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LOMA LINDA UNIVERSITY
School of Behavioral Health
in conjunction with the
Faculty of Graduate Studies

Adverse Childhood Experiences and Depressive Symptoms:
Protective Effects of Dietary Flavonoids

by

Alison Tan

A Dissertation submitted in partial satisfaction of
the requirements for the degree
Doctor of Philosophy in Clinical Psychology

March 2020

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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ABBREVIATIONS

ACEs	Adverse Childhood Experiences
AHS-2	Adventist Health Study-2
BBB	Blood Brain Barrier
BRHS	Biopsychosocial Religion and Health Study
CES-D	Center for Epidemiological Studies Depression Scale
HPA	Hypothalamic Pituitary Adrenal
ROS	Reactive Oxygen Species
SNS	Sympathetic Nervous System

ABSTRACT OF THE DISSERTATION

Adverse Childhood Experiences and Depressive Symptoms:
Protective Effects of Dietary Flavonoids

By

Alison Tan

Doctor of Philosophy, Graduate Program in Clinical Psychology
Loma Linda University, March 2020
Dr. Kelly Morton, Chairperson

The Adverse Childhood Experiences (ACEs) researchers report that childhood adversity is relatively common, often co-occurs with multiple types of exposures, and has a dose-response relationship to many leading causes of morbidity and mortality in the U.S. Prolonged exposure to stress during early brain development can lead to inflammation and oxidative stress that disrupts brain functioning associated with depressive symptoms. Flavonoids may protect the brain through anti-inflammatory, antioxidant, and additional mechanisms to assist in the survival, maintenance, and growth of neurons. Thus, flavonoids may buffer depressive symptoms after ACEs exposure. In the current longitudinal study, we will examine the relationship between ACEs, perceived stress, depression, and flavonoid intake while controlling for demographic characteristics (e.g., age, gender, ethnicity, education, difficulty meeting expenses, energy). The study sample consisted of 6404 (67.4% female, 67.9% white, $M_{\text{age}} = 61.9$, $SD = 12.7$) participants who completed the Adventist Health Study-2 (AHS-2), and both waves of the Biopsychosocial Religion and Health Study (BRHS). The study aim was to examine whether early chronic stress exposure leads to stress sensitivity and depressive symptoms that can be ameliorated with dietary flavonoids. No studies to date have examined the

relationship between dietary flavonoids and mental health after stress risk exposures. Study findings indicate that perceived stress significantly mediated the relationship between ACEs and depressive symptoms; and flavonoids significantly moderated the relationship between perceived stress and depressive symptoms; higher consumption of flavonoids was associated with less depressive symptoms after ACE exposure. More human studies are needed to understand the relationship between flavonoids and mental health and whether diet is sufficient to produce the positive effects found in clinical studies.

CHAPTER ONE

Adverse Childhood Experiences

In the early 1990s, the medical community identified health risk behaviors (e.g., smoking, diet, sedentary lifestyle) as essential components driving the leading causes of morbidity and early mortality in the U.S. (McGinnis & Foege, 1993). Researchers and healthcare providers then cited consistent evidence that childhood adversity often preceded these same health risk behaviors. Felitti and colleagues (1998) examined cumulative exposure via an Adverse Childhood Experiences (ACE) self-report survey and linked these exposures to health outcomes in 45,000 adults. Felitti's team initially examined seven dimensions of childhood adversity: neglect; physical, psychological, or sexual abuse; violence against the mother; as well as substance abusing, incarcerated and/or mentally ill household members (Felitti et al., 1998). These ACEs were strongly associated with adult diseases including ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver diseases. Felitti and colleagues (1998) postulated that the relationship between ACEs and chronic illnesses might be explained by risky health behaviors (e.g., smoking, diet, sedentary lifestyle) that are used as coping strategies when facing chronic stress and the inability to cope adaptively with stress after ACEs.

Studies have confirmed the relationship between ACEs and long-term physical and mental health outcomes (Crouch, Stropolis, Bennett, Morse, & Radcliff, 2017; Danese et al., 2009), including links to substance abuse, risky sexual behaviors, obesity, depression, anxiety, cancer, cardiovascular disease, diabetes, and suicidality (Allem, Soto, Baezconde-Garbanati, & Unger, 2015; Almuneef, ElChoueiry, Saleheen, & Al-Eissa, 2017; Anda et al., 2008; Bellis, Lowey, Leckenby, Hughes, & Harrison, 2014;

Brown, Thacker, & Cohen, 2013; Chapman et al., 2004; Dube, Felitti, Dong, Giles, & Anda, 2003; Felitti et al., 1998; Felitti, 2002; Jewkes, Dunkle, Nduna, Jama, & Puren, 2010; Karatekin, 2017; Merrick et al., 2017; Rothman, Edwards, Heeren, & Hingson, 2008; Sachs-Ericsson, Sheffler, Stanley, Piazza, & Preacher, 2017), as well as increased health care utilization and premature death (Bonomi et al., 2008; Brown et al., 2009; Felitti & Anda, 2009). Global estimates indicate that 6 in 10 people have been exposed to at least one ACE (Brown et al., 2013). The Center for Disease Control and Prevention (CDC) reports 59.4% of Behavioral Risk Factor Surveillance System (BRFSS) respondents in 2009 reported having at least one ACE, 25% of adults reported three or more ACEs, and 8.7% reported five or more ACEs (Bynam et al., 2010). Those exposed to one ACE are 80% more likely to be exposed to additional ACEs (Felitti et al., 2002). These prevalence estimates highlight the importance of preventing ACEs and treating the outcomes of ACEs at any point in life.

ACEs and Stress

One hypothesis is that ACEs harm health by creating maladaptive stress reactivity and subsequently maladaptive coping responses to stress. While the stress response is essential for survival, prolonged elevated stress levels can be toxic (Dube et al., 2009; McEwen, 1998; McEwen & Seeman, 1999). Shonkoff and colleagues (2012) define toxic stress effects as disruptions in brain functioning during sensitive developmental periods after chronic stress exposures like ACEs (Heim & Nemeroff, 2002; Nemeroff, 2016). Toxic stress exposure therefore may alter physiological and behavioral responses by dysregulating the Hypothalamic Pituitary Adrenal (HPA) axis and Sympathetic Nervous

System (SNS). When these systems are activated by stress exposures, catecholamines are released, leading to corticotropin secretion from the pituitary gland, which mediates the release of cortisol from the adrenal cortex. Once the stressor has been addressed and the danger is no longer present, the system typically returns to baseline levels of cortisol and catecholamine secretion. However, if inactivation does not occur, stress hormones are overproduced. If such overproduction continues over weeks, months, or years, the allostatic load associated with constant exposure to stress hormones can lead to pathophysiological consequences, including cardiovascular disease, type II diabetes, hypertension, obesity, and other common chronic diseases (McEwen, 1998; McEwen & Seeman, 1999). In addition, chronic stress exposure can also dysregulate the autoimmune system, which increases the risk of physical and mental illnesses such as autoimmune, mood, and anxiety disorders (Sachs-Ericsson et al., 2017).

Chronic stress exposure can alter the brain's structure and functioning by interfering with the body's endogenous antioxidant defenses (e.g., cellular oxidation-reduction processes), leading to increased levels of free radicals such as reactive oxygen species (ROS) (Durackova, 2010). This oxidative environment eventually damages lipids, proteins, and DNA to ultimately create dysfunction and cell death (*via* apoptosis or necrosis) in the brain and other organs (Durackova, 2010; Trebatická & uřuračková, 2015). There is evidence that exposure to psychological stress is linked with more oxidative damage in cells (Forlenza & Miller, 2006; Irie, Asami, Ikeda, & Kasai, 2003). For example, in post-menopausal female caregivers, heightened cortisol levels mediate the relationship between oxidative stress damage (higher levels of 8-hydroxy-2-deoxyguanosin) and perceived stress (Aschbacher et al., 2013). These findings indicate a

potential link between stress exposures, sustained activation of the HPA axis, and oxidative stress damage. Thus, ACEs exposure may induce a heightened response to perceived stress, leading to chronically elevated cortisol levels that interfere with the body's endogenous antioxidant defenses leading to increased oxidative stress. These physiological dysregulations constitute a continual biological reaction of stress that carries forward through development (Hertzman & Boyce, 2010; Jaffee & Christian, 2014). Altered neurobiological processes that result from childhood adversity appear to increase sensitization to stress, which shows an additional pathway that ACEs may be the basis of the developmental origins of impaired adult mental health (Nurius, Green, Logan-Greene, & Borja, 2015). Specifically, studies have shown that early adversity sensitizes individuals to later psychopathology, such as depression, by reducing their tolerance to subsequent, even minor stressors (Hammen, Henry, & Daley, 2000; Harkness, Bruce, & Lumley, 2006). Thus, increased sensitization to stress would predict more perceived stress in adults who have experienced ACEs.

Stress and Depression

Oxidative stress is associated with depression, which is the third leading cause of disability (World Health Organization, 2008). It is estimated that depressed individuals lose 28.9 years of quality-adjusted life years, which is double the years lost as a result of chronic illnesses such as heart disease, hypertension, diabetes, and stroke (Jia, Zack, Thompson, Crosby, & Gottesman, 2015).

Some biological processes involved in the pathology of depression include compromised neurogenesis and synaptic plasticity, HPA axis dysfunction, mitochondrial

dysfunction, disturbances in neurotransmitters, and increased inflammatory processes (Trebatická & uřuračková, 2015; Gomez-Pinilla & Nguyen, 2012). Some mechanisms that explain the relationship between oxidative stress and depression include metabolic mitochondrial dysfunction, decreases in antioxidant defense systems, and abnormal changes in biological molecules including lipids, proteins, and DNA, which contribute to the neurotoxicity and neurodegeneration commonly seen in depression (Berk et al., 2011; Maes, Galecki, Chang, & Berk, 2011; Nabavi et al., 2014; Ng, Berk, Dean, & Bush, 2008; Tobe, 2013). Many of these processes are similar to the symptoms associated with excessive stress such as ACEs (Almuneef et al., 2017; Danese et al., 2009), which are also linked with depression and anxiety (Chapman et al., 2004; Danese et al., 2009; Vincent J Felitti, 2002; Karatekin, 2017; Merrick et al., 2017; Sachs-Ericsson et al., 2017). The chronic stress of ACEs may contribute to depressive symptoms through chronic activation of the HPA axis and subsequent oxidative stress. Childhood maltreatment stress likely disrupts the development of the HPA axis, leading to exacerbated neuroinflammation (Frodl & O'Keane, 2013), which is a main cause of oxidative stress in neurodegenerative diseases (Mosely et al., 2006).

Inflammation, in which the immune system produces cytokines (cell signaling proteins), is the body's protective reaction to unwanted intruders. However, too much (or prolonged) inflammation can alter serotonin synthesis and reduce the availability of serotonin, leading to degenerative diseases and depression (Dobos, 2014; Dowlati et al., 2010; Goeb et al., 2005; Su et al., 2010). Inflammation can also induce increased oxidative stress using similar mechanisms as chronic stress. For example, inflammation produces more free radicals through the activation of protein-kinases signaling, which

can disrupt homeostasis and cause oxidative stress (Federico, Morgillo, Tuccillo, Ciardiello, & Loguercio, 2007). Thus, factors such as diet that alleviate chronic neuroinflammation and oxidative stress may reduce neuronal damage and buffer the effects of ACEs on adult depressive symptoms.

Diet and Depressive Symptoms

Recently, research has established that diet can influence brain functions. A healthy dietary pattern can delay age-related health declines and protect the brain from neurological illnesses and injury (Gomez-Pinilla & Tyagi, 2013; Meeusen, 2014). Specifically, dietary patterns can modulate oxidative stress, influencing learning, memory, cognition, mood, and neurogenesis (the birth of new neurons in the hippocampus and subventricular zone) (Stangl & Thuret, 2009). For example, excessive caloric consumption creates increased metabolic activity and reactive oxygen species, ultimately leading to impaired cognitive function and worse mental health (Gómez-pinilla, 2008; Gomez-Pinilla & Nguyen, 2012; Gomez-Pinilla & Tyagi, 2013). This may be a risk factor for individuals who experience ACEs, since palatable and energy dense foods are often used as stress coping strategies (Adam & Epel, 2007). As previously stated, research has shown that ACEs are related to diseases that are linked to poor diet; including, cardiovascular disease, diabetes, and obesity (Felitti et al., 1998). These palatable—high fat or sugary (e.g., fried food, butter, desserts)—foods, which tend to be prevalent in poor diets, have been shown to activate the brain's reward system by releasing opioids, dopamine, and endocannabinoids, similar to drug addiction (Cota, Tschop, Horvath, & Levine, 2005). When the threat that triggered the activation of the

stress response has been eliminated, the HPA axis elicits the release of endogenous opioids to turn off the system—negative feedback (Volkow & Wise, 2005). Thus, additional opioids from other sources would be able to help shut off the stress response sooner, providing short term relief. If the stress is chronic and eating palatable foods have been a somewhat effective coping strategy, the behavior will be repeated and used in future stressful situations leading to an unhealthy dietary pattern. Thus, it is important to determine what aspects of diet can protect against neurodegeneration and to decrease the risk of depression.

Dietary Flavonoids

A diet rich in flavonoids are commonly linked to neuroprotective properties. Flavonoids are the most common class of polyphenols (also known as polyhydroxyphenols), which are secondary metabolites produced by plants to protect themselves from other organisms (Trebatická & uřuračková, 2015; Tsao, 2010). There are over 4000 derivatives of flavonoids including isoflavones, neoflavonoids, chalcones, anthocyanins, flavan-3-ols, flavones, flavanones, and flavonols. Flavonoids are known for their antioxidant and anti-inflammatory activity. They can be found in legumes, fruits, tea leaves, cacao beans, vegetables, and grains (Cassidy, Hanley, & Lamuela-Raventos, 2000; Spencer, Abd El Mohsen, Minihane, & Mathers, 2008; Tsao, 2010). At large doses, flavonoids have the potential to be carcinogenic, neurotoxic, or cardiotoxic. However, the levels consumed are normally considerably below toxic levels (Mattson, Son, & Camandola, 2007).

The brain naturally produces endogenous antioxidants (e.g., superoxide dismutase, alpha lipoic acid, coenzyme Q10, catalase, glutathione peroxidase), which protect it from the oxidative load associated with everyday metabolism. However, the brain's endogenous antioxidant capacity can be overwhelmed *via* increased metabolic byproducts (e.g., excessive caloric consumption) or inflammation (e.g., chronic stress) (Forlenza & Miller, 2006; Gómez-pinilla, 2008; Gomez-Pinilla & Nguyen, 2012). Flavonoids act as an antioxidant by stabilizing ROS with a donated hydrogen atom from their hydroxyl group (Gomez-Pinilla & Nguyen, 2012; Pandey & Rizvi, 2009). The antioxidant properties can help provide that extra protection when oxidation is at a higher rate than the brain can manage. However, due to the diverse outcomes of phenolic compounds by intestinal enzyme metabolism, their bioavailability to the brain (i.e., their ability to cross the blood-brain barrier [BBB]) can be limited (Chovanová et al., 2006; Gomez-Pinilla & Nguyen, 2012; Halliwell, Rafter, & Jenner, 2005). Polyphenol molecules are generally too large to be absorbed by the intestine, and must be metabolized by enterocyte enzymes and gut microflora into smaller molecules that can then be absorbed in the colon and travel through the blood to tissues and organs such as the brain (Manach, Scalbert, Morand, Remesy, & Jiminez, 2004). Some flavonoids have been shown to traverse the BBB (K. A. Youdim, Shukitt-Hale, & Joseph, 2004; K. a Youdim et al., 2003), many are associated with neuroprotective effects even though they are unable to cross the BBB (K. a Youdim et al., 2003).

Flavonoids also have anti-inflammatory properties, which can help ameliorate symptoms related to ACEs. Childhood maltreatment stress can disrupt the development of the HPA axis, leading to exacerbated neuroinflammation (Frodl & O'Keane, 2013),

which is a main cause of oxidative stress in neurodegenerative diseases (Mosely et al., 2006). Inflammation can also induce increased oxidative stress using similar mechanisms as chronic stress. For example, inflammation produces more free radicals through the activation of protein-kinases signaling, which can disrupt homeostasis and cause oxidative stress (Federico et al., 2007). Thus, factors that alleviate chronic neuroinflammation and oxidative stress may reduce neuronal damage and buffer the effects of ACEs on adult depressive symptoms. Specifically, flavonoids, directly and indirectly interfere with cytokine inhibition by blocking various components of the signal transduction pathways that lead to activation of pro-inflammatory genes (Aquilano, Baldelli, Rotilio, & Ciriolo, 2008; Spencer, 2008). For example, flavonols inhibit inflammatory cytokines such as protein kinase C (PKC), p38 MAPK, and NF-kB, which directly reduces inflammation and therefore indirectly reduces oxidative stress (Kempuraj et al., 2005; Kim, Son, Chang, & Kang, 2004; Wadworth, McDonald, & Koop, 2001).

Flavonoids can also induce neuroprotection by upregulating proteins associated with neuroplasticity, neurogenesis, learning, and memory (e.g., cAMP-response element-binding (CREB) protein and brain-derived neurotrophic factor [BDNF]) or by metabolizing polyphenols into smaller molecules that can cross the BBB (Williams et al., 2008; Bourtchouladze et al., 1994) to promote neuronal survival (R. Lee, Kermani, Teng, & Hempstead, 2001; Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998) associated with anti-depressant effects (Dias et al., 2012; R. Lee et al., 2001; Dulcich & Hartman). In addition, flavonoid-rich foods increase cortical blood flow associated with adult neurogenesis, learning, and memory (Fisher, Sorond, & Hollenberg, 2006; Francis, Head, Morris, & Macdonald, 2006; Harris & Kater, 1994; Palmer, Willhoite, & Gage, 2000).

Overall, flavonoids can address the biological processes underlying depression in multiple pathways. Therefore, flavonoids may be an effective protective factor after ACEs exposure.

ACEs, Stress, Depression, and Flavonoids

ACEs are a common risk factor for poor mental health in adulthood due to the excessive stress experienced early in life that disrupts brain functioning and leads to poor coping skills. Prolonged exposure to stress during early brain development can lead to inflammation and oxidative stress that disrupts brain functioning (*via* neurodegeneration, HPA axis dysfunction, and neurotransmitter imbalance) associated with depressive symptoms (Berk et al., 2011; Maes et al., 2011; Nabavi et al., 2014; Ng et al., 2008; Tobe, 2013). Dietary flavonoids may protect the brain through anti-inflammatory, antioxidant, and additional mechanisms to assist in the survival, maintenance, and growth of neurons. Thus, flavonoids may decrease depressive symptoms after ACEs exposure by moderating the effects of stress sensitivity.

The purpose of the current study is to examine the relationship between ACEs, perceived stress, and depressive symptoms and whether the stress and depressive symptom relationship is moderated by dietary flavonoids, after controls (i.e., gender, education, difficulty meeting basic needs, age, ethnicity, and kilocalories). ACEs exposure may increase stress responses and sensitivity to stress that lead to inflammation. Dietary flavonoid consumption may buffer the effects of stress through anti-inflammatory and antioxidant properties. Thus, we hypothesize that higher ACEs would predict higher depressive symptoms through the effects of perceived stress. Specifically, participants

who indicated experiencing ACEs, would report higher perceived stress since early exposure to stress is linked to sensitivity to stress across the lifespan. This stress sensitivity reaction will then predict depressive symptoms and flavonoids will moderate the perceived stress and depressive symptom relationship.

Hypotheses

In the current study, we examined the relationship between ACEs, perceived stress, depression, and flavonoid intake while controlling for demographic characteristics (e.g., age, gender, ethnicity, education, difficulty meeting expenses, energy). Since ACEs presumably changes stress reactivity by disrupting development during sensitive and critical periods, we hypothesize ACEs will be associated with worse adult perceived stress, which in turn will be associated with worse depressive symptoms. Additionally, given that previous studies demonstrate neuroprotective and affective effects of flavonoids, we predict that consumption of dietary flavonoids will moderate the relationship between perceived stress and depression. Specifically, the following hypotheses will be tested:

1. ACEs will be positively associated with perceived stress after controls (age, gender, ethnicity, education, difficulty meeting expenses, and energy)
2. ACEs will be positively associated with depressive symptoms after controls (age, gender, ethnicity, education, difficulty meeting expenses, and energy)
3. Flavonoids will be negatively associated with depressive symptoms after controls (age, gender, ethnicity, education, difficulty meeting expenses, energy)
4. Flavonoids will be negatively associated with perceived stress after controls (age, gender, ethnicity, education, difficulty meeting expenses, energy)

5. Perceived stress will mediate the relationship between ACEs and depressive symptoms after controls (age, gender, ethnicity, education, difficulty meeting expenses, energy)
6. Flavonoids will moderate the relationship between perceived stress and depressive symptoms after controls (age, gender, ethnicity, education, difficulty meeting expenses, energy)

CHAPTER TWO

Methods

Participants and Procedures

The Adventist Health Study-2 (AHS-2) was designed to investigate the effects of lifestyle factors on cancer, morbidity and mortality risk. Between 2002 and 2007, adults (Blacks aged 30 +; Whites aged 35 +) were recruited from a random sample of Adventist churches in North America. Over 96,000 participants completed questionnaires on diet, physical activity, supplement use, and medical history (Butler et al., 2008). To validate AHS-2 data on self-reported diet and physical activity, a calibration substudy was conducted between 2002 and 2007 (Jaceldo-siegl et al., 2010). In addition to the baseline AHS-2 Food Frequency Questionnaire (FFQ), participants of the AHS-2 calibration study (n = 1011) provided two sets of three 24-hour dietary recalls (24-HRs) and an FFQ similar to that completed at baseline. In the middle of the 24-HRs, participants attended a clinic at their church where an overnight urine sample, blood sample, and body composition measurements were collected. The calibration study showed no significant differences in the distribution of dietary pattern than the baseline FFQ and validated the measurement (Jaceldo-siegl et al., 2010). The AHS-2 participants are a health-oriented population with very low rates of smoking (1%) and alcohol intake (6.6%; usually at very low quantities), and dietary patterns ranging from vegan to omnivorous with more endorsing vegetarian diets than the general population (Fraser, 2003). The diversity in diets introduces varying intakes of polyphenol-rich foods, including fruits and vegetables, grains, soy products, and other vegetarian protein sources.

A random sample of 21,000 participants from the AHS-2 were selected for the Biopsychosocial Religion and Health Study (BRHS) in 2006-7, to examine religion, stress, as well as mental and physical health (Lee et al., 2008) and 10,988 responded with complete questionnaires. The BRHS survey included measures of depression and mental health, while the original AHS-2 FFQ survey provided information on dietary intake. In 2010-11, the BRHS was sent again to the individuals who completed the 2006-7 survey with additional questions to screen for Adverse Childhood Experiences (ACEs). Of the 10,988 subjects, 6500 responded.

All respondents that completed both AHS-2 and both BRHS surveys were eligible for the present analyses (N=6500). Individuals with extreme energy intakes of <2093 kJ/d (<500 kcal) or 828kJ/d (>4500kcal/d) were excluded (N= 96) leaving 6404.

Dietary Assessments

The flavonoid content of foods in the AHS-2 cohort was produced by using a combination of all available data on polyphenol concentrations in foods derived from chromatography analysis (Burkholder-Cooley, Rajaram, Haddad, Fraser, & Jaceldo-Siegl, 2016). The concentrations of flavonoids in various foods were gathered from various databases (Phenol-Explorer 3.6, Neveu et al., 2010; USDA flavonoid version 3.1, Bhagwat, Haytowitz, & Holden, 2011; isoflavones version 2.0; Bhagwat, Haytowitz, & Holden, 2008) and the published literature (e.g., Arapitsas, 2008 for okra, Tian, Nakamura, & Kayahara, 2004 for rice flour, and Mattila, Pihlava, & Hellstrom, 2005 for oat bran and millet). Of all the data points, 78% came from Phenol-Explorer, 21% from USDA databases, and 1% from individual research literature. The USDA isoflavones

database provided data for a variety of soy foods, which allowed more comprehensive estimates of flavonoid intake in the AHS-2. The data obtained refer to intact polyphenols (i.e., glycosides and esters) for most compounds, except for values that were obtained from chromatography after hydrolysis or from USDA databases. Foods with unknown polyphenol concentrations (e.g., cottonseed oil, wheat gluten, coconut milk, and cola) were considered to have no polyphenols. It is likely that phenolic content or consumption of these food was negligible; thus, contribution of these foods to total flavonoid intake is considered minimal (Burkholder-Cooley et al., 2016). Flavonoid concentrations for foods were standardized to milligrams per 100 g, and the data acquired for individual foods were expanded to incorporate the calculation of recipes as well as estimations of missing values.

Estimating flavonoid intake

Total dietary flavonoid intake for each participant was estimated by using the following: $FFQ = \sum P_n \times F_n \times G_n \times S_n$, where P = milligrams of phenolic compounds per 100 g food_n, F = the reported frequency of intake of food_n, G = the standard serving size of food_n in grams, and S = the reported servings of food_n.

Measures

Demographic variables

The ethnicity (White or Black-Black African American, Black West Indian/Caribbean, and Black African), education (Grade School, Some High School, High School diploma, Trade School diploma, Some college, Associate degree, Bachelors

degree, Masters degree, or Doctoral degree), and gender (female or male) of participants were based on responses from the Adventist Health Study-2 in 2003-6 (AHS-2).

Difficulty meeting expenses last year (Not at all or Very) and the age of the participant was reported in BRHS 2006-7 (Pudrovska, Schieman, Pearlin, & Nguyen, 2005).

Energy

The average amount of kilocalories consumed per day calculated by summing kilocalories across the FFQ. Nutrient intake = sum [(weighted frequency of use of a food) x (weighted portion size consumed of that food) x (amount of that nutrient in a standard serving size of that food)] (Jaceldo-siegl et al., 2010).

Adverse Childhood Experiences

ACEs were summed as a 0-9 count of psychological, sexual, or physical abuse; neglect; substance abuse; mental illness; incarceration or domestic violence in the household; and separation/divorce for the total number of ACEs experienced. Participants were given a score of one for each ACE category if they endorsed one or more items within that category. Six categories were assessed in the 2006-7 BRHS survey; three categories (domestic violence, mental illness and family member incarcerated) were assessed in the 2010-11 BRHS survey (see Appendix A). Since participants were reporting on childhood experiences all answers were aggregated to create the total ACE score for this investigation.

Psychological Abuse

Psychological abuse was assessed with three items (Ryff, Singer, & Palmersheim, 2004) including “*between ages 5 and 15 years did the mother/woman or father/man who raised you...insult, swear at, or ignore you?*”; and, “*How often did a parent or adult act in a way that made you fear you might be physically hurt?*” Any yes response was coded as 1; else 0.

Sexual Abuse

Sexual abuse was assessed with three items (Cusak, Frueh, & Brady, 2004) including “*ever [had] sexual contact with anyone who was at least 5 years older than you before you reached the age of 13?*” Any yes response was coded as 1; else 0.

Physical Abuse

Physical abuse was assessed with five items (Ryff, Singer, & Palmersheim, 2004) including “*Between ages 5 and 15, did the mother/woman or father/man who raised you...push, slap, or throw objects at you?*” and/or “*kick, bite, or strike you with an object?*” Participants were also asked if “*a parent or other adult in your household hit you so hard that you had marks or were injured?*” Any yes response was coded as 1; else 0.

Neglect

Neglect was assessed with one item (Ryff, Singer, & Palmersheim, 2004): “*How often would you say you were neglected while you were growing up, that is left on your own to fend for yourself?*” Any yes response was coded as 1; else 0.

Substance Abuse

Substance abuse was assessed with “*in your childhood, did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?*” (Felitti, et al., 1998). Any yes response was coded as 1; else 0.

Domestic Violence

Parental domestic violence was assessed with four items (Dong, Anda, Felitti, Williamson, Dube, Brown, & Giles, 2005): “*How often would you say that a parent or other adult in the household behaved violently toward a family member of visitor in your home?*”; “*how often “mother/stepmother [was] pushed, grabbed, or slapped,” “bitten or kicked,” “repeatedly hit,” and, “threatened with a gun or knife.”* Any yes response was coded as 1; else 0.

Parental Mental Illness

Parental mental illness was assessed with two items if either item was indicated to have occurred before age 18 (Felitti et al., 1998) including: “*Was a household member depressed or mentally ill?*” and “*Did a household member attempt suicide?*” Any yes response was coded as 1; else 0.

Divorce / Separation

Parental divorce was assessed with one item (Dong et al., 2005: “*parents got divorced when you were younger than 18.*” Any yes response was coded as 1; else 0.

Incarceration

Parental incarceration was assessed with a single item (Felitti et al., 1998): “*Did a household member go to prison?*” Yes before age 18 was coded as 1; else 0.

Perceived Stress

Perceived stress was measured using four-item short form global measure of perceived stress (Cohen, Kamarck, & Mermelstein, 1983). The items measured participants’ perception of stress in the past month. The following items were rated on a five-point Likert scale (1 = Never; 5 = Very often): “How often have you felt that you were unable to control the important things in your life?”, “How often have you felt confident about your ability to handle your personal problems?”, “How often have you felt that things were going your way?”, “How often have you felt difficulties were piling up so high that you could not overcome them?”. Items were coded and averaged such that a higher score indicated higher levels of perceived stress ($\alpha = .77$).

Depression

Depression was assessed with the 11-item short form Center for Epidemiological Studies Depression Scale in the 2010-11 BRHS survey (CES-D; Kohout, Berkman, Evans, & Cornoni-Huntley, 1993). The items measured symptoms of depression in the past week on a four-point Likert scale (1 = Rarely or none of the time; 4 = Most or all of the time: See Appendix B). Thus, a higher score demonstrates more depressive symptoms. Nine items were positively coded (e.g. “*I felt that everything I did was an effort*”) and two items were negatively coded (e.g. “*I was happy*”). Each 4-point response

scale ranging from 1 to 4 was converted to a 3-point response scale ranging from 0 to 2 with the top two categories collapsed (0 = Rarely or none of the time; 1 = Some of the time; 2 = Much or most of the time). Furthermore, reliability was increased through generalized *T* score transformation, which shifts the mean and standard deviation of genders without affecting the shape of the distribution. This was accomplished by standardizing gender scores against NHANES-I, which are the national norms for CES-D; then multiplying the standard deviation of the criterion distribution; and adding the mean of the criterion distribution to each score (Kohout et al., 1993). This sample demonstrates reasonable reliability ($\alpha = .80$).

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CHAPTER THREE

PUBLISHED PAPER

Adverse Childhood Experiences and Depressive Symptoms: Protective Effects of Dietary Flavonoids

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Abstract

Objectives

Adverse childhood experiences (ACEs) are associated with increased inflammation, stress, and depression. Diet patterns rich in flavonoids may buffer the effects of ACEs on depression through neuroprotective mechanisms. No studies have examined the protective effects of dietary flavonoids on depressive symptoms after ACEs. We examine the relationships among ACEs, perceived stress, depressive symptoms, and flavonoid intake in older adults.

Methods

In this longitudinal cohort study, flavonoid intake was provided by 6404 Seventh-day Adventist adults in North America who, as part of the Adventist Health Study-2, completed a validated food frequency questionnaire in 2002–6. ACEs, perceived stress, and depressive symptoms were assessed in the Biopsychosocial Religion and Health Study in 2006-7 and 2010-11. Bootstrapping models predicting depression were tested after controls.

Results

ACEs were associated with adult depressive symptoms and perceived stress mediated this relationship. A moderated mediation model indicates that flavonoid intake buffers the association between perceived stress and depressive symptoms after ACEs. Flavonoid consumption was negatively associated with depressive symptoms ($\beta = -.034$, $p = .03$). As ACEs increased by one standard deviation, depressive symptoms increased through the interaction of perceived stress and flavonoids when flavonoids were consumed a standard deviation below the mean (*effect* = .040 SD, BC 95% CI [.030, .052]).

Depressive symptoms were lower for those that consumed flavonoids a standard deviation above the mean (*effect* = .035 SD, BC 95% CI [.025, .046]).

Conclusion

A varied diet rich in flavonoids may reduce depressive symptoms associated with perceived stress following ACEs exposure. 248 words

Keywords: Flavonoids, Adverse Childhood Experiences, stress reactivity, Depressive Symptoms

1. Introduction

Adverse childhood experiences (ACEs) expose children's developing brains to chronic stress that results in increased stress reactivity, maladaptive coping, and depression in adulthood (1,2). Exposure to ACEs has strong associations with poor mental and physical health outcomes in adulthood (1,3). Global estimates indicate that 60% of U.S. adults have been exposed to at least one ACE (4) and that those exposed to one ACE are 80% more likely to be exposed to additional ACEs (5). Some researchers estimate that 54% of depression diagnoses and 58% of suicide attempts in women can be attributed to the after effects of ACEs exposures (6). These prevalence estimates highlight the importance of preventing and providing treatment after ACE exposures.

Early adversity can impair growth and subsequent functioning in brain structures and neuroendocrine functioning in the stress response of the hypothalamic-pituitary-adrenal axis (7). Early chronic stress exposure such as ACEs can alter the brain by interfering with the body's endogenous antioxidant defenses (e.g., cellular oxidation-reduction processes), leading to increased levels of free radicals such as reactive oxygen species (ROS) (8). Such an oxidative environment damages lipids, proteins, and DNA to create dysfunction and cell death (via apoptosis or necrosis) in the brain and other organs (8,9) resulting in a continuous biological stress reaction across the lifespan (10,11). As a result, after ACEs, tolerance for even minor stressors is dramatically reduced, and risk of psychopathology (e.g., depression) is increased (12). Thus, stress sensitization after ACEs should predict higher stress reactivity assessed as current *perceived* stress in adults and result in inflammation and oxidative stress that disrupts brain functioning (*via* neurodegeneration, HPA axis dysfunction, and neurotransmitter imbalance). As such,

chronic stress reactivity is associated with depressive symptoms (adverse arousal, appetite, sleep and sexual behavior changes) (13,14). Our labs previous work indicates that dietary patterns that are high in fruits, vegetables, and legumes are associated with improved affect and emotional regulation that may be protective of depressive symptoms (15). Dietary pattern changes may therefore lead to less depressive symptoms after chronic stress exposures like ACEs. The underlying mechanism in dietary pattern effects is possibly increased polyphenols that buffers oxidative stress.

Flavonoids are the most common class of polyphenols (also known as polyhydroxyphenols) with over 4000 derivatives found in legumes, fruits, tea leaves, cacao beans, vegetables, and grains (9,16). Dietary flavonoids are hypothesized to protect the brain from depressive symptoms through anti-inflammatory and antioxidant mechanisms to assist in the survival, maintenance, and growth of neurons (17,18). Healthy diets that include vegetables and legumes are associated with an improved affect in humans (35), and, a polyphenol-enriched diet protects mice from depression-like symptoms induced by irradiation (20). Consumption of phytochemicals produced by plants, such as flavonoids may provide several mechanisms for antidepressant-like effects.

For example, flavonoids have anti-inflammatory properties that can ameliorate chronic low-grade inflammation associated with ACEs. Specifically, they directly and indirectly interfere with cytokine inhibition by blocking components of the signal transduction pathways that activate pro-inflammatory genes (17,21). For example, flavonols (pigment compounds in the anthoxanthin class of flavonoids) inhibit inflammatory cytokines such as protein kinase C (PKC), p38 MAPK, and NF-kB, which

directly reduce inflammation and indirectly reduce oxidative stress (22). Phytochemicals that humans consume have mild irritant properties as plants defense systems that may induce a hormetic response of adapting to a mild stressor with increased resiliency and neuroprotection (23). Flavonoid-rich foods can also increase cortical blood flow, which is associated with adult neurogenesis, learning, and memory (24). There is sufficient evidence to suggest that dietary flavonoid intake could protect the brain via improved emotions, decreased stress reactions, inflammation, and oxidative stress to buffer depressive symptoms after ACEs.

The purpose of the current study is to examine the relationship between ACEs, perceived stress (to assess stress reactivity), and depressive symptoms, and to determine whether the stress and depressive symptom relationship is moderated by levels of dietary flavonoids after controlling for other factors (gender, education, difficulty meeting expenses for basic needs last year and before the age of 18, age, ethnicity, exercise, vegetarian status, and caloric consumption). First, we hypothesize that participants with higher ACEs will report higher depressive symptoms as adults. Second, we hypothesize that chronically dysregulated stress responses (e.g., perceived stress) after ACEs will predict higher levels of depressive symptoms. In other words, perceived stress will mediate the ACEs and depressive symptoms relationship. Third, we also hypothesize that flavonoid consumption will moderate the perceived stress and depressive symptom relationship; specifically, higher consumption of dietary flavonoids will be associated with lower depressive symptoms after ACEs by buffering the effects of perceived stress on depressive symptoms.

2. Methods

2.1 Participants and design

This longitudinal cohort study is a secondary data analysis of the Adventist Health Study-2 (AHS-2) and Biopsychosocial Religion and Health Cohort studies (BRHS) conducted from 2002-2011. The BRHS study received expedited approval at minimal risk from the Loma Linda University IRB; participant returned surveys that included a consent document. Linking codes to participant identifiers and survey responses are maintained separately by the AHS-2 study. Recruitment methodologies of both studies are described in previous literature (25,26). The predictor (dietary) variables were assessed from 2002–2006 in AHS-2 participants. In brief, the AHS-2 cohort included approximately 96,000 participants over 30 years of age who filled out a 50-page mailed questionnaire regarding their medical histories, lifestyle, and dietary intakes. In 2006-7, ACEs, perceived stress, and depression were assessed in the BRHS, a sub-population of the AHS-2 study (25,26), which examined stress, religion, and health in a random sample of 21,000 AHS-2 participants. Of these, 10,988 participants completed the 20-page mailed questionnaire; these participants were similar to the broader AHS-2 study sample. In 2010-11, the BRHS was sent again to the individuals who completed both the AHS-2 and initial BRHS surveys with three additional ACEs screening items (domestic violence, mental illness, and family member incarcerated). Of the original 10,988 subjects, 6500 who had current addresses and were still living responded to the follow-up questionnaire. Individuals with extreme daily energy intakes (less than 2093 kJ / 500 kcal or more than 828 kJ / 4500 kcal) were excluded (N= 96) leaving a total sample size of 6404 for analysis.

2.2 Dietary flavonoid assessment

Dietary intake was assessed by a self-administered food frequency questionnaire (FFQ) that contained a list of over 200 food items, including fruit, vegetables, legumes, grains, oils, dairy, fish, eggs and beverages, and commercially prepared products. This FFQ was designed to assess dietary intake among the study cohort of Seventh-day Adventists of which 50% are vegetarian (27). It is assumed that though there is a 1-3 year time lag between dietary reports and BRHS reports, that most adults do not significantly change their dietary habits (28). Respondents reported food intake during the past year: 1 to 3 times/month, *X* times/week (where *X* was 1, 2-4, or 5-6), or *Y* times/day (where *Y* was 1, 2-3, or 4+). Portion sizes included *standard* (amount was dependent upon food item), half a portion or less, and >1.5 a portion with photos depicting portion sizes for reference. The FFQ was previously validated against six 24-hour dietary recalls for intake of nutrients (29) and selected foods/food groups (27).

The flavonoid content of foods in the AHS-2 cohort was calculated using chromatography-derived flavonoid concentrations in foods (30) reported in several databases (Phenol-Explorer 3.6, USDA flavonoid version 3.1, isoflavones version 2.0) and published literature (e.g., 27–29 for okra, rice flour, oat bran and millet). Of all the data points, 78% came from Phenol-Explorer, 21% from USDA databases, and 1% from peer-reviewed articles. The USDA isoflavones database provided data for a variety of soy foods often consumed by vegetarians. The data obtained refer to intact flavonoids (i.e., glycosides and esters) for most compounds, except for values that were obtained from chromatography after hydrolysis or from USDA databases. Foods with unknown flavonoid concentrations (e.g., cottonseed oil, wheat gluten, coconut milk, and cola) were

considered to have no flavonoids (30). Flavonoid concentrations for foods were standardized to milligrams per 100 g, and the data acquired for individual foods were expanded to incorporate the calculation of recipes (i.e., we standardized the fruits that are typically in a fruit salad, or the vegetables typically in vegetable soup to estimate flavonoids in such food intake reports).

2.3 Measures

2.3.1. Demographics. The ethnicity (White or Black-Black African American, Black West Indian/Caribbean, Black African, and Other), education (Grade School, Some High School, High School diploma, Trade School diploma, Some college, Associate degree, Bachelor's degree, Master's degree, or Doctoral degree), and gender (female or male) of participants were based on responses from the Adventist Health Study-2 in 2002-6 (AHS-2). Difficulty meeting expenses for basic needs (food, clothing, housing) last year and before the age of 18 (1-7; *Not at all* to *Very*) and the age of the participant was reported in BRHS 2006-7 (34).

2.3.2. Kilocalories. A control variable for average daily caloric consumption. This was calculated by summing kilocalories across the FFQ. Nutrient intake = sum [(weighted frequency of use of a food) x (weighted portion size consumed of that food) x (amount of that nutrient in a standard serving size of that food)] (29). In this manner, an individual's proportion of flavonoids in the diet will be examined so that those with higher caloric intake do not immediately have higher flavonoid intake; this will vary by the size and gender of the participant. Scores range from 505 to 4492.

2.3.3. *Exercise*. A control variable for vigorous activities, “such as brisk walking, jogging, bicycling, etc., long enough or with enough intensity to work up a sweat, get your heart thumping or get out of breath” to determine if flavonoids rather than a healthy lifestyle are related to depressive symptoms. This was calculated by multiplying an eight-point Likert scale for average vigorous activities completed per week (1 = *Never*; 8 = *6+ times per week*) x and eight-point Likert for the average minutes per session (1 = *Never*; 8 = *More than 1 hour*). This was measured in 2006-7 BRHS. Scores can range from 1 to 64.

2.3.4. *Vegetarian status*. A control variable that describes individuals’ dietary patterns (vegan, lacto-ovo-vegetarian, pescatarian, semi-vegetarian, and non-vegetarian). This control will allow us to determine whether flavonoids rather than simply a healthier diet pattern is related to depressive symptoms.

2.3.5. *Adverse Childhood Experiences*. ACEs were summed as a 0-9 count of psychological, sexual, or physical abuse; neglect; substance abuse; mental illness; incarceration or domestic violence in the household; and parental separation/divorce. Participants were given a score of one for each ACE category if they endorsed one or more items within that category. Six categories were assessed in the 2006-7 BRHS survey; three categories (domestic violence, mental illness, and family member incarcerated) were assessed in 2010-11. Since participants reported childhood experiences before age 15 years, all reports were summed and scores could range from 0-9.

(1) *Psychological Abuse*. Psychological abuse was assessed with three items (35) including “*between ages 5 and 15 years did the mother/woman or father/man who raised you...insult, swear at, or ignore you?*”; and, “*...act in a way that made you fear you might be physically hurt?*” Any yes response was coded as 1; else 0.

(2) *Sexual Abuse*. Sexual abuse was assessed with three items (36) including “*ever [had] sexual contact with anyone who was at least 5 years older than you before you reached the age of 13?*” Any yes response was coded as 1; else 0.

(3) *Physical Abuse*. Physical abuse was assessed with five items (35) including “*Between ages 5 and 15, did the mother/woman or father/man who raised you...push, slap, or throw objects at you?*” and/or “*kick, bite, or strike you with an object?*” Any yes response was coded as 1; else 0.

(4) *Neglect*. Neglect was assessed with one item (35): “*How often would you say you were neglected while you were growing up, that is left on your own to fend for yourself?*” Any yes response was coded as 1; else 0.

(5) *Substance Abuse*. Substance abuse was assessed with: “*in your childhood, did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?*” (1). Any yes response was coded as 1; else 0.

(6) *Domestic Violence*. Parental domestic violence was assessed with four items (37) including: “*How often would you say that a parent or other adult in the household behaved violently toward a family member or visitor in your home?*”; “*how often “mother/stepmother [was] pushed, grabbed, or slapped,*” “*bitten or kicked,*” “*repeatedly hit,*” and, “*threatened with a gun or knife.*” Any yes response was coded as 1; else 0.

(7) *Parental Mental Illness*. Parental mental illness before age 18 years was assessed with two items (1) including: “*Was a household member depressed or mentally ill?*” and “*Did a household member attempt suicide?*” Any yes response was coded as 1; else 0.

(8) *Divorce/Separation*. Parental divorce was assessed with one item (33): “*parents got divorced when you were younger than 18.*” Any yes response was coded as 1; else 0.

(9) *Incarceration*. Family member’s incarceration was assessed with a single item (1): “*Did a household member go to prison?*” Yes before age 18 was coded as 1; else 0.

2.3.6. *Perceived Stress Scale*. The Perceived Stress Scale is used as a proxy measure of stress reactivity. Assessed with the four-item, global, short form measure of perceived stress in the 2006-7 (38). The items measured participants’ perception of stress in the past month rated on a five-point Likert scale (1 = *Never*; 5 = *Very often*). Items were coded and averaged so that scores could range from 1-5; higher scores indicate higher levels of perceived stress ($\alpha = .77$).

2.3.7. *Depression*. Depression was assessed with the 11-item short form Center for Epidemiological Studies Depression Scale in the 2010-11 (CES-D; 35). Because chronology is important in mediation analyses, the 2010-11 survey was selected to ensure the depression items were measured after the Perceived Stress items from the 2006-7 survey. The items measured symptoms of depression in the past week on a four-point

Likert scale (1 = *Rarely or none of the time*; 4 = *Most or all of the time*; $\alpha = .80$) with scores ranging from 1-4.

2.4 Statistical Analysis

Flavonoid intake was energy adjusted using the residual method to account for the relationship between nutrients and energy that the nutrient contains, which is different from total energy intake. Missing data were addressed using multiple imputation, which produces the least biased estimates and lowest loss of power and allows for the use of auxiliary variables to further reduce bias and increase power (40). SPSS (version 25) multiple imputation routines were used on 47 variables. All variables used in any analysis were included. To reduce bias and increase power, a variety of auxiliary variables not used in any analysis were included in the multiple imputation (40) such as negative affect, pessimism, self-esteem, satisfaction with life, and neuroticism. Imputation from too few multiple data sets results in a loss of power (41) so we imputed 10 data sets and calculated all analyses across all 10 sets. Descriptive statistics were reported for all measures (Table 1).

Bootstrapping was used to test mediation effects because this method does not require the distribution of the mediation effect to be normal (42) and reduces Type 1 Error. Bootstrapping estimates indirect effects (i.e., the relationship through the mediator) by taking a specified sample with replacement from the entire sample. The computer repeats the process k times to produce estimated indirect effects.

The PROCESS macro for SPSS, which performs moderated mediation using bootstrapping, was used to conduct the mediation analyses (43). The process was

repeated 1000 times and bias-corrected (BC) 95% confidence intervals (CI) were reported as they are considered the most accurate (44). Depression was the dependent variable and ACEs was the independent variable; perceived stress was the mediator with flavonoids moderating the relationship between perceived stress and depressive symptoms, while gender, ethnicity, education, difficulty meeting expenses, age, caloric intake, vegetarian status, and exercise were controlled. Chronology of variables is important in mediation analyses. ACEs happened first in childhood, flavonoid intake was then measured in adulthood from 2002-6, perceived stress was assessed in 2006-7, and finally, depressive symptoms in 2010-11. This order ensures that depression was measured after perceived stress, since we argue that early stress reactivity contributes to stress sensitivity assessed here as perceived stress, leading to depression in later life.

3. Results

The sample consisted of 6404 Seventh-day Adventist (SDA) adults (67.4 % female) with a mean ACE of 2.0 ($SD = 1.9$), flavonoid consumption 487.4 ($SD = 386.0$) mg/day, and age 61.9 ($SD = 2.6$) years. Flavonoid intake was within range of intakes observed in European populations (45,46). The majority of participants were White (67.9%) and college educated (58.8%); additional demographics can be found in Table 1.

The Pearson correlation coefficients between Adverse Childhood Experiences (ACEs), perceived stress, depressive symptoms, and flavonoids are shown in Table 2. ACEs were positively correlated with perceived stress ($r = .16$; $p < .001$) and depressive symptoms ($r = .17$; $p < .001$). Flavonoid intake was negatively correlated with perceived stress ($r = -.03$; $p = .01$) and depressive symptoms ($r = -.05$; $p < .001$), but not ACEs ($r = .01$; $p = .23$).

Our first hypothesis that participants with higher ACEs will report higher depressive symptoms as adults was supported. After controlling for gender, ethnicity, education, difficulty meeting expenses currently and under the age of 18, age, caloric intake, vegetarian status, and exercise, ACEs predicted depressive symptoms. Specifically, as ACEs increase by 1 standard deviation, depressive symptoms increased .148 standard deviations ($\beta = .15$; $p < .001$, Figure 1).

The second hypothesis that higher ACEs would predict worse depressive symptoms through the effects of perceived stress was also supported (Table 3). Perceived stress was tested as a mediator of the relationship between ACEs and depressive symptoms using bootstrapping. Perceived stress significantly mediated the relationship between ACEs and depressive symptoms (Index = -.003, BC 95% CI [-.007, -.001]).

Our third hypothesis, that flavonoid consumption will moderate the perceived stress and depressive symptom relationship; specifically, higher consumption of dietary flavonoids will be associated with lower depressive symptoms after ACEs, was supported. Flavonoid intake did moderate the perceived stress and depression relationship (Figure 1 and Table 3). Table 4 demonstrates how flavonoids moderated the indirect relationship of ACEs on depressive symptoms through perceived stress. Specifically, as ACEs increased by one standard deviation, depressive symptoms increased by .040 standard deviations through the interaction of perceived stress and flavonoids when flavonoids were consumed at one standard deviation below the mean (*effect* = .040 SD, BC 95% CI [.030, .052]). However, depressive symptoms were lower for those that consumed flavonoids at one standard deviation above the mean (*effect* = .035 SD, BC 95% CI [.025, .046]). Flavonoid intake did not moderate the ACEs and depressive

symptom relationship, which was tested through a flavonoid ACEs continuous interaction ($p = .06$).

Table 1
Descriptive characteristics of study sample n = 6404.

Variable	N (%)	M (SD)
Gender		
Female	4317 (67.4)	
Male	2087 (32.6)	
Race/Ethnicity		
White	4351 (67.9)	
Black	1762 (27.5)	
Other	291 (4.5)	
Education		
College degree or higher	3766 (58.8)	
Some college	1329 (20.8)	
High School diploma	733 (11.4)	
Trade School Diploma	295 (4.6)	
Below High school	281 (4.4)	
Difficulty meeting expenses (under 18)		
Not at all	1639 (25.6)	
A little	1412 (22.0)	
Somewhat	1396 (21.8)	
Fairly	986 (15.4)	
Very	971 (15.2)	
Difficulty meeting expenses (last year)		
Not at all	4687 (73.2)	
A little	950 (14.8)	
Somewhat	358 (5.6)	
Fairly	237 (3.7)	
Very	172 (2.7)	
Vegetarian Status		
Non-vegetarian	2218 (39.7)	
Lacto-ovo	1963 (35.2)	
Pesco	571 (10.2)	
Vegan	512 (9.2)	
Semi-vegetarian	300 (5.4)	
Age		61.9 (12.6)
Flavonoids (mg/d)		487.4 (386.0)
Kilocalories		1924.9 (741.3)
Exercise		19.2 (16.0)
Perceived Stress		2.1 (0.7)
Mean Depressive Symptoms		1.4 (0.4)
Total ACEs		2.0 (1.9)

Table 2

Pearson correlation coefficients between the measures used for the mediation analyses
(N=6404)

	Perceived Stress	Depression	Flavonoids
ACEs	.158**	.167**	.015
Perceived Stress	-	.437**	-.031*
Depression	-	-	-.050**

* $p < .05$, ** $p < .001$

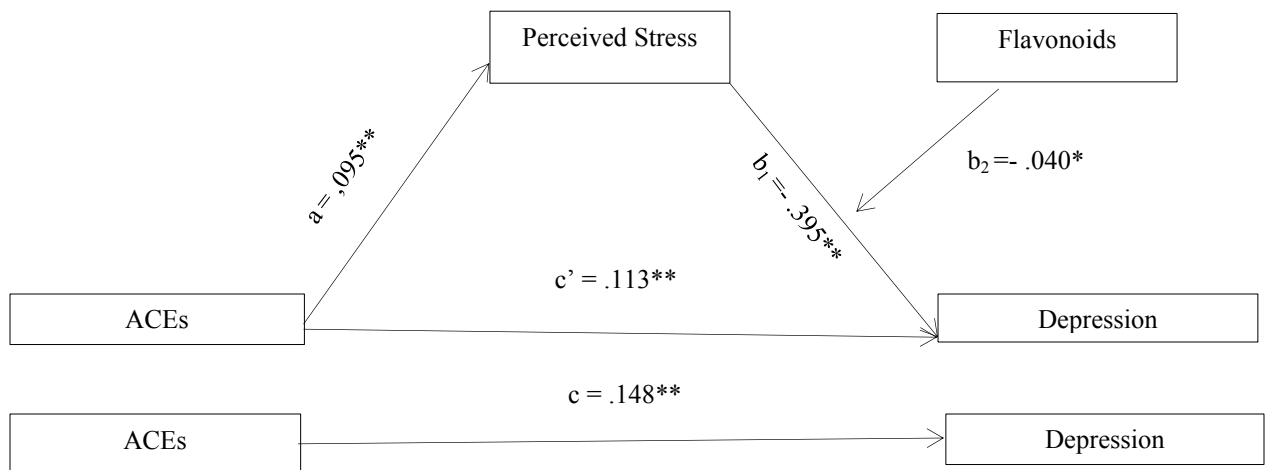


Fig. 1. Model of moderated mediation analysis testing flavonoids as a moderator of the relationship between perceived stress and depression for the full sample.

a = direct effect of ACEs on perceived stress

b_1 = direct effect of perceived stress on depression

b_2 = direct effect of interaction between perceived stress and flavonoids on depression

c' = direct effect of ACEs on depression controlling for mediator

c = total effect of ACEs on depression

* $p < .05$, ** $p < .001$

Table 3

ACEs and Depressive Symptoms Mediated by Perceived Stress with Flavonoid Intake Moderating the Perceived Stress and Depressive Symptom Relationship (N=6404)

Mediator	Index	SE	BC 95% CI
Perceived Stress	-.003	.002	[-.007, -.001]
	M = Perceived Stress		Y = Depressive Symptoms
Antecedent	β	SE	p
X = ACEs	.095	.013	$p < .001$
M = Perceived Stress			.395 .015 $p < .001$
V = Flavonoid			-.040 .014 $p = .005$
I = Perceived Stress x Flavonoid			-.034 .016 $p = .03$
Constant	.001	.012	$p = .93$
	F (11; 6392) = 78.865;		F (14; 6389) = 82.082;
	$p < .001$		$p < .001$

Note: SE = Standard error; M= Mediator; Y = Outcome variable; X = Independent variable; V= Moderator; I = Interaction.

Table 4

Conditional Indirect Effect of ACEs on Depressive Symptoms at Values of Flavonoid After Controls

Mediator	Flavonoid	effect	SE	BC 95% CI
Perceived Stress	-1 SD	.040	.006	[.030, .052]
Perceived Stress	Mean	.038	.005	[.028, .048]
Perceived Stress	+ 1 SD	.035	.005	[.025, .046]

Note: BC 95% CI = bias-corrected 95% confidence interval.

4. Discussion

The goal of the current study was to examine the relationships among ACEs, perceived stress, depressive symptoms, and dietary flavonoid intake. In addition, we sought to examine whether the effects were significant above demographic and other aspects of healthy lifestyle (e.g., exercise, vegetarian status, caloric intake). Early exposure to chronic stress can create maladaptive stress reactivity that harms mental health throughout adulthood (12). The Perceived Stress Scale was used as a proxy measure of stress reactivity. Our hypothesis that ACEs would be associated with higher depressive symptoms through higher perceived stress was confirmed. Studies have shown that stressors like ACEs produce biological symptoms similar to those seen in individuals with depression. These symptoms include compromised neurogenesis and synaptic plasticity, HPA axis and mitochondrial dysfunction, disturbances in neurotransmitters, and increased inflammation (14). Flavonoids have previously been found to ameliorate some of these same pathways by decreasing oxidative stress and inflammation, increasing cellular resilience, and increasing cerebral blood flow (18,47). This study confirmed our hypothesis that increased dietary flavonoid intake moderated the relationship between perceived stress and depressive symptoms after ACEs exposure. Heightened reactivity to stress as an adult, initiated by adverse experiences in childhood, was associated with increased levels of depression. However, consuming higher than average levels of dietary flavonoids reduces this effect.

This study adds to the existing literature in two ways. First, ACEs are associated with depression as others have found (5,12), however, this study also demonstrates that ACEs are linked to depression through heightened stress reactivity (e.g., current

perceived stress) that continues into middle and late life. Second, dietary pattern choices that are high in flavonoid content buffered the effects of perceived stress on depression above and beyond exercise and vegetarian diet pattern. It could be that flavonoids block the effects of stress reactivity on inflammation, oxidative stress, reduced cellular resiliency, and reduced blood flow in the brain to prevent perceived stress from leading to depressive symptoms (17,21,22). Greater consumption of flavonoids after ACEs is associated with fewer depressive symptoms. However, because ACEs have been linked to poor lifestyle choices that are associated with higher BMI, sedentary lifestyle, and risk for diabetes (6) it is unclear what leads to better dietary choices after ACEs. The study sample included those who were from the Seventh-day Adventist church (SDA), which promotes doctrinal beliefs regarding a healthy lifestyle including a vegetarian diet pattern and regular exercise. In fact, our lab has demonstrated that one path by which religiousness in SDAs operates is through healthy diet and exercise to reduce early mortality rates (48). However, flavonoid intake was predictive of depressive symptoms above and beyond exercise and a vegetarian diet and all participants were SDA in this study. Therefore, it is uncertain what characteristics are leading participants to consume greater amounts of flavonoids.

There are several limitations to this study. First, the study uses self-report measures, meaning that accuracy of food consumption and psychological measures are dependent on participant's memory and insight. Dietary data was reported one to four years prior to the psychological measures and may have changed though there is evidence diet remains relatively consistent across the lifespan (28). Although ACEs reports are uncorroborated, studies have shown retrospective self-report of abuse is typically

accurate or under-reported, and therefore our effects may be underestimated (49). Second, because the study was conducted using archival data from the Adventist Health Study-2, all of the participants were Seventh-day Adventists. These results may not generalize to the general population since Adventists emphasize a healthy lifestyle and promote vegetarian diets. Though studies have shown a link between vegetarian diet and depression, our analyses indicate flavonoid consumption cannot be explained by vegetarian diet pattern alone (49). Future research should examine the consumption of legumes and other alternative protein sources that are favored by SDAs and are flavonoid rich to further understand the link between vegetarianism and depression. Furthermore, with archival data additional cofounders such as family history of depression and use of antidepressants were not available as controls and cannot be ruled out as additional explanatory variables regarding depressive symptoms after ACEs. In fact, though we do control for other aspects of a healthy lifestyle such as exercise and vegetarian diet patterns, other confounding factors related to healthy lifestyle may have influenced these relationships as residual confounds. Further work should address other aspects of a healthy lifestyle that may also impact depression after adversity exposures. Third, as in most longitudinal cohort studies participant attritors were typically less educated and less healthy than those that continued to participate in the BRHS study in 2006 after the 2002 AHS-2 questionnaire.

The strengths of the study lie in its novelty. Previous studies have examined the effects of polyphenols in animals using polyphenol extracts or by examining the intake of specific foods rather than by examining a dietary pattern as a whole. Research from our group, for example, has shown that a polyphenol-enriched diet protects mice from

developing depression-like behaviors induced by irradiation (20), and that a diet that includes higher vegetable and fruit intakes predicts more positive emotional states in humans (15). The current study corroborates and expands upon these findings by demonstrating that a flavonoid-rich diet may protect adults who have experienced ACEs from developing depression by buffering stress reactivity effects. Though the effect size for the effects of flavonoids is small, we feel increasing the intake of fruits and vegetables high in flavonoids could potentially reach a large population of people and thereby have an impact on mental health outcomes. Future studies should conduct experimental manipulations of dietary flavonoid intake to help clarify the causal relationship between ACEs, perceived stress, and depressive symptoms. In addition, emerging research reveals a connection between unhealthy diets, the gut-microbiome, and depression (50). Future research should examine whether the gut microbiome as a potential flavonoid pathway that may influence mental health. Because plant-based diets that are possibly flavonoid rich may promote a more diverse microbiome that may decrease inflammation to impact health outcomes (51,52).

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Conflict of interest

The authors declare no conflict of interest

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APPENDIX A

Adverse Childhood Experiences (ACEs)

Adverse Childhood Experiences Items

	ACES	BRHS 2006 items
1	Psychological Abuse	Between ages 5-15 years did the mother/woman who raised you insult, swear at, or ignore you? Between ages 5-15 years did the father/man who raised you insult, swear at, or ignore you? Frequency of being fearful of being hit by a father or adult
2	Physical Abuse	Between ages 5-15 years did the mother/woman who raised you push, slap, or throw objects at you? Between ages 5-15 years did the mother/woman who raised you kick, bite, or strick you with an object? Between ages 5-15 years did the father/man who raised you throw objects at you? Between ages 5-15 years did the father/man who raised you kick, bite, or struck you with an object?
3	Child Sexual Abuse	ever have sexual contact with anyone who was at least 5 years older than you before you reached the age of 13? forced sexual contact before age 8 forced sexual contact between age 8-18 years
4	Neglect	How often would you say you were neglected while you were growing up, that is left on your own to fend for yourself?
5	Substance Abuse	In your childhood, did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?

APPENDIX B

Perceived Stress

The questions in this scale ask you about your feelings and thoughts during the last 4 weeks . In each case, please indicate how often you felt or thought a certain way.		Never	Almost Never	Some- times	Fairly often	Very often
19.	In the last 4 weeks, how often have you felt that you were unable to control the important things in your life?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20.	In the last 4 weeks, how often have you felt confident about your ability to handle your personal problems?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21.	In the last 4 weeks, how often have you felt that things were going your way?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22.	In the last 4 weeks, how often have you felt difficulties were piling up so high that you could not overcome them	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

APPENDIX C

Center of Epidemiological Studies Depression Scale (CES-D)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way **during the past week** by marking the appropriate bubble.

	Rarely or none of the time (Less than 1 day)	Some or a Little of the Time (1-2 days)	Occasionally or a Moderate Amount of the Time (3-4 days)	Most or All of the Time (5-7 days)
78. I did not feel like eating; my appetite was poor.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
79. I felt depressed.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
80. I felt that everything I did was an effort.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
81. My sleep was restless.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
82. I was happy.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
83. I felt lonely.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
84. People were unfriendly.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
85. I enjoyed life.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
86. I felt sad.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
87. I felt that people disliked me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
88. I could not get "going."	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>