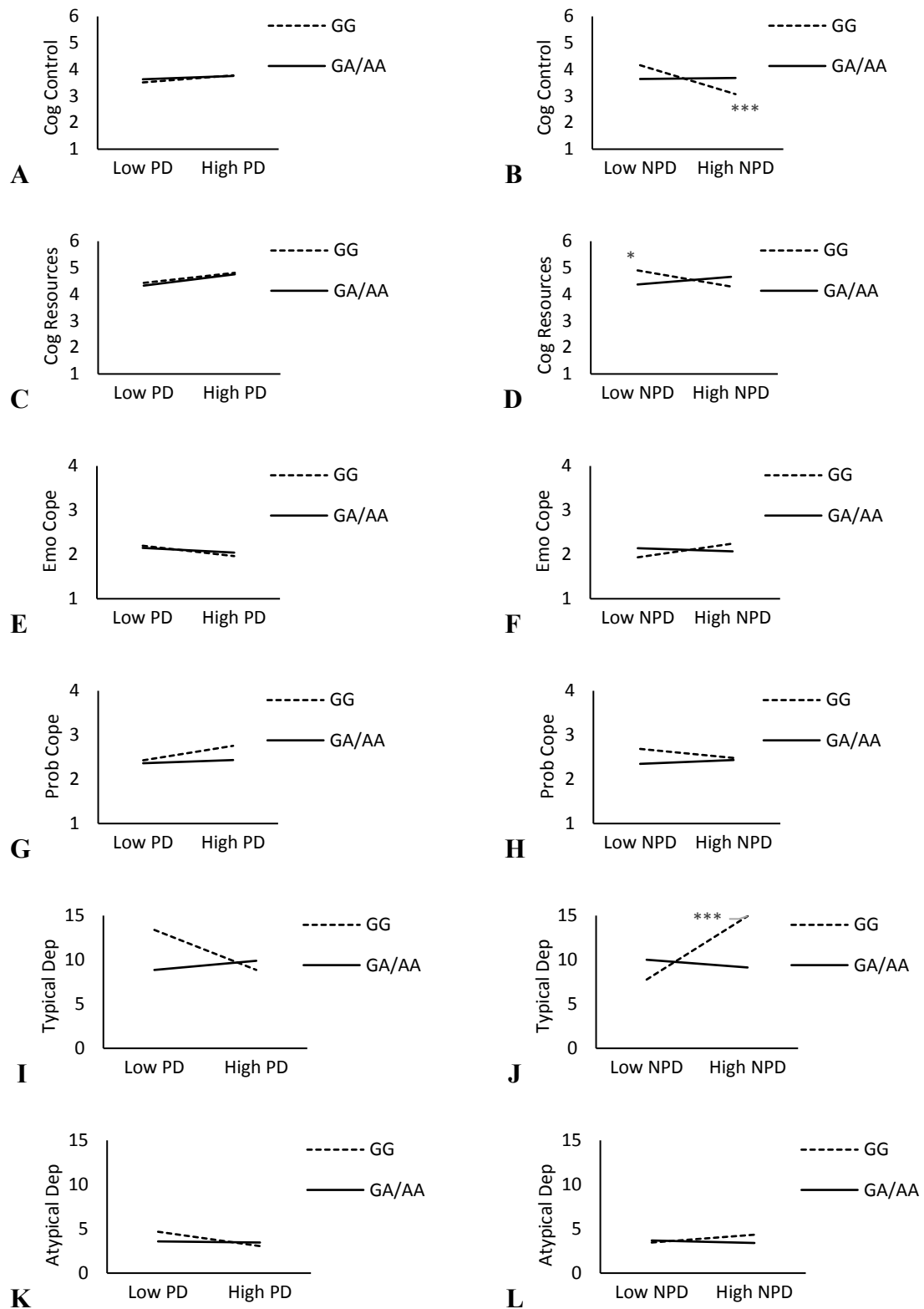


Figure 6. The moderating role of the IL-17A polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression. Note: \* $p < .05$ , \*\*\* $p < .001$

*IL-18 polymorphism and Sex, in relation to dietary pattern, cognitive flexibility, coping, and depression*

MANOVAs conducted on depression, cognitive flexibility, coping, and dietary scores revealed no significant main effects of Genotype, or Gene x Sex interactions.

*Moderating effects of the IL-18 polymorphism*

As depicted in Figure 7 (panels A-L), the IL-18 polymorphism did not moderate any relation between dietary pattern and any of the outcome variables, nor were there any significant main effects. However, it appeared that adherence to a prudent dietary pattern was inversely associated with typical depressive symptoms only for individuals with the GG Genotype, however, this interaction only approached significance ( $p = .049$ ; see Tables 8a and 8b for coefficients). In addition, Sex did not interact with Genotype and with either dietary pattern, in predicting any of the outcome measures.

Table 8a. Prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.0007	-.007	-.36
Cognitive resources	.01	.02	1.50
Emotion-focused coping	.004	.008	.83
Problem-focused coping	.001	-.004	-.46
Typical depression	.02	.25	1.98
Atypical depression	.01	.06	1.60

Table 8b. Non-prudent diet: Interaction R-square change, beta, and *t*-value, by outcome variable.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Cognitive control	.0000	.0008	.04
Cognitive resources	.003	.01	.71
Emotion-focused coping	.003	-.007	-.68
Problem-focused coping	.0006	-.003	-.32
Typical depression	.002	.07	.52
Atypical depression	.005	.04	.95

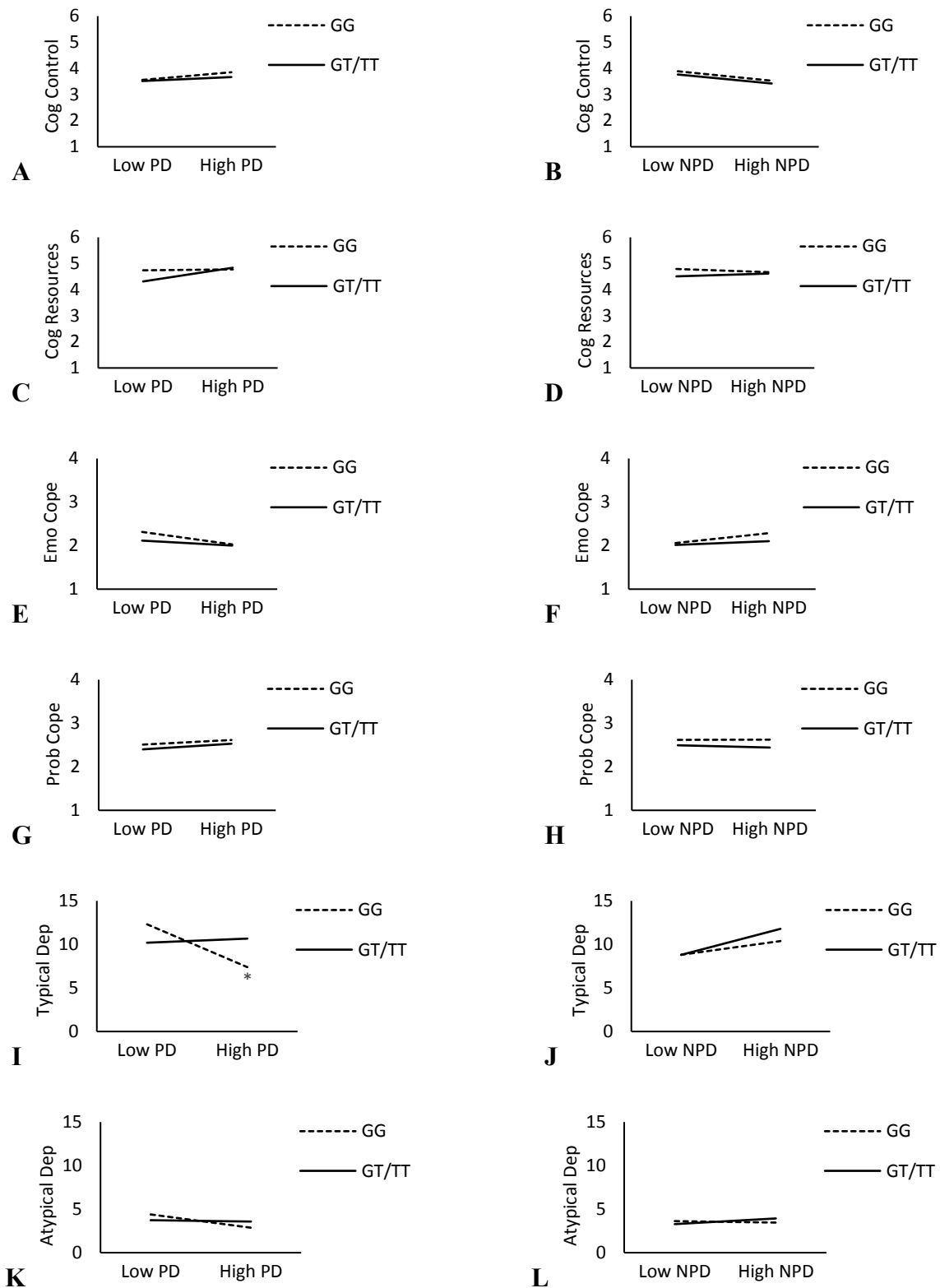


Figure 7. The moderating role of the IL-18 polymorphism in the relation between dietary pattern, and cognitive flexibility, coping, and depression. Note: \* $p < .05$

## **Discussion**

### **Zero-order correlations**

The present findings indicated that dietary patterns were not related to any of the outcome variables. This was somewhat surprising, given the abundance of past research indicating that diet may be predictive of cognition (e.g., Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014), coping (e.g., Kuczmarski et al., 2017), and depression (e.g., O'Neil et al., 2014). The present findings also revealed that both dimensions of cognitive flexibility (cognitive control and cognitive resources) were highly correlated, and that both dimensions were negatively associated with emotion-focused coping, typical and atypical depressive symptoms, and that only cognitive resources was positively correlated with problem-focused coping, which is in line with previous research (Gabrys, Anisman, & Matheson, 2018). In addition, persistent use of emotion-focused coping was related to both types of depression, and problem-focused coping was negatively related to typical depressive symptoms, which again corresponded with past research (e.g., Abdollahi et al., 2018; Matheson & Anisman, 2003; Whatley et al., 1998).

### **Sex differences in diet and depression**

Males seemed to report a higher intake of non-prudent dietary items, which appears to be consistent with earlier reports (Leblanc, Bégin, Corneau, Dodin, & Lemieux, 2015) showing that females tended to have higher levels of eating-related self-determined motivation than did men. In addition, atypical depressive symptoms were higher among females than males, as previously reported (Halbreich & Kahn, 2007). The source for this is uncertain, but may involve a variety of hormonal factors.

## **Gene polymorphisms and sex in relation to on dietary pattern, cognitive flexibility, coping, and depression**

The present findings indicated that A carriers of the TNF- $\alpha$  polymorphism exhibited less cognitive control than did those with the GG genotype. This finding seems to be in contrast to the majority of previous findings, which indicated that the A allele is associated with enhanced attentional selection compared to individuals with the GG genotype (for review see Trenova, Slavov, Manova, & Miteva, 2018). The authors suggested that the effect is likely due to the facilitating effect of TNF- $\alpha$  on glutamatergic functioning, which may explain the enhancement of attentional control. There is research among elderly individuals, however, which seem to support our finding that the A allele is associated with poorer attentional function. It was suggested that the detrimental effect of the A allele, which is associated with higher production of TNF- $\alpha$  (Kroeger, Carville, & Abraham, 1997), is due to the damaging effect TNF- $\alpha$  can promote *over time* on structural neuronal networks that contribute to attentional processes (Gajewski et al., 2013). It also appeared that A carriers of the TNF- $\alpha$  polymorphism adhered more to a non-prudent dietary pattern than did those with the GG genotype. This effect is difficult to speculate upon given the lack of research regarding immune related SNPs and dietary behavior. However, it is possible that higher levels of inflammation might have a detrimental effect on decision making by influencing prefrontal cortex neuronal functioning (reviewed in Anisman, Hayley, & Kusnecov, 2018).

In addition to the potential contribution of TNF- $\alpha$ , carriers of the C allele of the IL-6 polymorphism, displayed increased levels of cognitive resources compared to individuals with the GG genotype. This finding is consistent with previous research indicating that lower levels of IL-6, which occurs with this polymorphism (Fishman et al., 1998), is related to better cognition



(Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014). However, this findings might seem to be in contradiction with that of the TNF- $\alpha$  polymorphisms, in that lower levels of this pro-inflammatory cytokine seem to have a beneficial effect on cognition. It is difficult to explain the differences in these effects, especially given that IL-6 can also act in an anti-inflammatory capacity in some circumstances, such as by inhibiting the synthesis of TNF- $\alpha$ , and increasing the expression of IL-1 receptor antagonist (Wilson, Finch, & Cohen, 2002).

It was also found that males with the GG genotype of the IL-17A polymorphism had higher prudent dietary scores than females with the GG genotype. It is again difficult to speculate on why a polymorphism associated with lower levels of inflammation (Espinoza et al., 2011) would predict dietary pattern, and especially why this would be moderated by sex. At the moment there are simply insufficient data available that would allow for informed conclusion or speculation.

### **Interactive effects of genotype, sex, and dietary pattern**

Despite the abundance of research indicating that both dietary pattern and genetic polymorphisms are related to mental health disorders, there has been little research examining the interactive effects between diet and immune related gene mutations, and their potential link to mental health outcomes. In the present investigation, some of the polymorphisms interacted with dietary pattern in predicting cognitive flexibility, coping, and depressive symptoms. First, a greater intake of a non-prudent dietary pattern was associated with lower levels of cognitive control, but this relation only existed for the GG genotype of the IL-6 polymorphism. The positive relation between a non-prudent dietary pattern and impaired cognition is well established, along with an abundance of research suggesting that inflammatory pathways play a role in this regard (Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014). It is possible that

higher levels of inflammation associated with the GG genotype (Fishman et al., 1998), coupled with the elevated levels of IL-6 from consumption of a non-prudent diet, might compound or create excessive levels of inflammation, which may contribute to the impairment of cognitive flexibility. It was further observed that a positive relation existed between the non-prudent dietary pattern and emotion focused coping, but again, only for individuals with the GG genotype. This positive relation between a non-prudent dietary pattern and emotion focused coping is in line with previous research (Kuczmarski et al., 2017). Again, given the possibility that the dietary pattern and genotype might produce excessive amounts of inflammation and impair cognitive flexibility, this impairment may also contribute to persistent use of emotion-focused coping strategies, as individuals who are less flexible in the use of their coping methods tend to endorse emotion-focused coping strategies to a greater degree (Gabrys, Anisman, & Matheson, 2018).

Beyond these pro-inflammatory polymorphisms, an inverse relation existed between prudent dietary adherence and emotion-focused coping, but this was only apparent for males with the CC genotype of the IL-10 polymorphism. Although the negative relation between the dietary pattern and emotion-focused coping is not fully in line with past research, in general, prudent dietary choices are associated greater with problem-focused coping strategies (Shimai, Kawabata, Nishioka, & Haruki, 2000), and emotion-focused coping strategies are associated with non-prudent dietary consumption (Kuczmarski et al., 2017). Once again, it is difficult to speculate on the conditional nature of this relation, however, it is possible that the CC genotype, which is associated with lower levels of inflammation (Raguema et al., 2018), may have allowed for different cognitive processes that come to affect coping methods. To be sure, this is highly speculative, but is nonetheless a testable position.

Finally, a positive relation between a non-prudent dietary pattern and depressive symptoms existed, which is again, in line with previous studies (for example see O'Neil et al., 2014). However, this relation only existed for the lower inflammation producing GG genotype of the IL-17A polymorphism, which is again, difficult to explain. Just as well, a negative relation existed between the non-prudent dietary pattern and cognitive flexibility (both cognitive control and cognitive resources) among individuals with the GG genotype. These relations are supported by past research (e.g., Freeman et al., 2014), however, contrary to what was predicted, these relations were only significant for individuals who possessed the genotype associated with *less* inflammation (the GG genotype; Espinoza et al., 2011). Why a diet that is associated with higher inflammation would not show these effects among individuals with a higher inflammatory profile (i.e., individuals carrying the A allele) is uncertain.

In summary, it seems that genotypes associated with lower levels of inflammation, are associated with beneficial dietary choice, as well as cognitive flexibility and coping strategies. It also appeared that dietary pattern is related to cognitive flexibility, coping strategies, and depressive symptoms, and that genotypes associated with less inflammation were linked in this relation. This positive quality, however, seems to exist primarily for males with regards to dietary behavior and coping. Puzzlingly, it appears that in some instances, genotypes associated with less inflammation, might actually pose as a risk factor when consuming higher quantities of unhealthy food (e.g., IL-17A).

Several limitations of the present study need to be addressed, as detailed in Study 1, the present investigation included use of self-report food and exercise frequency questionnaires, which are subject to biases. In addition, given that SNPs vary across ethnicities, and the potential behavioral differences associated with these SNPs, the present study only included Euro-

Caucasian participants. With this being said, it is not possible to generalize our findings across other ethnicities.

## **CHAPTER 3**

### **The moderating role of immune related gene polymorphisms in the relation between lifestyle factors and executive functioning**

#### **Abstract**

Given that immune related polymorphisms and dietary patterns might interact in predicting risk for depression, as suggested in the previous study, the present study examined the interaction between exercise (in addition to dietary patterns) and immune related polymorphisms in predicting executive functioning, which is often impaired among depressed individuals. Among male and female undergraduate students ( $N=144$ ), a positive relation existed between exercise frequency and performance on the Iowa Gambling Task (IGT; a measure of executive functioning), but only for individuals with the GG genotype of the TNF- $\alpha$  polymorphism. It was also observed that a negative relation existed between prudent dietary pattern adherence and performance on the IGT, but only for A carriers of the IL-1 $\beta$  polymorphism. This polymorphism also interacted with strenuous exercise and sex, in that a positive relation existed between exercise frequency and IGT performance, but only for females with the GG genotype. Finally, the IL-6 polymorphism also interacted with these lifestyle factors in predicting IGT performance. Specifically, a negative relation between non-prudent dietary pattern adherence and performance on the IGT existed, but only for individuals carrying the C allele. Finally, a positive relation existed between frequency of strenuous exercise and performance on the IGT, but only for the GG genotype. Although speculative and based on correlational data, these findings are consistent with the view that lifestyle factors and immune related gene mutations, might be working together in regulating immune function, which in turn, might impact executive functioning. This alteration in executive functioning may also be associated with alterations in mood regulation

and coping selection, which play a role in the development of mood disorders such as depression.

### **Introduction**

It is well established that lifestyle factors, such as dietary pattern (Khalid, Williams, & Reynolds, 2016) and exercise (Schuch et al., 2016), can play a role in the emergence and maintenance of depressive symptoms. These symptoms often include an impairment in executive functions, such as decision making, inhibitory control, and planning. Indeed, it seems that individuals with symptoms of depression and anxiety, or who experienced chronic stress, exhibit impairments in a variety of executive function tasks compared to healthy controls (Ajilchi & Nejati, 2017). Moreover, it seems that inhibitory control and planning, are positively related to fruit and vegetable consumption (Wyckoff et al., 2017), and frequent aerobic exercise has also been associated with enhanced executive functioning (Guiney & Machado, 2013).

It has been reported that lifestyle factors are associated with changes of inflammatory functioning, which may mediate the relation between lifestyle factors and both depression and executive functioning. Indeed, a prudent dietary pattern, which is characterized by a higher intake of vegetables, fruits, and fish, was associated with a reduction in pro-inflammatory makers, such as C-reactive protein (CRP), IL-6, IL-18, and TNF- $\alpha$  (Lopresti, Hood, & Drummond, 2013). In contrast, a non-prudent dietary pattern, which is characterized by a higher consumption of food items such as processed meats, high glycemic carbohydrates, and unhealthy fats, is associated with a higher production of inflammatory markers (Barbaresko et al., 2013). Exercise is also associated with inflammation; acutely, exercise increases inflammatory markers, whereas levels of pro-inflammatory markers such as CRP, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, are diminished in the long term (Lopresti et al., 2013).

Inflammation is associated with depression (Haapakoski et al., 2015), and more pertinent to the present investigation, impaired cognitive functioning, although this relation is complex. For example, pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , which, are associated with both positive and negative effects on learning and memory, depending upon the age of the individual, and/or the magnitude and duration of the elevation (acute vs. chronic), whereas elevated levels of IL-1 $\beta$  seems to have negative effects on learning and memory (Yirmiya & Goshen, 2011). To date, there seems to be limited data concerning the association between cytokines and executive function and/or altered activity within regions of the brain associated with executive function (e.g., the orbital frontal cortex). Despite the lack of research in humans, it has been reported that in mice, experimentally altering IL-6 levels either chronically or acutely in the orbital frontal cortex, was associated with enhanced cognitive flexibility, although it was emphasized that negative effects could arise with excessive levels of IL-6 (Donegan et al., 2014). In addition to the limited research, the influence of TNF- $\alpha$  and IL-1 $\beta$ , or excessive levels of pro-inflammatory cytokines, on executive function and/or the orbital frontal cortex, is unclear.

In addition to lifestyle factors, cytokine production may also be influenced by single nucleotide polymorphisms (SNPs), and in some cases, these SNPs may be associated with altered cognitive function. For example, the mutant allele of the IL-1 $\beta$  SNP (rs16944) which facilitates the production of IL-1 $\beta$  (Kovacs et al., 2016), was associated with poorer memory performance (Baune et al., 2008), and inhibition of long term potentiation (McAfoose & Baune, 2009). As well, allele variants of other IL-1 $\beta$  related genes (e.g., the IL-1 $\beta$ -converting enzyme), were associated with lower serum levels of IL-1 $\beta$ , and better performance on tasks of executive functioning among the elderly (Trompet et al., 2008). Further supporting a link between SNPs and cognition, the A allele of the TNF- $\alpha$  polymorphism (rs1800629), which is associated with

higher production of TNF- $\alpha$  (Kroegeer, Carville, & Abraham, 1997), was also associated with enhanced attentional selection compared to that evident among individuals with the GG genotype (Beste et al., 2010a, b). Unlike the IL-1 $\beta$  and TNF- $\alpha$  polymorphisms, there are limited reports indicating a link between IL-6 polymorphisms and cognition or to executive functioning (Trenova et al., 2018), despite the effects that the IL-6 polymorphism (rs1800795) can have on IL-6 production (Fishman et al., 1998).

Taken together, despite the complexity of the association between cytokines and cognition, it seems that during basal conditions, inflammation plays a beneficial role. However, when the immune system is chronically activated, and excessive levels of pro-inflammatory cytokines are produced (e.g., in the case of unhealthy lifestyle choices), increased excitotoxicity, apoptosis, and neurodegeneration may result, which may in turn impair cognition (Yirmiya & Goshen, 2011). Much less is known regarding the interactive effects of lifestyle factors and immune related SNPs on executive functioning. This said, given that both lifestyle factors and SNPs can influence immune functioning as well as cognition, it is possible that lifestyle factors and immune related SNPs may interact in predicting performance on cognitive tasks related to executive performance. Specifically, it is expected that prudent dietary pattern adherence, and both total exercise and strenuous exercise, would be positively associated with executive functioning, reflected by decision making performance in the Iowa Gambling Task (IGT), and that these relationships would be stronger for individuals carrying allele(s) associated with lower levels of inflammation. In contrast, greater adherence to a non-prudent dietary pattern would be associated with poorer IGT performance scores, and that this relation would be stronger among individuals carrying one or more copies of an allele associated with higher levels of inflammation.



## Methods

### Participants

The study included female ( $n = 93$ ) and male ( $n = 51$ ) undergraduate students ( $M_{age} = 19.73$ ,  $SD = 3.67$ ) attending Carleton University, that were recruited on-line using Carleton University's SONA system (although  $N$  did vary slightly across genes). Due to the variability in frequencies of polymorphisms across ethnicities, all participants were of self-reported Euro-Caucasian decent.

### Procedure

Once consent was received, participants provided a saliva sample for genotyping, and then completed a series of questionnaires pertaining to demographic variables (e.g., ethnicity, age), dietary pattern, and exercise frequency. Once this was completed, participants engaged in a computerized version of the Iowa Gambling Task. All procedures were approved by the Carleton University Ethics Committee for Psychological Research.

### Genotyping

Samples for genotyping were collected using Norgen collection kits (Norgen Biotek Corp., Thorold, Ontario Canada). Genomic DNA was extracted from the sample collection kits according to the manufacturer's instructions, and diluted to approximately equal concentration (30 ng/ $\mu$ L). The samples were sent to McGill University and G  nome Qu  bec Innovation Center (Montreal, Canada) for genotyping. A multiplex PCR was performed on 20ng of template genomic DNA in a 5uL reaction mixture. Some PCR reactions were ran on QIAxcel (QIAGEN) to assess the amplification. A shrimp-alkaline-phosphatase (SAP) treatment was done to remove the unused nucleotides, followed by a primer extension reaction (iPLEX Gold) in multiplex. The products were then desalted with 6mg of resin (Agena Bioscience) and spotted on a 384-point

SpectroCHIP (Agena Bioscience) using a nanodispenser (Agena Bioscience). The distinct masses were detected by MALDI-TOF mass-spectrometry and the data were analyzed using

MassARRAY Typer Analyser software. Primer sequences were as follows:

TNF- $\alpha$  forward: ACGTTGGATGTTCTGGGCCACTGACTGATT  
TNF- $\alpha$  reverse: ACGTTGGATGAAGGAAACAGACCACAGACC  
TNF- $\alpha$  probe: ctAGGCTGAACCCCGTCC

IL-1 $\beta$  forward: ACGTTGGATGCTGTCTGTATTGAGGGTGTG  
IL-1 $\beta$  reverse: ACGTTGGATGATTTTCTCCTCAGAGGCTCC  
IL-1 $\beta$  probe: tCCTTGGGTGCTGTTCTCTGCCTC

IL-6 forward: ACGTTGGATGGATTGTGCAATGTGACGTCC  
IL-6 reverse: ACGTTGGATGAGTGGTTCTGCTTCTTAGCG  
IL-6 probe: cccaacGTGACGTCCTTTAGCAT

The distributions of each gene were as follows:

TNF- $\alpha$ : 106 GG (36 male, 70 female), 32 GA (12 male, 20 female), and 6 AA (3 male, 3 female).

IL-1 $\beta$ : 56 GG (21 male, 35 female), 68 GA (23 male, 45 female), and 19 AA (7 male, 12 female).

IL-6: 55 GG (19 male, 36 female), 59 GC (22 male, 37 female), and 27 CC (8 male, 19 female).

Note: in each distribution, alleles did not violate Hardy-Weinberg Equilibrium expectations, and due to the infrequency of the minor alleles, we collapsed all across mutant allele carriers for further analyses.

## Measures

*Physical Exercise.* Physical exercise was assessed using the Godin-Shepard Leisure-Time Activity Questionnaire (Godin, 2011; Modified), a 3-item measure that instructed participants to indicate the frequency in which they participate in mild, moderate, and strenuous exercise, for more than 15 minutes per week.

*Dietary Pattern.* Dietary pattern was assessed using a modified food frequency questionnaire (FFQ) (Hu et al., 1999), a 44-item measure that instructs participants to indicate the frequency they consumer various dietary items (e.g., lean proteins, dairy products, green leafy vegetables, etc.) per week on average over the past year. The food items were then grouped into either a prudent dietary pattern (leafy vegetables, other vegetables, tomatoes, fruits, cruciferous vegetables, salad dressing, and fish;  $\alpha = .78$ ) and a non-prudent dietary pattern (desserts, processed meats, fried food, sweets, refined grain, high-fat dairy, and condiments;  $\alpha = .76$ ) based on Akbaraly et al. (2009).

### *Executive function: Iowa Gambling Task*

In this task participants select cards from four decks displayed on-screen. Participants are instructed that the selection of each card will result in winning or losing money. The objective is to attempt to win as much money as possible. On each trial, participants select a card from one of four decks; two ‘disadvantage’ decks offer a higher reward on most trials, but also higher possible loss and lower overall expected value, whereas two ‘advantage’ decks offer a lower reward on most trials, but lower possible loss and higher expected value. Participants learn the nature of the decks through trial-and-error. Performance on this task was measured by the amount of cards chosen from the advantaged decks across all the trials.

## Statistical Analyses

The statistical analyses were performed using IBM SPSS Statistics 20 for Windows (Armonk, NY: IBM Corp.). Analyses assessing differences in dietary pattern, exercise, and Iowa Gambling Task Performance, as a function of Sex and Genotype, were determined by ANOVA and MANOVA. Correlational analysis was performed using Pearson product moment correlations. Interactions between Genotype and lifestyle factors on Iowa Gambling Task performance were conducted separately using the PROCESS macro (Hayes, 2013) in SPSS.

## Results

### *TNF- $\alpha$ polymorphism and Sex, in relation to lifestyle factors and Iowa Gambling Task performance*

An ANOVA conducted on Iowa Gambling Task (IGT) performance scores revealed a non-significant main effect of Genotype,  $F(1, 138) = 0.81, p > .05$ , and a significant main effect of Sex, in that males seemed to choose more from the advantaged decks than females (depicted in Table 1),  $F(1, 138) = 5.95, p < .02$ . However, Sex and Genotype did not interact in predicting performance on the IGT. A MANOVA conducted on the two dietary patterns as a function of Genotype and Sex, indicated that Genotype did not have an effect on the prudent  $F(1, 138) = 0.56, p > .05$ , or non-prudent dietary pattern  $F(1, 138) = 0.90, p > .05$ . However, Sex influenced the non-prudent dietary pattern, in that males consumed more unhealthy foods than did females (as depicted in Table 1),  $F(1, 138) = 21.07, p < .01$ .

It was further observed that Sex and Genotype interacted in predicting non-prudent dietary scores,  $F(1, 138) = 6.35, p < .02$ . Males carrying the A allele had higher non-prudent dietary scores ( $M = 62.67, SE = 3.25$ ) than female A carriers ( $M = 45.13, SE = 2.62$ ),  $F(1, 138) = 17.65, p < .01$ . In addition, females with the GG Genotype ( $M = 53.69, SE = 1.50$ ) seemed to

adhere more to a non-prudent dietary pattern, than females carrying the A allele ( $M = 45.13$ ,  $SE = 2.62$ ),  $F(1, 138) = 8.01$ ,  $p < .01$ . There were no differences as a function of Sex on prudent dietary scores  $F(1, 138) = 0.20$ ,  $p > .05$ , nor did Sex interact with Genotype in predicting prudent dietary scores. Furthermore, a MANOVA conducted on total exercise and strenuous exercise scores revealed that there was no main effect of Sex or Genotype, nor a significant Sex x Genotype interaction.

Table 1. Means ( $M$ ) and standard deviations ( $SD$ ) by Sex on predictor and outcome variables.

	Male		Female	
	$M$	$SD$	$M$	$SD$
1. Prudent diet	72.02	15.26	73.55	15.15
2. Non-prudent diet	59.98**	13.97	51.57	12.29
3. Total exercise	61.08	28.93	53.76	27.60
4. Strenuous exercise	3.35	2.01	2.56	2.03
5. Iowa Gambling Task	64.42*	16.94	59.18	14.87

Note: \* $p < 0.05$ , \*\* $p < 0.01$

### *Zero-order correlations between dietary pattern, exercise, and IGT performance*

Table 2 shows the intercorrelations between dietary patterns, exercise, and performance on the IGT. As seen in this table, strenuous exercise was positively associated with both prudent dietary adherence, and total exercise.

Table 2. Zero-order correlations between dietary patterns, exercise, and IGT performance.

	1.	2.	3.	4.
1. Prudent diet pattern	-	-	-	-
2. Non-prudent diet pattern	.05	-	-	-
3. Total exercise	.15	-.03	-	-
4. Strenuous exercise	.33**	-.04	.64**	-
5. Iowa Gambling Task	-.11	-.06	.12	.04

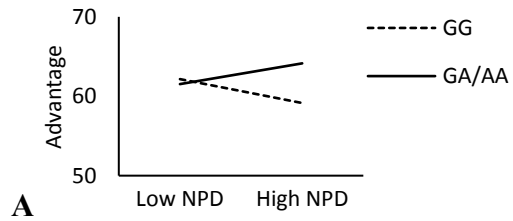
Note: \*\* $p < 0.01$

### *Moderating effects of the TNF- $\alpha$ polymorphism*

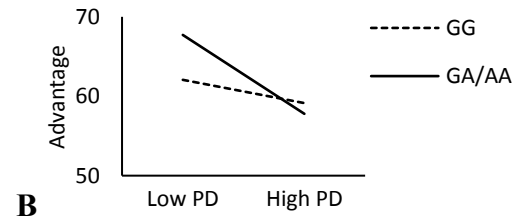
As shown in Figure 1 (panels A and B), the TNF- $\alpha$  polymorphism did not moderate the relation between either dietary pattern on IGT performance, nor were there any main effects of Genotype, Sex, or dietary pattern. Figure 1 (panel C) shows that the interaction between total exercise and the TNF- $\alpha$  polymorphism approached significance, in that there was a positive relation between total exercise and IGT performance, but this relation only existed for the GG Genotype,  $\Delta R^2 = .03$ ,  $b = -.20$ ,  $t = -1.89$ ,  $p = .06$ . Strenuous exercise did not interact with the polymorphism, nor were there any main effects of Genotype, Sex, or strenuous exercise, in predicting IGT performance. Given the numerous regressions assessed, the modest interaction observed between exercise and the TNF- $\alpha$  polymorphism was not necessarily deemed to be a reliable outcome.

## Diet

### Non-prudent dietary pattern

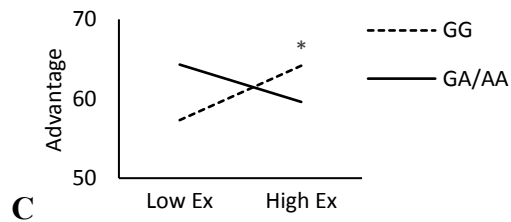


### Prudent dietary pattern



## Exercise

### Total exercise



### Strenuous exercise

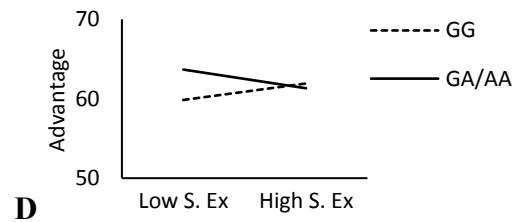


Figure 1. The moderating role of the TNF- $\alpha$  polymorphism in the relation between lifestyle factors and Iowa Gambling Task performance. Note:  $*p < .05$

*IL-1 $\beta$  polymorphism and Sex, in relation to lifestyle factors and Iowa Gambling Task performance*

Neither Genotype nor the interaction between Sex and Genotype, were significant in predicting performance on the IGT. Likewise, a MANOVA of both dietary patterns indicated that Genotype, or the interaction between Genotype and Sex, were not significant. A further MANOVA, conducted on both types of exercise as a function of Genotype and Sex, indicated a non-significant interaction, however, males engaged in strenuous exercise more frequently ( $M = 3.35$ ,  $SD = 2.01$ ), than females ( $M = 2.57$ ,  $SD = 2.04$ ),  $F(1, 133) = 4.53$ ,  $p < .05$ .

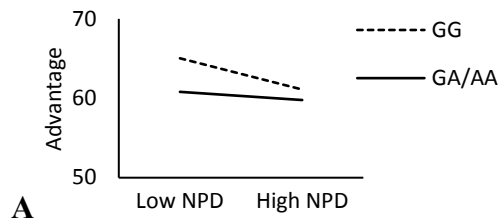
*Moderating effects of the IL-1 $\beta$  polymorphism*

As shown in Figure 2 (panel B), the IL-1 $\beta$  polymorphism moderated the relation between the prudent dietary pattern and IGT performance ( $\Delta R^2 = .03$ ,  $b = -.37$ ,  $t = -2.10$ ,  $p < .05$ ), such that there was a negative relation between the prudent dietary pattern and IGT performance, but this relation was only significant for individuals carrying the A allele. Although the polymorphism did not moderate the relation between both forms of exercise and IGT performance, there was a significant three-way interaction between the polymorphism, Sex, and strenuous exercise ( $\Delta R^2 = .03$ ,  $b = -5.63$ ,  $t = -2.01$ ,  $p < .05$ ), such that strenuous exercise and IGT performance was positively correlated, but this relation only existed among females with the GG Genotype (see Figure 2 panels E and F).

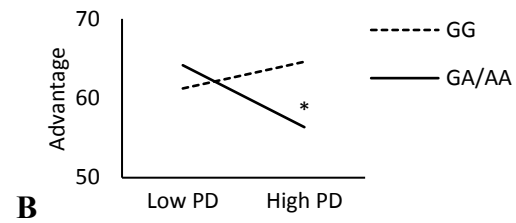


## Diet

Non-prudent dietary pattern

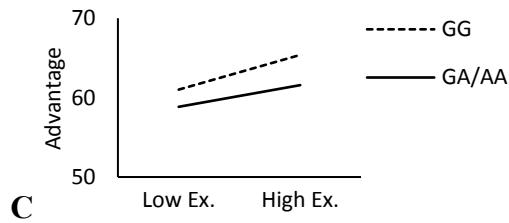


Prudent dietary pattern

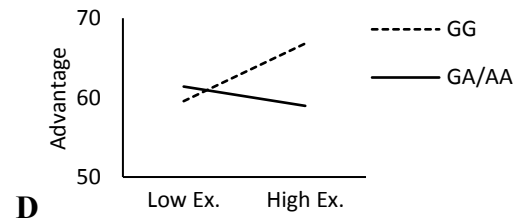


## Exercise

Total exercise

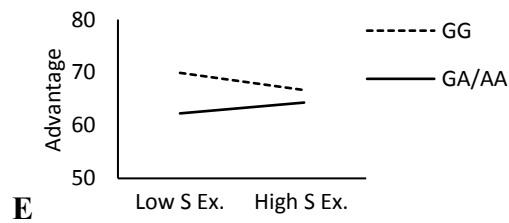


Strenuous exercise



## Strenuous exercise 3-way interaction

Male



Female

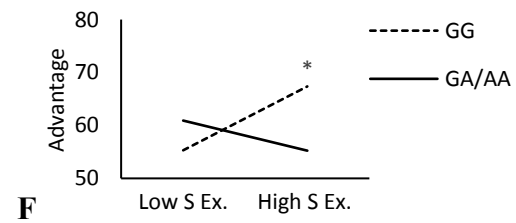


Figure 2. The moderating role of the IL-1 $\beta$  polymorphism and Sex, in the relation between lifestyle factors and Iowa Gambling Task performance. Note: \* $p < .05$

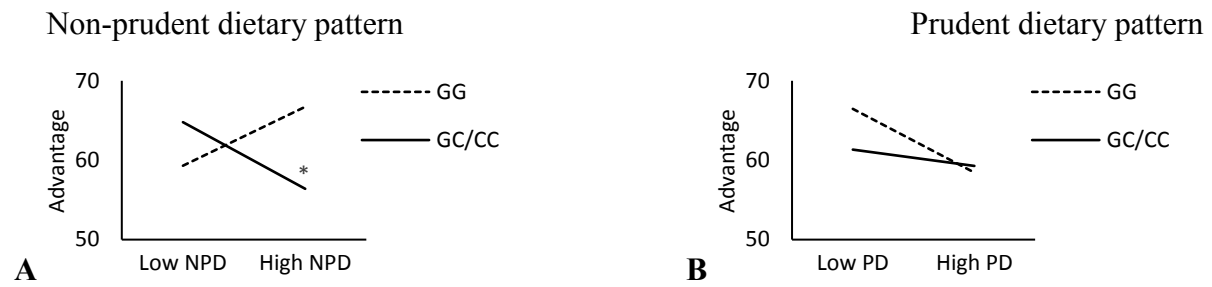
### *IL-6 polymorphism and Sex, in relation to lifestyle factors and Iowa Gambling Task performance*

It appears that neither Genotype nor the interaction between Sex and Genotype, were statistically significant in predicting performance on the IGT. Similarly, MANOVAs revealed that Genotype, or the interaction between Genotype and Sex were predictive of dietary patterns, or either forms of exercise.

### *Moderating effects of the IL-6 polymorphism*

As shown in Figure 3 (panel A), the IL-6 polymorphism moderated the relation between the non-prudent dietary pattern and IGT performance ( $\Delta R^2 = .06$ ,  $b = -.59$ ,  $t = -2.94$ ,  $p < .01$ ), such that a negative relation existed between non-prudent dietary adherence and IGT performance, but only for individuals carrying the mutant C allele. It also appeared that the relation between strenuous exercise and IGT performance was moderated by the polymorphism ( $\Delta R^2 = .04$ ,  $b = -2.88$ ,  $t = -2.24$ ,  $p < .05$ ), in that IGT performance and strenuous exercise frequency were positively related, but this was significant only for individuals with the GG Genotype.

## Diet



## Exercise



Figure 3. The moderating role of the IL-6 polymorphism in the relation between lifestyle factors and Iowa Gambling Task performance. Note:  $*p < .05$

## Discussion

### *Gene polymorphisms and Sex in relation to Lifestyle factors and Iowa Gambling Task performance*

It was observed that males chose from the advantaged decks on the Iowa Gambling Task (IGT) more than females did. This is in line with past research showing that males focus more on long-term pay-off than do females. It was suggested that this may, in part, be due to differences in neural activity in the orbitofrontal cortex and dorsolateral prefrontal cortex, stemming from the effects that hormones can have on neural organization in early-life (van den Bos, Homberg, & de Visser, 2013). As frequently observed, females reported healthier dietary behavior than did males, which might be due to the higher levels of eating-related self-determined motivation among women than men (Leblanc et al., 2015). Furthermore, Sex and the TNF- $\alpha$  polymorphism interacted in predicting dietary pattern, in that the A allele, which is associated with higher levels of TNF- $\alpha$  (Kroeger, Carville, & Abraham, 1997), was protective against greater consumption of unhealthy foods, but only for females. The association between this allele and dietary choice is difficult to explain, although the A allele is associated with enhanced cognitive benefits (Baune et al., 2008; Beste et al., 2010a; Beste et al., 2010b), which may play a role in dietary behavior.

The differences between lifestyle factors and IGT performance as a function of Sex and Genotype aside, a positive association was apparent between strenuous exercise and the prudent dietary pattern. This is intuitively appealing, although there is limited research supporting this relation. Most research tended to examine how these factors relate to health outcomes, rather than how they are intercorrelated. Nonetheless, there is research indicating that exercise can have beneficial effects on dietary intake in the short term (Martins, Morgan, & Truby, 2008), and that fitness branded food may *decrease* the likelihood of engaging in physical activity (Koenigstorfer & Baumgartner, 2016).

### *Interactive effects of Genotype, Sex, and Lifestyle factors*

Total exercise and performance on the IGT were positively related, and this relation seemed to only exist among individuals with the GG genotype of the TNF- $\alpha$  polymorphism, however, this interaction only approached significance. The positive relation between frequency of exercise and executive function has been supported by earlier research (Guiney & Machado, 2013); however, the contingency of this relation based upon a genotype associated with lower levels of TNF- $\alpha$  is complex. Indeed, for as yet undetermined mechanisms, TNF- $\alpha$  has both neuroprotective and neurodegenerative effects (McAfoose & Baune, 2009; Yirmiya & Goshen, 2011), and there is limited research connecting TNF- $\alpha$  levels, and TNF- $\alpha$  related SNPs, to executive functioning. Nonetheless, past research indicated that carriers of the A allele, which has been associated with a higher production of TNF- $\alpha$ , exhibited enhanced attentional selection, and elevated activity in occipital and temporal brain regions, compared to individuals with the GG genotype (Beste et al., 2010a; Beste et al., 2010b). However, TNF- $\alpha$  might have different effects on executive function and its associated brain regions, such as the prefrontal cortex. Indeed, by modifying brain-derived neurotrophic factor signaling, TNF- $\alpha$  has been associated with adverse effects in basal ganglia structures (Sriram et al., 2006), and protective effects in occipital structures (Kaneko et al., 2008). However, it is difficult to compare across studies given that variations of dose, age, and immunological condition, might influence the effect associated with TNF- $\alpha$  (Yirmiya & Goshen, 2011). In the present investigation, it seemed that exercise was associated with enhanced executive function, but this relation might have depended on the lower levels of TNF- $\alpha$  associated with the GG genotype. This might suggest that frequent exercise, which is associated with lower levels of TNF- $\alpha$  (Lopresti et al., 2013), and the GG genotype,

might be synergistically reducing overall TNF- $\alpha$  levels, and in turn enhancing executive function.

A *negative* relation existed between the prudent dietary pattern and IGT performance, but only for individuals carrying one or two copies of the A allele of the IL-1 $\beta$  polymorphism, which has been associated with a higher production of IL-1 $\beta$  (Kovacs et al., 2016). This interaction is difficult to interpret given the negative relation between the prudent dietary pattern and IGT performance, which seems to run counter to most past research demonstrating that healthy dietary patterns (Wyckoff et al., 2017), as well as essential components of these patterns (e.g., presence of omega-3 fatty acids) (Bauer et al., 2014), are positively associated with cognitive functioning. Moreover, these patterns are also inversely related to indices of mental disturbances, such as depressive symptoms (Lopresti et al., 2013). With this being said, due to the counterintuitive relation between the prudent diet and IGT performance, it would not be meaningful to speculate on the moderating effect of the IL-1 $\beta$  SNP in this regard.

As predicted, a positive relation was found between strenuous exercise and IGT performance, but only for females with the low IL-1 $\beta$  producing GG genotype. Again, the relation between exercise and executive functioning is well supported (Guiney & Machado, 2013), and the contingency upon the GG genotype, which is associated with both lower levels of IL-1 $\beta$  and enhanced cognitive function (Baune et al., 2008), seems to suggest that exercise, which has a IL-1 $\beta$  reducing effect as well (Lopresti et al., 2013), and the GG genotype might be working together in reducing overall IL-1 $\beta$  levels, and in turn enhancing executive functioning. To be sure, earlier research has indicated that higher levels of IL-1 $\beta$  are associated with negative effects in other domains of cognition, such as learning and memory (Yirmiya & Goshen, 2011).

The interaction based upon sex is difficult to explain, although performance on the IGT does vary by Sex. As indicated earlier, hormonal differences related to sex may contribute to differences on structure and function in the prefrontal cortex (van den Bos, Homberg, & de Visser, 2013). Moreover, these hormonal differences may also influence the production of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$  (Fish, 2008). Although speculative, it is possible that these hormonal differences might explain the sex differences in these interactions.

A negative relation existed between non-prudent dietary adherence and IGT performance, but this relation existed only for individuals carrying the mutant C allele of the IL-6 polymorphism, which is associated with lower plasma levels of IL-6 (Fishman et al., 1998). Although a negative relation between the non-prudent dietary pattern and IGT performance seems intuitive, it might be difficult to directly compare it to past research, as earlier studies focused mainly on the effects of prudent dietary patterns, and their positive association with cognition (e.g., Wyckoff et al., 2017). This said, there is evidence indicating that in animals, a high fat lard diet is associated with cognitive impairments and increased expression of TNF- $\alpha$  and IL-6 in the cerebral cortex (Pistell et al., 2010), although a causal connection between neural inflammation and impaired cognition could not be made. Adding to this, it has been suggested that a non-prudent dietary pattern may promote the accumulation of white adipose tissue, which can essentially act as an endocrine gland, and produce excessive amounts of pro-inflammatory markers, including TNF- $\alpha$ , IL-6, leptin, resistin, and C-reactive protein (Manzel et al., 2014), which may in turn impact cognition.

Contrary to prediction, the non-prudent diet was only related to IGT performance when coupled with the *lower* levels of IL-6 associated with the C allele. On the one hand, there is evidence suggesting that adherence to a non-prudent dietary pattern is associated with higher

levels of IL-6. On the other hand, the C allele is associated with lower levels of IL-6, but both of these findings are associated with an impairment in executive function. It is possible that lower levels of IL-6 associated with the C allele of the IL-6 polymorphism, might be having a detrimental effect on cognition, and the higher adherence to an unhealthy diet might be further exacerbating these effects independent of IL-6 levels. To be sure, the non-prudent diet is linked to increases in oxidative stress in the brain, altered neurotransmitter production, a decrease in neurotrophic factors, and an increase in other pro-inflammatory cytokines (Lopresti et al., 2013), which may in turn affect cognition. Speculation on this effect is complicated; as indicated earlier, IL-6 can have both positive and negative effects on cognition, but this may depend on factors such as age, and/or the magnitude and duration of the elevation, although it seems that chronically elevated levels are detrimental (Yirmiya & Goshen, 2011). At present, there is insufficient data available that would allow any firm conclusions on the effects of IL-6 on executive function to be made.

A positive relation existed between strenuous exercise and IGT performance, which as mentioned previously, is consistent with past research. Again, contrary to expectation, it appeared that exercise was only associated with beneficial effects on executive function when coupled with *higher* levels of IL-6, which again is difficult to explain, as exercise is associated with both a decrease in levels of IL-6 (Lopresti et al., 2013) and an increase in cognitive functioning. It is possible that exercise might have contributed to the enhanced executive function independently of IL-6 levels, as described earlier. Overall, both regression models with IL-6 suggest that lifestyle factors are associated with executive functioning, but both higher and lower levels of IL-6 might be amplifying their effects.



Taken together, the present findings suggests that SNPs associated with a change in the production of pro-inflammatory cytokines levels, can augment the relation between lifestyle factors and executive functioning. Specifically, it seems that SNPs associated with lower levels of the pro-inflammatory markers TNF- $\alpha$  and IL-1 $\beta$ , can enhance the relation between frequent physical activity and executive function, which contrasts with the effect of the IL-6 SNP that was associated with both *higher* levels of IL-6 and enhanced performance on the IGT. It also appeared that lower levels of IL-6 production seem to intensify the negative relation between an unhealthy diet and executive function. It is also worth noting, that the interaction between the IL-1 $\beta$  SNP and diet might be a spurious finding, given the counterintuitive relation between diet and IGT performance. In view of the complexity of the findings, it is difficult to compare the present outcomes to past research, especially given the region specific effects of these cytokines.

Several limitations of the present study need to be addressed, as in Study 1, the present investigation included use of self-report food and exercise frequency questionnaires, which are subject to recall biases. In addition, given that SNPs vary across ethnicities, and the potential behavioral differences associated with these SNPs, the present study only included Euro-Caucasian participants. With this being said, it is not possible to generalize our findings across other ethnicities.

## **CHAPTER 4**

### **The moderating role of lifestyle factors in the relation between a socio-evaluative stressor and cortisol response**

#### **Abstract**

As exaggerated responses to stressors can be linked to pathology, and lifestyle factors are related to both hypothalamic-pituitary-adrenal axis (HPA) axis functioning and depression, the present investigation examined the potential role dietary pattern and exercise frequency in predicting cortisol response to the Trier Social Stress Test (TSST). Among university students ( $N=81$ ), the TSST was associated with increased levels of cortisol, however, this relation was particularly stronger among individuals with a greater adherence to an unhealthy dietary pattern. However, healthy dietary pattern adherence, or frequency of exercise, did not moderate cortisol levels in response to the TSST. These findings suggest that the immune dysregulating effects associated with an unhealthy dietary pattern, might be influence HPA functioning, and in turn, exacerbate cortisol response to a stressor.

## **Introduction**

Of the many stress responses that have been examined, particular attention has been devoted to hypothalamic-pituitary-adrenal axis (HPA) axis functioning, culminating in cortisol production and release. However, considerable interindividual variability is common, such that only some individuals exhibit pronounced cortisol changes, which can then mobilizes the body's energy resources to counter an impending threat. Furthermore, lifestyle factors such as diet and exercise, can play a role in individual variation of the stress response.

It is well established that stressors can influence dietary behavior, such that individuals with a higher stressor-provoked cortisol response, tended to consume more calories than individuals who were not responsive to the stressor (Epel et al., 2001). Moreover, following a stressor, individuals with a higher cortisol response tended to prefer foods rich in carbohydrates. Essentially, individuals may be 'self-medicating', as carbohydrate rich food could potentially mitigate some of the negative effects of a stressor (Dallman, 2010), which can also lead to obesity. Excess body fat can further increase cortisol reactivity in response to a stressor (Epel et al., 2001; Lorig et al., 2016), although this outcome is variable (Rodriguez et al., 2015).

Just as the presence of stressors can influence food consumption, diet can also influence HPA functioning, although the research seems inconsistent. For instance, calorically dense foods, such as sucrose and lard, can reduce plasma levels of adrenocorticotrophic hormone (ACTH) and corticosterone in response to a restraint stressor in rodents (Foster et al., 2008; Warne, 2009; Zeeni et al., 2012). This effect is thought to be mediated by changes in neural plasticity in brain regions associated with stressor- and reward-related processes, such as the nucleus accumbens and basolateral amygdala (Christiansen, Dekloet, Ulrich-Lai, & Herman, 2011; Ulrich-Lai et al., 2010).

In contrast to the evidence from animal models, human studies indicated that an unhealthy dietary pattern among children was associated with higher overall daily cortisol levels, and that a dietary pattern particularly rich in high glycemic carbohydrates, was related to elevated awakening cortisol levels (Michels et al., 2013). Adding to this, consumption of glucose immediately prior to undergoing a social stressor (Trier Social Stress Test; TSST), was associated with increased cortisol production (Gonzalez-Bono et al., 2002; Kirschbaum et al., 1997), although carbohydrates did not always produce this effect (Lemmens et al., 2011). Further, greater protein intake was accompanied by attenuated cortisol production in response to the TSST (Firk & Markus, 2009), although once again, more often than not, this outcome was not apparent (Gonzalez-Bono et al., 2002; Lemmens et al., 2011; Merens et al., 2005). In addition to carbohydrates and proteins, fat consumption, particularly polyunsaturated fatty acids such as omega-3, attenuated cortisol activity in response to a mental stressor (Delarue et al., 2003), whereas monounsaturated fatty acids seem to have no effect on cortisol response in the TSST (Gonzalez-Bono et al., 2002).

To date, the majority of the research assessing dietary effects on the stress response has examined consumption of macronutrients (i.e., fat, carbohydrates, and protein) immediately prior to a stressor being experienced, but there has been limited research addressing the relationship between dietary pattern and the effects on the stress response. Thus, the present investigation sought to address this gap by evaluating the link between self-reported dietary pattern over a 6-month period and subsequent cortisol levels in response to the TSST.

In addition to dietary components, physical activity can also interact with the impact of a stressor in predicting cortisol response to the TSST. Although exercise can increase both acute and basal levels of cortisol, it can also have a stress buffering effect. For example, higher levels

of physical activity were associated with lower levels of cortisol in response to the TSST (Childs & de Wit, 2014; Gerber et al., 2017; Klaperski et al., 2013; Martikainen et al., 2013; Rimmele et al., 2009), although this was not consistently observed among either men (Moya-Albiol et al., 2001; Strahler et al., 2016) or women (Jayasinghe et al., 2016). Given the limited research concerning the relation between chronic exercise and dietary patterns, and the potential interaction between these factors in predicting the biological stress response, the possibility was entertained that the cortisol changes elicited by the TSST would be subject to the interactive actions of dietary pattern and exercise regimens in which individuals had engaged.

It was hypothesized that a higher adherence to a ‘whole food’ dietary pattern, which is rich in vegetables, fruits, and fish (which often contain a significant amount of omega-3 fatty acids), would be associated with lower levels of salivary cortisol in response to the TSST. In contrast, a higher adherence to a ‘processed food’ dietary pattern, characterised by a higher consumption of food items such as processed meats, high glycemic carbohydrates, and unhealthy fats, would be associated with higher levels of salivary cortisol in response to the TSST. It was also hypothesized that more frequent physical activity, would be associated with lower salivary cortisol levels in response to the TSST. Moreover, diet and exercise might additively or synergistically influence the impact of the stressor on the cortisol response.

## **Methods**

### **Participants**

The study included female ( $n = 57$ ) and male ( $n = 24$ ) undergraduate students ( $M_{age} = 19.48$ ,  $SD = 2.01$ ), attending Carleton University, recruited on-line using Carleton University’s SONA system. Self-reported ethnicity included Caucasian (46.6%,  $n = 41$ ), Black (18.2%,  $n =$

16), Arab (11.4%,  $n = 10$ ), South Asian (6.8%,  $n = 6$ ), other (e.g., mixed ethnicity, 4.5%,  $n = 4$ ), Latin American (3.4%,  $n = 3$ ), and Asian (1.1%,  $n = 1$ ).

### **Saliva Collection**

Participants provided saliva samples for the determination of cortisol concentration. This entailed participants providing saliva samples by chewing on a piece of dental cotton and then placing it into a Salivette, and stored at  $-80^{\circ}\text{C}$  until cortisol determination. Cortisol concentration was then determined in duplicate by radio-immuno assay using kits obtained from ICN Biomedicals, CA. The assays were performed according to the manufacturer's instructions. The samples were assayed in a single run, and the intra-assay variability was less than 10%.

### **Procedure**

Once informed consent was received, participants began completing measures assessing physical activity as well as dietary pattern. After 30 minutes, participants provided the first saliva sample, after which they were randomly assigned to either the stress or the control condition. In the stress condition, participants completed the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), a laboratory task designed to elicit a psychological and physiological stress response. The TSST was split into three phases. In the first phase, participants in the stress condition were told they would engage in a public speaking task (about applying for a research assistant position) and they then had to complete a mental arithmetic task in front of three judges. Participants were then given 5 minutes to prepare, after which they made their public presentation. During the final phase, which was also 5 min in duration, participants were asked to subtract by 17, beginning with the number 1762. In the control condition, participants were asked to write about their positive qualities on a job application form, which took 10 minutes, and no audience was present. Once the experimental (or control) tasks were

completed, participants were instructed to provide a series of saliva samples at 5, 15, 30, and 45 minutes following the stressor or control condition. During this time participants were engaged in several computerized cognitive and decision making tasks (e.g., Wisconsin Card Sorting Task).

## **Measures**

*Physical Exercise.* Physical exercise was assessed using the Godin-Shepard Leisure-Time Activity Questionnaire (Godin, 2011; Modified), a 3-item measure that instructs participants to indicate the frequency in which they ordinarily participate in mild, moderate, and strenuous exercise, for more than 15 minutes per week.

*Dietary Pattern.* Dietary pattern was assessed using a modified food frequency questionnaire (FFQ) (Hu et al., 1998), a 39-item measure that instructs participants to indicate the frequency they consume various food groups (e.g., Fruit: raisins, apples, bananas, etc.) per week on average over the past year. The food groups were then grouped into either a whole food dietary pattern (leafy vegetables, other vegetables, tomatoes, fruits, cruciferous vegetables, salad dressing, and fish) and a processed food pattern (desserts, processed meats, fried food, sweets, refined grain, high-fat dairy, and condiments) based on Akbaraly et al. (2009).

## **Statistical Analyses**

The statistical analyses were performed using IBM SPSS Statistics 20 for Windows (Armonk, NY: IBM Corp.) A mixed-design ANOVA was performed assessing the interactive effect of Stress Condition and Time on the cortisol response. Follow-up Bonferonni corrected *t*-tests were then performed on cortisol concentrations at each time point (5, 15, 30, and 45 min) following the TSST in the experimental condition. In addition, in order to confirm that the stressor was effective, the area under the curve (AUC<sub>i</sub>) was calculated for each condition and

compared using an independent samples *t*-test. Finally, Moderation and simple slope analyses were conducted using the PROCESS macro (Hayes, 2013) in SPSS, with condition entered as a predictor variable, cortisol AUC<sub>i</sub> (Pruessner et al., 2003) as an outcome variable, and dietary pattern and exercise entered as moderators (in separate analyses).

## Results

### *Stressor condition on salivary cortisol*

Results of the mixed-measures ANOVA indicated a Condition x Time interaction  $F(4, 78) = 7.18, p < .001$ . Follow-up tests indicated increased cortisol concentrations at 5, 15, 30, and 45 minutes following the TSST relative to participants in the control condition (see Figure 1). In addition, a larger AUC<sub>i</sub> was apparent in the stressor condition ( $M = 15.64, SD = 31.96$ ) compared to the control condition ( $M = -8.69, SD = 27.60$ ),  $t(81) = -3.65, p < .001$ .

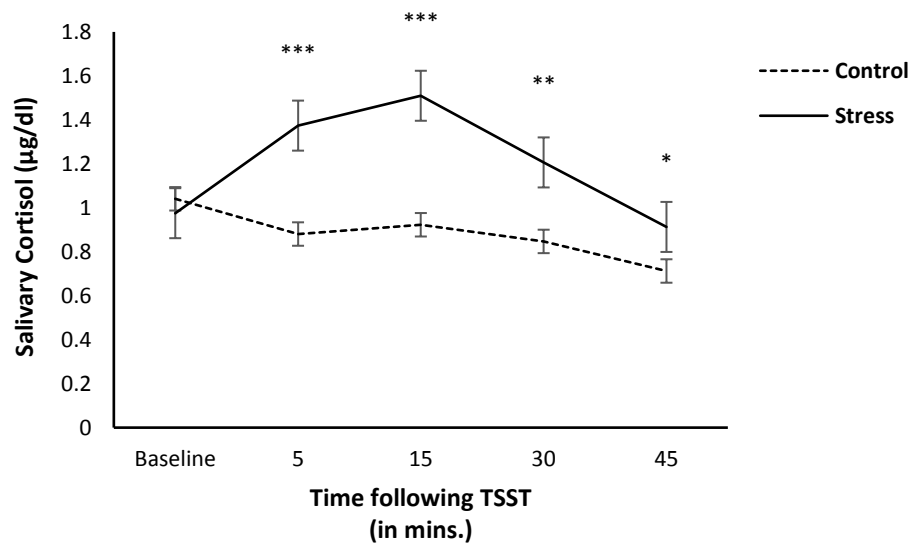


Figure 1. Salivary cortisol levels as a function of stressor condition. Note: \*\*\*  $p < .001$ , \*\*  $p < .01$ , \*  $p < .05$ .



*Zero-order correlations between dietary patterns, exercise, and  $AUC_I$*

Table 1 shows the intercorrelations between dietary pattern and exercise. As seen in Table 1, frequency of exercise and the whole food dietary pattern are positively related.

Table 1. Zero-order correlations between dietary patterns and exercise.

	Whole food pattern	Processed food pattern
Whole food pattern	-	-
Processed food pattern	-.03	-
Exercise	.40***	-.02

Note. \*\*\* $p < 0.001$

### *Moderating effects of dietary pattern and exercise in predicting AUC<sub>I</sub>*

As shown in Figure 2A, moderation analyses indicated a significant interaction between stressor condition and the processed food dietary pattern, in predicting AUC<sub>I</sub> (see Table 2 for coefficients). Specifically, the stressor condition was associated with a higher AUC<sub>I</sub> at higher levels of adherence to a processed food dietary pattern, but not at lower levels. Conversely, as depicted in Figure 2B, a non-significant moderating effect for the whole food dietary pattern in the relation between stressor condition and AUC<sub>I</sub> is indicated. Moderation analyses assessing the concurrent contribution of exercise and dietary pattern revealed that exercise alone (depicted in Figure 2C), or in combination with dietary pattern, did not moderate the effect of the TSST on AUC<sub>I</sub>.

Table 2. Moderation R-square change, beta, *t*-value, and *p* value, by moderator.

	$\Delta R^2$	<i>b</i>	<i>t</i>
Processed food pattern	.06	1.65	2.31*
Whole food pattern	.0004	.12	.18
Exercise	.0001	-.03	-.10
Exercise and processed food	.0007	.009	.24
Exercise and whole food	.0002	-.006	-.12

Note: \*  $p < .05$ .

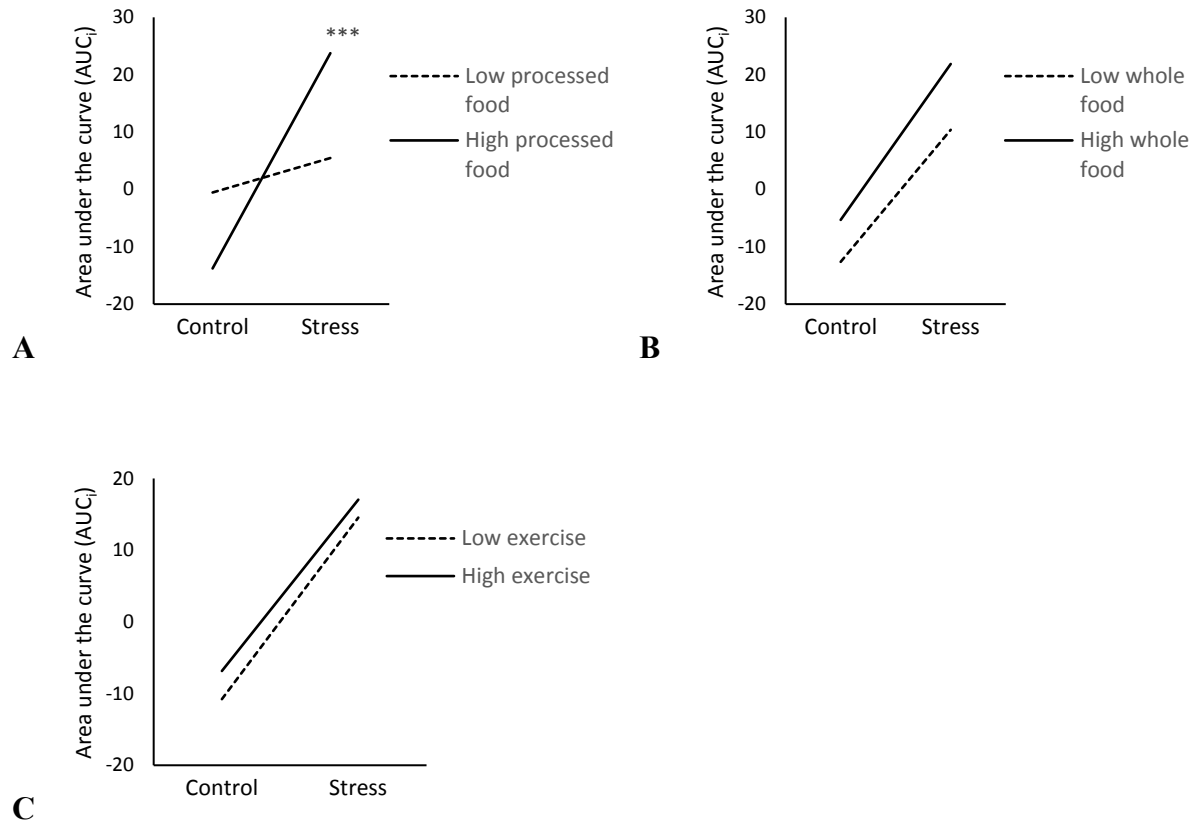


Figure 2. The moderating role of dietary pattern and exercise in the relation between stressor condition and cortisol AUC<sub>i</sub>. Note: low levels of adherence to either dietary pattern or low frequency of exercise = 1 *SD* below the mean, high levels of adherence to either dietary pattern or high frequency of exercise = 1 *SD* above the mean. Note. \*\*\* $p < 0.001$

## **Discussion**

### **Zero-order correlations**

The present findings indicated a positive relation between frequency of exercise and the whole foods dietary pattern. This is not surprising, as individuals who consume healthier foods might exercise more. This would seem intuitive, but most research examining lifestyle factors, such as diet and exercise, have assessed how they predict health outcomes, rather than how they intercorrelate. Adding to this, comparing these findings to previous research is complex, as both diet and exercise can be broadly defined, and there is considerable variability in the operational definitions that have been endorsed. This said, there is some research indicating that long-term exercise interventions do not have an effect on total food intake (see review in Martins, Morgan, & Truby, 2008), and that dietary choices may have an effect on exercise behavior, such that ‘fitness branded’ food, which is generally higher in protein, is associated with *less* physical activity (Koenigstorfer & Baumgartner, 2016).

### **Stressor effects on cortisol**

Consistent with previous research (Kirschbaum et al., 1993), cortisol concentrations were elevated in response to the Trier Social Stress Test (TSST). However, this effect varied with the participant’s self-reported eating preferences. Specifically, the rise of cortisol elicited in the stress test was more pronounced among individuals who reported a greater adherence to a processed food dietary pattern. However, interactions were not apparent with respect to frequency of exercise, or the interaction between either dietary pattern and exercise, in predicting cortisol levels.

The present findings indicating significant moderating effects of a processed food dietary pattern on cortisol production in response to a stressor are difficult to compare to previous studies, as earlier research was limited to the effects of macronutrients (i.e., protein, fats, and

carbohydrates) consumed immediately prior to a stressor. However, our findings are in line with previous research examining the effects of macronutrients that comprise a processed food dietary pattern. For example, it had been reported that consumption of a high glycemic carbohydrate (glucose) prior to undergoing a stressor, increased cortisol levels following the TSST (Kirschbaum et al., 1997). However, it has also been reported that cortisol reactivity in response to a stressor was not influenced by carbohydrate consumption (Lemmens et al., 2011), but procedural differences may have contributed to this discrepancy. For instance, Kirschbaum et al. (1997) instructed participants to fast prior to consumption of glucose before the TSST, which can influence the HPA response to a stressor (e.g., Akana, Strack, Hanson, Dallman, 1994; De Boer, Koopmans, Slangen, van der Gugten, 1989). In contrast, Lemmens et al. (2011) had participants consume a meal high in carbohydrates, which also contained fat, which can slow glucose absorption (Josse et al., 2007). In addition, the ‘high carbohydrate meal’ utilized by Lemmens et al. (2011) mentioned only that it was high in carbohydrates, but were not specific as to what kind of carbohydrates (i.e., a fast digesting glucose or a slower digesting fructose) were used.

The processed food diet, as defined in the present investigation, is also characterized by greater intake of omega-6 fatty acids, and when consumed in large amounts can be pro-inflammatory and hence impact the stress response. Indeed, previous animal research indicated that a diet high in fat from corn oil was followed by elevated levels of ACTH and corticosterone in response to a stressor (Tannenbaum et al., 1997).

Our non-significant moderating effect of a whole food dietary pattern on the cortisol response is again difficult to compare to previous research; however, in line with previous research, it generally seems that consumption of omega-3 (Giles et al., 2015) and monounsaturated fatty acids (Gonzalez-Bono et al., 2002), which are abundant in a whole food

dietary pattern, were unrelated to cortisol levels in response to the TSST. However, previous research indicated that omega-3 fatty acids can attenuate cortisol activity in response to a stressor (Delarue et al., 2003), as well as other markers of physiological stress, namely plasma epinephrine and norepinephrine (Hamazaki et al., 1999). This discrepancy in previous research may be attributed to potency of the stressor used, as Giles et al. (2015) used the TSST, whereas Delarue et al. (2003) used a mental arithmetic and the Stroop test.

Like the contribution of carbohydrates and fat, it is difficult to identify the specific contribution of protein in the cortisol response in the TSST. Protein quality can vary by amino acid profile, but, it is rarely broken down into its amino acid profile on food labels. This is relevant as certain amino acids can impact the stress response. Although these amino acids were not measured, their importance is considerable. By example, among individuals who consumed a tryptophan enriched protein drink (which can augment serotonergic functioning, and thereby mitigate some of the stress effects), it was observed that the cortisol response to the TSST was attenuated (Firk & Markus, 2009), although it was also reported that a tryptophan enriched protein drink did not affect cortisol levels in response to a stressor (Merens et al., 2005). The differences in results may be attributed to the stressor used, as Merens et al. (2005) used a mental math task with a loud noise present, which may not have been as potent stressor as the TSST. In addition, Firk and Markus (2009) used a hydrolyzed source of protein, which is known to cause a greater increase in tryptophan than the  $\alpha$ -lactalbumin used in Merens et al. (2005).

It is difficult to speculate on the mechanisms underlying the elevated cortisol response to the TSST associated with increased intake of carbohydrates, as much of the research indicates differential effects on cortisol production. On the one hand, it has been observed that in humans glucose loading can increase levels of tryptophan (Kirschbaum et al., 1997), which in turn, can

increase synthesis of serotonin and stimulate the HPA axis (Spinedi & Gaillard, 1991). In addition, animal research suggests that the availability of energy stores from carbohydrates are necessary for activation of the HPA axis in response to stress (Hanson et al., 1994; Wronska, Niezgoda, Sechman, Bobek, 1990). On the other hand, animal research also suggests that carbohydrates can have an *attenuating* effect on cortisol response to a stressor, mainly through areas of the brain associated with reward. For example, rats fed sucrose or saccharin (a non-caloric sweetener) prior to undergoing a stressor displayed less corticotropin-releasing hormone (CRH) mRNA expression in the paraventricular nucleus of the hypothalamus, compared to rats given only water, suggesting that the palatability and not the calories, is necessary for the stress dampening effect (Ulrich-Lai et al., 2007). Furthermore, consumption of sucrose increases mRNA and protein expression in the basolateral amygdala (BLA), a component of the reward circuitry, and lesions of the BLA ceased the stress attenuating effect (Ulrich-Lai et al., 2010).

The biological mechanism responsible for the effect of protein consumption on cortisol response with respect to the current findings is puzzling, as past research has indicated that protein consumption *reduces* cortisol levels in response to stressors, and that this effect occurs as a result of increased tryptophan, which can attenuate HPA axis reactivity (Porter et al., 2004). However, past research has mainly used enriched sources of protein (e.g., hydrolyzed protein or  $\alpha$ -lactalbumin), that provide substrate for tryptophan synthesis, which can have a greater effect on HPA axis functioning than consumption of other amino acids. This is in contrast to the present investigation in which only general protein intake patterns were measured, and hence the amino acid profile of the protein consumed was nonspecific.

Dietary fat may have its influence on the HPA axis via the immune system. For example, diets higher in omega-6 rather than omega-3 polyunsaturated fatty acids create a more pro-

inflammatory environment, as omega-6 fatty acids provide substrate for pro-inflammatory mediators, which can then activate the HPA axis (Husted & Bouzinova, 2016). In addition, increased levels of omega-6 fatty acids can lower serotonin levels (Husted & Bouzinova, 2016), which as mentioned earlier in regard to carbohydrate consumption, can affect cortisol levels in response to a stressor. Saturated fat can stimulate the immune system as well, given that saturated fat is a naturally occurring ligand that can stimulate Toll-like receptor 4 (TLR4), which may then activate pro-inflammatory transcription factors, such as nuclear factor- $\beta$  (Suganami et al., 2007), and in turn, can influence HPA activity.

The present findings indicating that exercise does not have an effect on cortisol levels in response to a stressor, seems to be consistent with research among older populations (Jayasinghe et al., 2016; Moya-Albiol et al., 2001; Strahler et al., 2016). However, our findings are puzzling when compared to results among undergraduate populations, as studies using both self-report measures of exercise (Childs & de Wit, 2014; Klaperski et al., 2013), as well as a device worn by participants to objectively assess physical activity (Gerber et al., 2017), indicated that exercise does have an attenuating effect on cortisol levels. Indeed, this was also observed both among children (Martikainen et al., 2013) and young male athletes (Rimmele et al., 2009). It is difficult to speculate on the inconsistency between the present findings and previous research with self-report measures of exercise. However, it is possible that differences in self-report measures may have contributed to this inconsistency. By example, Klaperski et al. (2013) had participants indicate the exercise they engaged in, and the frequency and duration of the exercise, which may have provided a different index of total physical activity than in the present study, which only assessed the frequency of a cluster of exercises ranked in order of intensity. The present findings also revealed that exercise did not interact with either dietary pattern. However, it is difficult to



compare the present findings with past research due to the lack of research on the interaction between dietary pattern and exercise, in predicting the stress response.

Several limitations of the present study need to be addressed, as in Study 1, the present investigation included use of self-report food and exercise frequency questionnaires, which are subject to recall biases. These caveats aside, the present investigation suggests that a processed food dietary pattern was negatively related to stressor reactivity, whereas this was not apparent among participants who favored a whole food diet. Contrary to prediction, exercise did not affect the cortisol response elicited by the stressor, and did not protect against the elevated cortisol associated with the processed food diet. Although the precise mechanisms through which the effects of the processed food diet might occur were not explored in the present study, it is possible that the gut microbiome may have been involved, as diet can affect the composition of gut bacteria (Javitt & Javitt, 2018), which can, in turn, affect HPA activity (Scriven et al., 2018). In general, the present findings may have broader implications in the treatment of stress-related diseases, such as depression, as these illnesses are often associated with altered HPA functioning (Jurueña et al., 2018), gut dysbiosis (Foster & Neufeld, 2013), and processed food dietary patterns (Li et al., 2017). With this said, examining differences in diet may provide insight into factors that contribute to physical and psychological disorders, as well as in the development of treatment interventions.

## **General Discussion**

Dietary pattern and exercise have long been considered as being fundamental components of well-being. In this regard, they certainly play a role in physical health, but their functioning in relation to mental health, has only recently received appreciable attention (Anisman, Hayley, & Kusnecov, 2018; Chekroud et al., 2018). Moreover, limited research has examined how these lifestyle factors might interact with genetic mutations, in this regard. In the present investigation, it was demonstrated that genetic polymorphisms of immune related genes moderated the relation between lifestyle factors and depressive symptoms, and measures related to executive functioning, such as performance in the Iowa Gambling Task (IGT), as well as coping selection and coping flexibility. It was also demonstrated that unhealthy dietary behavior can amplify the relation between early-life stressors and psychological indices of mental health (depressive symptoms and creative problem solving), and the relation between a current socio-evaluative stressor and cortisol response.

Consistent across Studies 1-3, sex played a role in dietary choice, in that females reported healthier dietary behavior than did males, either by virtue of a greater intake of healthy food, or a reduced intake of unhealthy food. These findings are consistent with reports showing that females tend to have higher levels of eating-related self-determined motivation than males, although it was not possible to determine this in the present investigation (Leblanc et al., 2015). Curiously, in Study 2, it appeared that males adhered more to a prudent dietary pattern than did females, but this relation was dependent upon genotype, in that this effect was only present among males and females with the typical IL-17 GG genotype. Interestingly, in Study 3, males exercised more than females did, but this outcome was not evident in the two preceding studies. At best, this is a weak effect, although similar outcomes were reported in earlier research

(Bauman et al., 2012; Hallal et al., 2012). In Studies 1 and 2, females reported higher depressive symptoms than did males, which is in line with considerable research. Indeed, the gap in both symptoms and diagnoses of depression can be detected as early as the age of 12 (Salk et al., 2017). A recent imaging study also indicated that relative to non-depressed controls, depressed males and females displayed differences in activity in brain regions such as the posterior cingulate and supramarginal gyrus, when shown emotionally charged words. Moreover, the activation pattern of females was lower than that of males (Chuang et al., 2017).

Measures of executive function also differed by sex, as males displayed enhanced performance on the IGT (Study 3), and reported more cognitive control when experiencing stressful situations than did females, although this relation only occurred among A carriers of the IL-17A gene (Study 2). Moreover, females of the same genotype in Study 2, also reported greater use of emotion-focused coping strategies than did males of the same genotype, which again might be due to an impairment of executive functioning, as IGT performance and coping selection are both related to this cognitive process (Compas, 2006). These findings seem to be largely aligned with past research indicating that males outperform females on the IGT task (van den Bos et al., 2013), although females outperform males on other indices of executive function, such as the Stroop test (Upadhayay & Guragain, 2014). Despite the connections between sex and the measures related to executive function in Studies 1 and 2, no sex differences were apparent in the Remote Associates Test (Study 3), which is also associated with prefrontal cortical activity (Dietrich, 2004), although multiple brain regions might also be involved (Dietrich & Kanso, 2010). As will be discussed shortly, it is uncertain why the divergent sex-related outcomes were noted across studies. It is likely, however, that the different tasks involve several independent processes and hence might be subject to varied influences.

The influence of sex aside, there also seemed to be a relation between the TNF- $\alpha$  polymorphism and dietary choice in Studies 2 and 3, in that the minor allele was associated with greater intake of unhealthy foods, although in Study 3, this relation was also dependent upon sex. In addition, this allele, along with the IL-6 GG genotype (Study 2), were both associated with a reduction in cognitive flexibility, however, these genotypes did not show the same relation to IGT performance in Study 3. It is difficult to speculate why these relations did not exist in Study 3, considering that cognitive flexibility and IGT performance are both associated with activity in prefrontal and striatal regions, however, coping flexibility, might also be affected by regions of the brain associated with stress, such as the HPA axis, which can also be affected by pro-inflammatory cytokines (Raison et al., 2006). Despite the relations these SNPs had with dietary pattern and measures related to executive functioning, there was no direct link between any of the SNPs examined and depressive symptoms, which may not be that surprising given the appreciable variability in gene association studies (Barnes et al., 2017).

Just as sex and genotype may be associated with the variables previously discussed, both dietary pattern (Quirk et al., 2013), and exercise (Daley, 2008), have been linked to risk of depression. However these relations were not found in the present investigation (Studies 1 and 2), just as other research has also failed to demonstrate these outcomes. In fact, earlier research suggested that the inconsistency in these relations was likely due to differences in methodology and an overestimation of treatment effects. Despite the links between lifestyle factors and executive functioning previously reported, only Study 2 indicated a positive association between a healthy dietary pattern and coping flexibility. Why a similar outcome among variables associated with executive functioning was not apparent in Studies 1 and 3 is uncertain, but

speaks to this outcome as being a weak one, and conclusions pertaining to this linkage need to be held in abeyance pending further studies.

It appeared that only the IL-6 polymorphism interacted with lifestyle factors in predicting mental health related outcomes. Indeed, the non-prudent diet was negatively related to coping flexibility (Study 2) and IGT performance (Study 3). However, in Study 2, this relation existed only for individuals with the GG genotype, which is associated with higher levels of IL-6 (Fishman et al., 1998), whereas in Study 3, this relation was only apparent among individuals carrying the C allele for the IL-6 gene. The findings from Study 2 might have suggested that elevated levels of IL-6 from both the genotype and the non-prudent diet, might have had compound actions and would be associated with impaired coping flexibility. Yet, the results from Study 3 seemed to suggest that elevated levels of IL-6 may be *beneficial* to executive functioning related measures (IGT performance), and that the non-prudent diet and exercise, may be linked to poorer cognitive performance through other pathways. Together these findings seem to be contradictory, however, as described earlier, coping flexibility and IGT performance likely involve diverse processes and thus might be affected by different neurobiological substrates.

Just as cytokine related polymorphisms interacted with lifestyle factors in predicting mental health related outcomes, a current stressor, and stressors experienced early in life, interacted with these factors. Indeed, Study 1 suggested that unhealthy dietary behavior, comprising greater intake of unhealthy foods or consumption of a reduced quantity of healthy foods, was accompanied by greater negative effects of stressors experienced early in life, on creative problem solving (Remote Associates Test performance) and depressive symptoms. Due to the correlational nature of the study, it was not possible to draw causal connections between dietary intake and these outcomes, although unhealthy dietary patterns are associated with pro-

inflammatory states (Lopresti et al., 2013), and this may be adding to the already pro-inflammatory profile of individuals who had experienced early-life trauma. Although it is also possible that early-life trauma might influence dietary pattern and performance on the Remote Associates Test independently of one another, as early-life trauma is associated with both increases in unhealthy foods following stressful encounters later in life (Schrepf et al., 2014), at this time it is difficult to dissociate these from one another, and still more difficult to draw causal connection in relation broad cognitive processes.

The results of Study 4 seemed to build upon the findings from Study 1, in that an unhealthy dietary pattern exacerbated the biological response to a socio-evaluative stressor. Again, however, it is not possible to determine whether the non-prudent dietary pattern amplified the cortisol response, or whether individuals who are more reactive to stress in general, consume more non-prudent dietary items. There is evidence that both explanations are plausible, as non-prudent dietary items, such as high glycemic carbohydrates, can exacerbate the stress response when consumed prior to undergoing the TSST (Kirschbaum et al., 1997), and individuals who had higher levels of cortisol in response to the TSST, consumed more calories in the days following the stressor (Epel et al., 2001). However, neither of these findings address the effect of dietary *pattern* in this regard.

#### *Limitations and conclusions*

As discussed previously in each of the chapters, limitations to the studies need to be addressed. Across all studies, the self-report nature of the lifestyle measures might be subject to recall biases, as previously reviewed (e.g., Ioannidis, 2013). In addition, these studies were conducted primarily using healthy and young undergraduate students, which may limit the generalizability to a clinical population. Adding to this, studying the effects of exercise treatment

in clinical populations are made more difficult due to the high rates of attrition among randomized controlled trials (Lawlor & Hopker, 2001). With regard to the gene related studies (Studies 2 and 3), the students that comprised these samples were all White, which limits the generalizability of our findings to other ethnicities. Furthermore, due to the infrequency of the minor alleles, we collapsed across mutant allele carriers for analyses, which limits the interpretability of all possible genotypes for each gene. The smaller sample sizes may have also reduced power in detecting Sex x Genotype interactions, and limited our ability to analyze Genotype x Genotype interactions.

These limitations notwithstanding, the present investigation suggests that dietary pattern and exercise habits, can interact with both stressors and immune related SNPs in predicting mental health related outcomes (Figure 1), which may have implications for a personalized medicine approach. Specifically, results from Studies 1 and 4 support the view that improvements in dietary quality (i.e., reducing high glycemic carbohydrate and *trans* fat intake, and increasing consumption of healthy fats, fruits, and vegetables) may be accompanied by diminished negative sequelae associated with stressors experienced early in life, or potential stressors in the future. It was also shown that sex and the controllability of a stressor, can interact with lifestyle factors in predicting psychosocial and mental health outcomes. Studies 2 and 3 seem to suggest that particular SNPs should be taken into account when considering the effectiveness of diet and exercise as a form of treatment for depression. As well, not all SNPs associated with elevated levels of pro-inflammatory cytokines are necessarily ‘risk’ alleles. Obviously, only a limited number of inflammatory gene polymorphisms were assessed in the present investigation, thus it is premature to discount the role played by such factors in the evolution of depression. In this regard, there has been a marked interest in determining whether

depression among some individuals may come about owing to the inflammatory-related kynurenine pathway and the neurodegenerative processes that ensue (e.g., Dantzer, 2016; Leonard & Maes, 2012). At present, the link between diet and exercise to kynurenine functioning has not been assessed, but in light of it being influenced by inflammatory processes, the relations between these factors warrants detailed evaluation.



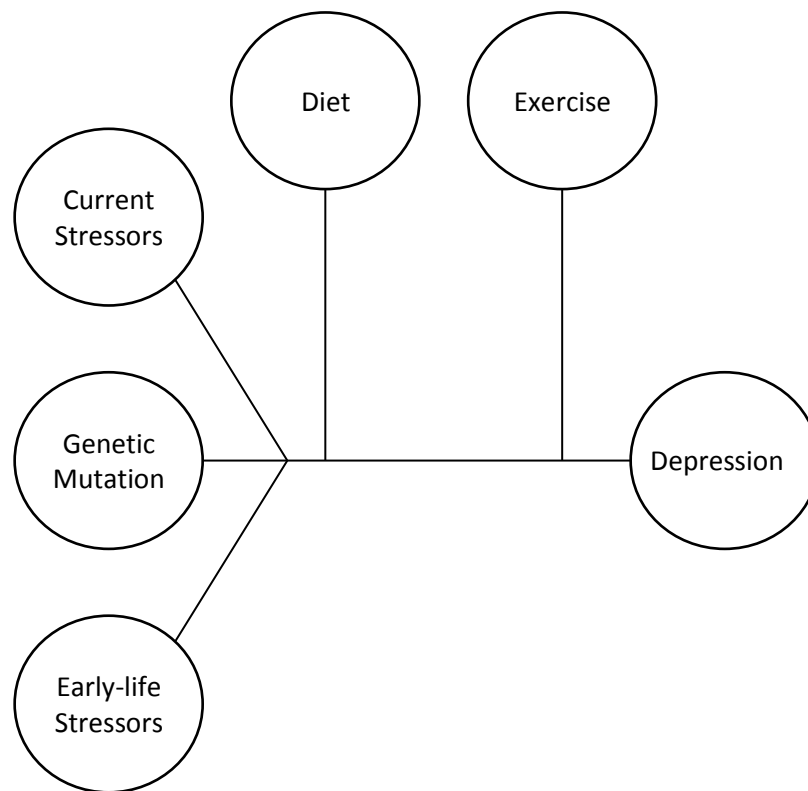


Figure 1. The moderating role of dietary pattern and exercise, in the relation between risk factors (current stressors, genetic mutations, and early-life stressors) and depression. Of course, given the correlational nature of the variables, we cannot rule out the possibility of bidirectional relationships.

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## Appendix A: Measures

### Godin Leisure-Time Exercise Questionnaire

Considering **A TYPICAL WEEK in the past 6 months**, how many times on average do you do the following kinds of exercise for more than 20 minutes during your free time (**write the appropriate number of times per week on the line**).

#### **A) STRENUOUS/VIGOROUS PHYSICAL ACTIVITY (HEART BEATS RAPIDLY)**

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, exercise classes, weight lifting, crossfit training, MMA)

\_\_\_\_\_ Times per Week

Please specify activity(s) \_\_\_\_\_

#### **B) MODERATE PHYSICAL ACTIVITY (NOT EXHAUSTING)**

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

\_\_\_\_\_ Times per Week

Please specify activity(s) \_\_\_\_\_

**C) MILD PHYSICAL ACTIVITY (NOT EXHAUSTING)**

(e.g., yoga, archery, fishing from a river bank, bowling, horseshoes, golf, show-mobbing, easy walking)

\_\_\_\_\_ Times per Week

Please specify activity(s) \_\_\_\_\_



### Survey of Coping Profiles Endorsed (SCOPE) -A

Imagine that you get your term paper back and received a much lower grade than you anticipated and, as a result you may not pass the course. You asked the professor whether you can somehow make up for the bad grade but he/she said there is nothing you can do about it at this point.

1. How threatening would you find this situation?

1	2	3	4	5	6	7
None at all						Total control

2. How much control do you think you would have over this situation?

1	2	3	4	5	6	7
None at all						Total control

3. How important would it be for you to achieve a good resolution in this situation?

1	2	3	4	5	6	7
None at all						Extremely important

4. Would you be able to cope effectively with this situation?

1	2	3	4	5	6	7
None at all						Total control

The following is a list of activities that you might do in response to the situation described above. After each activity, please indicate the extent to which you would use these as a way of dealing with this situation over the next 2 weeks.

	Never	Seldom	Sometimes	Often	Always
<b>Over the next couple of weeks, I</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
1. accept that there is nothing I could do to change the situation.	0	1	2	3	4
2. blame myself for my problems.	0	1	2	3	4
3. tell others that I was really upset.	0	1	2	3	4
4. ask others for help or advice.	0	1	2	3	4
5. spend a lot of time thinking about my problem.	0	1	2	3	4
6. take time for recreation or pleasure activities.	0	1	2	3	4
7. make plans to overcome my concerns or problem.	0	1	2	3	4
8. avoid thinking about the situation.	0	1	2	3	4
9. tell jokes about the situation.	0	1	2	3	4
10. think a lot about who was responsible for for this situation (besides me).	0	1	2	3	4
11. worry about the situation a lot.	0	1	2	3	4
12. make humorous comments or stories about the situation.	0	1	2	3	4
13. wish the situation would just go away or be over with	0	1	2	3	4
14. think a lot about how I brought the situation on myself.	0	1	2	3	4
15. decide to wait and see how things turned out.	0	1	2	3	4
16. try to keep my mind off things that were upsetting me.	0	1	2	3	4
17. seek reassurance and emotional support from others.	0	1	2	3	4
18. think about how the situation was caused by other people.	0	1	2	3	4
19. cry, even if someone else was around.	0	1	2	3	4
20. look for how I could grow and learn through the situation.	0	1	2	3	4
21. tell myself that other people have problems like mine.	0	1	2	3	4
22. do things to keep busy or active (eg., exercised, went out).	0	1	2	3	4

23. hold in my feelings.	0	1	2	3	4
24. daydream about how things may turn out.	0	1	2	3	4
25. try to act as if I wasn't feeling bad.	0	1	2	3	4
26. take steps to overcome the situation.	0	1	2	3	4
27. turn to God or my faith.	0	1	2	3	4

## Survey of Coping Profiles Endorsed (SCOPE) -B

Imagine that get your term paper back and you received a much lower grade than you anticipated and, as a result you may not pass the course. This time, when you ask the professor whether you can somehow make up for the bad grade, he/she said that you have the option to take an extra 2 weeks to improve your paper and potentially get a better grade.

1. How threatening would you find this situation?

1	2	3	4	5	6	7
None at all						Total control

2. How much control do you think you would have over this situation?

1	2	3	4	5	6	7
None at all						Total control

3. How important would it be for you to achieve a good resolution in this situation?

1	2	3	4	5	6	7
None at all						Extremely important

4. Would you be able to cope effectively with this situation?

1	2	3	4	5	6	7
None at all						Total control

The following is a list of activities that you might do in response to the situation described above. After each activity, please indicate the extent to which you would use these as a way of dealing with this situation over the next 2 weeks.

	Never	Seldom	Sometimes	Often	Always
<b>Over the next couple of weeks, I</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
1. accept that there is nothing I could do to change the situation.	0	1	2	3	4
2. blame myself for my problems.	0	1	2	3	4
3. tell others that I was really upset.	0	1	2	3	4
4. ask others for help or advice.	0	1	2	3	4
5. spend a lot of time thinking about my problem.	0	1	2	3	4
6. take time for recreation or pleasure activities.	0	1	2	3	4
7. make plans to overcome my concerns or problem.	0	1	2	3	4
8. avoid thinking about the situation.	0	1	2	3	4
9. tell jokes about the situation.	0	1	2	3	4
10. think a lot about who was responsible for for this situation (besides me).	0	1	2	3	4
11. worry about the situation a lot.	0	1	2	3	4
12. make humorous comments or stories about the situation.	0	1	2	3	4
13. wish the situation would just go away or be over with	0	1	2	3	4
14. think a lot about how I brought the situation on myself.	0	1	2	3	4
15. decide to wait and see how things turned out.	0	1	2	3	4
16. try to keep my mind off things that were upsetting me.	0	1	2	3	4
17. seek reassurance and emotional support from others.	0	1	2	3	4
18. think about how the situation was caused by other people.	0	1	2	3	4
19. cry, even if someone else was around.	0	1	2	3	4
20. look for how I could grow and learn through the situation.	0	1	2	3	4
21. tell myself that other people have problems like mine.	0	1	2	3	4
22. do things to keep busy or active (eg., exercised, went out).	0	1	2	3	4

23. hold in my feelings.	0	1	2	3	4
24. daydream about how things may turn out.	0	1	2	3	4
25. try to act as if I wasn't feeling bad.	0	1	2	3	4
26. take steps to overcome the situation.	0	1	2	3	4
27. turn to God or my faith.	0	1	2	3	4

## FFQ

**DIRECTIONS:** For the following food groupings, please indicate your average frequency of consumption over the past year by circling the appropriate number.

1. Processed meats: Processed meats, bacon, hot dogs

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

2. Red Meats: Beef, pork, lamb, hamburger

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

3. Organ meats: Beef, calf, and pork liver, chicken and turkey liver

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

4. Fish and other seafood: Canned tuna fish, dark-meat fish, other fish, shrimp, lobster, scallops

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

5. Poultry: Chicken or turkey with or without skin

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

6. Eggs

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

7. Butter

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

8. Margarine

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

9. Low-fat dairy products: Skim or low-fat milk, sherbet or ice milk, yogurt

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9



10. High-fat dairy products: Whole milk, cream, sour cream, ice cream, cream cheese, other cheese

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

11. Liquor

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

12. Wine: Red or White

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

13. Beer

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

14. Tea

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

15. Coffee

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

16. Fruit: Raisins or grapes, avocado, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches, apricots, plums

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

17. Fruit Juices: Apple or cider, orange juice, grapefruit juice, other fruit juice

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

18. Cruciferous vegetables: Broccoli, coleslaw and uncooked cabbage, cooked cabbage, cauliflower, Brussels sprouts, kale, mustard, chard greens, sauerkraut

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

19. Dark-yellow vegetables: Carrots, yellow (winter) squash, yams

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

20. Tomatoes: Tomatoes, tomato juice, tomato sauce

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

21. Green, leafy vegetables: Spinach, iceberg or head lettuce, romaine or leaf lettuce

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

22. Legumes: String beans, peas or lima beans, beans or lentils, tofu or soybeans, alfalfa sprouts

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

23. Other vegetables: Celery, mushrooms, green pepper, corn, mixed vegetables, eggplant, summer squash

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

24. Garlic

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

25. Potatoes

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

26. French fries

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

27. Whole grains: Cooked oatmeal, other cooked breakfast cereal, dark bread, brown rice, other grains, bran added to food, wheat germ

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

28. Cold breakfast cereal

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

29. Refined grains: White bread, English muffins, bagels or rolls, muffins or biscuits, white rice, pasta, pancakes or waffles

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

30. Pizza

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

31. Snacks: Potato chips or corn chips, crackers, popcorn

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

32. Nuts: Peanuts, other nuts, peanut butter

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

33. High-energy drinks: Cola with sugar, other carbonated beverages with sugar, fruit drinks

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

34. Low-energy drinks: Low-energy cola, other low-energy carbonated beverages

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

35. Oil and vinegar salad dressing

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

36. Mayonnaise and other creamy salad dressings

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

37. Chowder or cream soup

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

38. Other soup: Homemade soup, ready-made soup

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

39. Sweets and desserts: Chocolate bars or pieces, candy bars, cookies, brownies, doughnuts, cake, pie, sweet roll, coffee cake, pastry

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

40. Condiments: Red chili sauce (dry or prepared), mustard, pepper, soy or Worcestershire sauce, jam, jelly, syrup, honey

Almost Never	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day
1	2	3	4	5	6	7	8	9

### The Remote Associates Task

Here we would like you to think about the combination of three words. All three of these words are related in some way to a forth word that you must guess. Please see the example below.

\*Note all answers besides the example will not be shown

Words	Answer
Falling Actor Dust	STAR (example)
Broken Clear Eye	GLASS
Skunk Kings Boiled	CABBAGE
Widow Bite Monkey	SPIDER
Bass Complex Sleep	DEEP

Square Cardboard Open	BOX
Water Tobacco Stove	PIPE
Ache Hunter Cabbage	HEAD
Chamber Staff Box	MUSIC
High Book Sour	NOTE

Speak Money Street	EASY
Big Leaf Shade	TREE
Envy Golf Beans	GREEN
Hall Car Swimming	POOL
Ink Herring Neck	RED



Bump Throat Sum	LUMP
Shopping Washer Picture	WINDOW
Blank White Lines	PAPER
Stick Light Birthday	CANDLE
Sore Shoulder Sweat	COLD

## **Early Trauma Inventory Self Report-Short Form (ETISR-SF)**

**Please indicate how many times each of these events have happened to you (please put a '0' if this event has not happened to you).**

### **Part 1. General Traumas. Before the age of 18**

1. Were you ever exposed to a life-threatening natural disaster? \_\_\_\_\_
2. Were you involved in a serious accident? \_\_\_\_\_
3. Did you ever suffer a serious personal injury or illness? \_\_\_\_\_
4. Did you ever experience the death or serious illness of a parent or a primary Caretaker? \_\_\_\_\_
5. Did you experience the divorce or separation of your parents? \_\_\_\_\_
6. Did you experience the death or serious injury of a sibling? \_\_\_\_\_
7. Did you ever experience the death or serious injury of a friend? \_\_\_\_\_
8. Did you ever witness violence towards others, including family members? \_\_\_\_\_
9. Did anyone in your family ever suffer from mental or psychiatric illness or have a "breakdown"? \_\_\_\_\_
10. Did your parents or primary caretaker have a problem with alcoholism or drug abuse? \_\_\_\_\_
11. Did you ever see someone murdered? \_\_\_\_\_

### **Part 2. Physical Punishment. Before the age of 18**

1. Were you ever slapped in the face with an open hand? \_\_\_\_\_
2. Were you ever burned with hot water, a cigarette or something else? \_\_\_\_\_
3. Were you ever punched or kicked? \_\_\_\_\_
4. Were you ever hit with an object that was thrown at you? \_\_\_\_\_
5. Were you ever pushed or shoved? \_\_\_\_\_

### **Part 3. Emotional Abuse. Before the age of 18**

1. Were you often put down or ridiculed? \_\_\_\_\_
2. Were you often ignored or made to feel that you didn't count? \_\_\_\_\_
3. Were you often told you were no good? \_\_\_\_\_
4. Most of the time were you treated in a cold, uncaring way or made to feel like you

were not loved? \_\_\_\_\_

5. Did your parents or caretakers often fail to understand you or your needs? \_\_\_\_\_

**Part 4. Sexual Events. Before the age of 18**

1. Were you ever touched in an intimate or private part of your body (e.g. breast, thighs, genitals) in a way that surprised you or made you feel uncomfortable? \_\_\_\_\_

2. Did you ever experience someone rubbing their genitals against you? \_\_\_\_\_

3. Were you ever forced or coerced to touch another person in an intimate or private part of their body? \_\_\_\_\_

4. Did anyone ever have genital sex with you against your will? \_\_\_\_\_

5. Were you ever forced or coerced to perform oral sex on someone against your will? \_\_\_\_\_

6. Were you ever forced or coerced to kiss someone in a sexual rather than an affectionate way? \_\_\_\_\_

### Cognitive Flexibility Questionnaire 28-item (CFQ)

The purpose of this questionnaire is to determine what individuals generally think, feel, and do when experiencing stressful situations. Of course, you may respond differently depending on the situation, but think of what you usually do when you are under a lot of stress. Using the scale below, indicate the extent to which agree or disagree with the following statements. Please answer according to what you *actually* think/feel/do rather than what you think is the correct response.

<i>Strongly Disagree</i>	<i>Disagree</i>	<i>Slightly Disagree</i>	<i>Neutral</i>	<i>Slightly Agree</i>	<i>Agree</i>	<i>Strongly Agree</i>
1	2	3	4	5	6	7

***Generally, in stressful situations...***

1. I weigh out many options before choosing how to take action.	1	2	3	4	5	6	7
2. I can't focus on anything when I am upset.	1	2	3	4	5	6	7
3. It's hard to think of different ways of dealing with the situation	1	2	3	4	5	6	7
4. I control my thoughts and feelings by putting the situation in context.	1	2	3	4	5	6	7
5. I can remain in control over my thoughts and emotions.	1	2	3	4	5	6	7
6. It's difficult let go of intrusive thoughts or emotions.	1	2	3	4	5	6	7
7. It's hard for me to put things in perspective when I'm upset.	1	2	3	4	5	6	7
8. I have a hard time managing my emotions.	1	2	3	4	5	6	7
9. I take the time to see things from different perspectives before reacting.	1	2	3	4	5	6	7
10. I feel like I lose control over my thoughts and emotions.	1	2	3	4	5	6	7

<b>11. It's hard for me to shift my attention away from negative thoughts or feelings.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>12. I find it easy to look for something positive, even when I am stressed.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>13. I control negative thoughts and emotions by modifying the way I think about the situation.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>14. It is easy for me to ignore distracting thoughts.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>15. It's hard for me to ignore negative emotions once they have been provoked.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>16. I can think of multiple coping options before deciding how to respond.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>17. I get easily distracted by upsetting thoughts or feelings.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>18. I approach the situation from multiple angles.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>19. My thoughts and emotions interfere with my ability to concentrate.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>20. I take the time to think of more than one way to resolve the problem.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>21. It is easy for me to shift my attention to other things if I am upset.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>22. I manage my thoughts or feelings by reframing the situation.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>23. I find it difficult to think of many options for resolving the situation.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>24. Putting a positive spin on a bad experience comes fairly easy to me.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>25. I find it easy to set-aside unpleasant thought or emotions.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>

<b>26. It is easy for me to reassess a negative experience into a positive one.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>27. I can easily to suppress upsetting memories.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>28. I take the time to think of several ways to best cope with the situation before acting.</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>

## Beck Depression Inventory (BDI)

On this questionnaire are groups of statements. Please read the entire group of statements in each category. Then pick out ONE statement in that group which best describes the way you feel. Check off the number beside the statement you have chosen.

---

1. ☐ 0 = I do not feel sad  
☐ 1 = I feel sad or blue  
☐ 2a = I am blue or sad all of the time and I can't snap out of it  
☐ 2b = I am so sad or unhappy that it is very painful  
☐ 3 = I am so sad or unhappy that I can't stand it
  
2. ☐ 0 = I am not particularly pessimistic or discouraged about the future  
☐ 1 = I feel discouraged about the future  
☐ 2a = I feel I have nothing to look forward to  
☐ 2b = I feel I won't ever get over my troubles  
☐ 3 = I feel that the future is hopeless and things cannot improve
  
3. ☐ 0 = I do not feel like a failure  
☐ 1 = I feel I have failed more than the average person  
☐ 2a = I feel I have accomplished very little that is worthwhile or that means anything  
☐ 2b = As I look back on my life, all I can see is a lot of failures  
☐ 3 = I feel I am a complete failure as a person
  
4. ☐ 0 = I am not particularly dissatisfied  
☐ 1a = I feel bored most of the time  
☐ 1b = I don't enjoy things the way I used to  
☐ 2 = I don't get satisfaction out of anything anymore  
☐ 3 = I am dissatisfied with everything
  
5. ☐ 0 = I don't feel particularly guilty  
☐ 1 = I feel bad or unworthy a good part of the time  
☐ 2a = I feel quite guilty  
☐ 2b = I feel bad or unworthy practically of the time now  
☐ 3 = I feel as though I am very bad or worthless
  
6. ☐ 0 = I don't feel I am being punished  
☐ 1 = I have a feeling that something bad may happen to me  
☐ 2 = I feel I am being punished or will be punished  
☐ 3a = I feel I deserve to be punished  
☐ 3b = I want to be punished
  
7. ☐ 0 = I don't feel disappointed in myself  
☐ 1a = I am disappointed in myself  
☐ 1b = I don't like myself

- ☐ 2 = I am disgusted with myself  
☐ 3 = I hate myself
8. ☐ 0 = I do not feel I am any worse than anybody else  
☐ 1 = I am very critical of myself for my weaknesses or mistakes  
☐ 2a = I blame myself for everything that goes wrong  
☐ 2b = I feel I have many bad faults
9. ☐ 0 = I don't have thoughts of harming myself  
☐ 1 = I have thoughts of harming myself but I would not carry them out  
☐ 2a = I feel I would be better off dead  
☐ 2b = I have definite plans about committing suicide  
☐ 2c = I feel my family would be better off if I were dead  
☐ 3 = I would kill myself if I could
10. ☐ 0 = I don't cry anymore than usual  
☐ 1 = I cry more now than I used to  
☐ 2 = I cry all the time now. I can't stop it  
☐ 3 = I used to be able to cry but now I can't cry at all even though I want to
11. ☐ 0 = I am no more irritable than usual  
☐ 1 = I am more irritable than usual  
☐ 2 = I am much more irritable than usual  
☐ 3 = I am irritable all the time
12. ☐ 0 = I have not lost interest in other people  
☐ 1 = I am less interested in other people than I used to be  
☐ 2 = I have lost most of my interest in other people and I have little feeling for them  
☐ 3 = I have lost all my interest in other people and don't care about them at all
13. ☐ 0 = I make decisions about as well as ever  
☐ 1 = I am less sure of myself now and try to put off making decisions  
☐ 2 = I can't make decisions anymore without help  
☐ 3 = I can't make decisions at all anymore
14. ☐ 0 = I don't feel I look any worse than I used to  
☐ 1 = I am worried that I am looking old or unattractive  
☐ 2 = I feel that there are permanent changes in my appearance and they make me look unattractive  
☐ 3 = I feel that I am ugly or repulsive looking
15. ☐ 0 = I can work about as well as before  
☐ 1a = It takes extra effort to get started at doing something  
☐ 1b = I don't work as well as I used to  
☐ 2 = I have to push myself very hard to do anything  
☐ 3 = I can't do any work at all



16. \_\_\_ 0 = I can sleep as well as usual  
 \_\_\_ 1 = I wake up more tired in the morning than I used to  
 \_\_\_ 2 = I wake up 1-2 hours earlier than usual and find it hard to get back to sleep  
 \_\_\_ 3 = I wake up early every day and can't get more than 5 hours sleep
17. \_\_\_ 0 = I don't get any more tired than usual  
 \_\_\_ 1 = I get tired more easily than I used to  
 \_\_\_ 2 = I get tired from doing anything  
 \_\_\_ 3 = I get too tired to do anything
- 18a. \_\_\_ 0 = My appetite is no worse than usual  
 \_\_\_ 1 = My appetite is not as good as it used to be  
 \_\_\_ 2 = My appetite is much worse now  
 \_\_\_ 3 = I have no appetite at all any more
- 18b. \_\_\_ 0 = I am not eating more than usual  
 \_\_\_ 1 = I am eating a little more than usual  
 \_\_\_ 2 = I am eating somewhat more than usual  
 \_\_\_ 3 = I am eating a lot more than usual
- 18c. \_\_\_ 0 = I have had no change in food preferences lately  
 \_\_\_ 1 = I have been craving more carbohydrates (starches or sweets lately)  
 \_\_\_ 2 = I have had irresistible craving for sweets and starches lately
- 19a. \_\_\_ 0 = I haven't lost much weight, if any, lately  
 \_\_\_ 1 = I have lost more than 5 pounds  
 \_\_\_ 2 = I have lost more than 10 pounds  
 \_\_\_ 3 = I have lost more than 15 pounds
- 19b. \_\_\_ 0 = I have not gained any weight lately  
 \_\_\_ 1 = I have gained more than 5 pounds  
 \_\_\_ 2 = I have gained more than 10 pounds  
 \_\_\_ 3 = I have gained more than 15 pounds
20. \_\_\_ 0 = I am no more concerned about my health than usual  
 \_\_\_ 1 = I am concerned about aches and pains or upset stomach or constipation or other unpleasant feelings in my body  
 \_\_\_ 2 = I am so concerned with how I feel or what I feel that it's hard to think of much else  
 \_\_\_ 3 = I am completely absorbed in what I feel
21. \_\_\_ 0 = I have not noticed any recent change in my interest in sex  
 \_\_\_ 1 = I am less interested in sex than I used to be  
 \_\_\_ 2 = I am much less interested in sex now

\_\_\_ 3 = I have lost interest in sex completely

22. \_\_\_ 0 = I have not had any increase in nightly sleep length lately

\_\_\_ 1 = I have had at least 1-hour increase in sleep length

\_\_\_ 2 = I have had at least 2-hour increase in sleep length

\_\_\_ 3 = I have had at least 3-hour increase in sleep length

My average nightly sleep length in the past week is: \_\_\_\_\_ hours

23. \_\_\_ 0 = I am not feeling more fatigued than usual

\_\_\_ 1 = I feel more fatigued than usual lately, but it does not interfere with my daily functioning

\_\_\_ 2 = I feel more fatigued than usual lately, and it interferes somewhat with my daily functioning

\_\_\_ 3 = I feel more fatigued than usual lately, and it significantly interferes with my daily functioning

24. \_\_\_ 0 = I have not had any mood swings or slumps lately

\_\_\_ 1 = I have had some mood swings or slumps lately but very minor

\_\_\_ 2 = I have had more mood swings or slumps than usual

\_\_\_ 3 = I have had severe mood swings or slumps lately

### Survey of Coping Profiles Endorsed (SCOPE)

The purpose of this questionnaire is to find out how people deal with their problems or the stresses in their lives. The following are activities that you may have done. After each activity, please indicate the extent to which you would use this as a way of dealing with problems or stresses in recent weeks.

*Ordinarily, in recent weeks have you*                      *Never Seldom Sometimes Often Almost always*

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| 1. accepted that there was nothing you could do to change your situation?  | 0 | 1 | 2 | 3 | 4 |
| 2. tried to just take whatever came your way?  | 0 | 1 | 2 | 3 | 4 |
| 3. talked with friends or relatives about your problems?   | 0 | 1 | 2 | 3 | 4 |
| 4. tried to do things which you typically enjoy?   | 0 | 1 | 2 | 3 | 4 |
| 5. sought out information that would help you resolve your problems?   | 0 | 1 | 2 | 3 | 4 |
| 6. blamed others for creating your problems or making them worse?  | 0 | 1 | 2 | 3 | 4 |
| 7. sought the advice of others to resolve your problems?   | 0 | 1 | 2 | 3 | 4 |
| 8. blamed yourself for your problems?  | 0 | 1 | 2 | 3 | 4 |
| 9. exercised?  | 0 | 1 | 2 | 3 | 4 |
| 10. fantasized or thought about unreal things (eg., the perfect revenge, or winning a million dollars) to feel better? | 0 | 1 | 2 | 3 | 4 |
| 11. been very emotional compared to your usual self?   | 0 | 1 | 2 | 3 | 4 |
| 12. gone over your problems in your mind over and over again?  | 0 | 1 | 2 | 3 | 4 |
| 13. asked others for help?   | 0 | 1 | 2 | 3 | 4 |
| 14. thought about your problems a lot?   | 0 | 1 | 2 | 3 | 4 |
| 15. became involved in recreation or pleasure activities?  | 0 | 1 | 2 | 3 | 4 |
| 16. worried about your problems a lot?   | 0 | 1 | 2 | 3 | 4 |
| 17. tried to keep your mind off things that are upsetting you?   | 0 | 1 | 2 | 3 | 4 |

18. tried to distract yourself from your troubles?	0	1	2	3	4
19. avoided thinking about your problems?	0	1	2	3	4
20. made plans to overcome your problems?	0	1	2	3	4
21. told jokes about your situation?	0	1	2	3	4
22. thought a lot about who is responsible for your problems (besides yourself)?	0	1	2	3	4
23. shared humorous stories etc. to cheer yourself and others up?	0	1	2	3	4
24. told yourself that other people have dealt with problems such as yours?	0	1	2	3	4
24. thought a lot about how you have brought your problems on yourself?	0	1	2	3	4
26. decided to wait and see how things turn out?	0	1	2	3	4
27. wished the situation would go away or be over with?	0	1	2	3	4
28. decided that your current problems are a result of your own past actions?	0	1	2	3	4
29. gone shopping?	0	1	2	3	4
30. asserted yourself and taken positive action on problems that are getting you down?	0	1	2	3	4
31. sought reassurance and moral support from others?	0	1	2	3	4
32. resigned yourself to your problems?	0	1	2	3	4
33. thought about how your problems have been caused by other people?	0	1	2	3	4
34. daydreamed about how things may turn out?	0	1	2	3	4
35. been very emotional in how you react, even to little things?	0	1	2	3	4
36. decided that you can grow and learn through your problems?	0	1	2	3	4
37. told yourself that other people have problems	0	1	2	3	4

like your own?

38. wished I was a stronger person or better at dealing 0 1 2 3 4

with problems?

39. looked for how you can learn something out of 0 1 2 3 4

your bad situation?

40. asked for God's guidance? 0 1 2 3 4

41. kept your feelings bottled up inside? 0 1 2 3 4

42. found yourself crying more than usual? 0 1 2 3 4

43. tried to act as if you were not upset? 0 1 2 3 4

44. prayed for help? 0 1 2 3 4

45. gone out? 0 1 2 3 4

46. held in your feelings? 0 1 2 3 4

47. tried to act as if you weren't feeling bad? 0 1 2 3 4

48. taken steps to overcome your problems? 0 1 2 3 4

49. made humorous comments or wise cracks? 0 1 2 3 4

50. told others that you were depressed or 0 1 2 3 4

emotionally upset