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Effects of Multivitamin-Mineral Supplementation on Mental Health among Young Adults

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Effects of Multivitamin-Mineral Supplementation on Mental Health among Young Adults

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Abstract

The percentage of young adults who had mental illnesses has increased from 2008 to 2015. However, few existing studies investigating the potential benefits of multivitamin-mineral (MVM) supplementation on mental health focused on young adults (18-24 years of age), whose eating behaviors are often unhealthy. The purpose of this study was to examine the effects of a MVM supplement on mental health in young adults. One hundred and thirty-three college students (M_{age}=20.59, SD=1.77; 80.15% female) participated in this randomized, double-blind, placebo-controlled trial. Participants consumed either a MVM supplement or a placebo for 30 days. The supplement contained B Vitamins, Vitamin C, calcium, magnesium, and zinc. Beck Anxiety Inventory (BAI), Center for Epidemiologic Studies Depression Scale (CES-D), Abbreviated Dysregulation Inventory (ADI) and a single item for self-esteem (SISE) were used to assess participants' symptoms of anxiety, depression, impulsivity/dysregulation, and self-esteem level at baseline and on day 30. ADI explored three aspects of dysregulation (behavioral, cognitive, and affective). Participants' height and weight were recorded using standardized protocols by trained staff. Data were analyzed using repeated measures ANCOVA. There was a difference in adjusted mean score changes in depression within MVM supplementation or within placebo-controlled group from baseline to Day 30 (p= 0.03). There was also a difference in adjusted mean score changes in depression in MVM supplementation group compared to placebo-controlled group (p= 0.02). In overweight/obese BMI group, no difference in adjusted mean scores of anxiety, depression, dysregulation, or self-esteem level was found. However, closer examination based on effect sizes revealed moderate effects of MVM supplementation

within-subjects on anxiety (η^2= 0.11) and behavioral dysregulation (η^2= 0.03) and between-subjects on self-esteem level (η^2= 0.03); within-subjects on anxiety (η^2= 0.07), depression (η^2= 0.07), and cognitive dysregulation (η^2= 0.07) and between-subjects on depression (η^2= 0.07) and self-esteem level (η^2= 0.04) in overweight/obese BMI group. The 30-day MVM supplementation may have beneficial effects on young adults' symptoms of depression. Although outcomes presented no significant difference between pre-intervention and post-intervention scores, some of them indicated relatively moderate effect sizes, and future work should replicate with larger samples.

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Chapter 1

1 Introduction

Mental health is an increasing risk for people in the United States. In 2015, about 43.4 million American adults who were 18 years old or older (17.9%) had a mental illness in the past year. [1] The percentage of adults with mental illnesses had been relatively stable since 2008; however, it increased from 2008 to 2015 among young adults (18-24 years old). [1] It has been suggested that nutritional status may have a role in some mental health-related conditions. Also, young adults aged 18-24 years are at a unique developmental stage as they transition out of their parents' home and are still shaping their identity and health behaviors. At this stage, young adults are likely to be sensitive to their body weight and shapes. [2] Therefore, weight status may influence their mental health as well.

The remainder of this introduction section will state the importance of our study in young adults. After that, some of these more common mental health status (namely anxiety disorder, depression, and impulsivity/dysregulation) and self-esteem will be defined. Moreover, the major risk factors of these psychological impairments will be discussed. Furthermore, existing studies of multivitamin-mineral (MVM) use and psychological health among adults, as well as the strengths and limitations of the studies will be addressed. Finally, recommendations for future studies will be suggested.

1.1 Young Adults are at a Unique Developmental Stage

Young adults aged 18-24 years are at a unique developmental stage in the theory of Arnett. [3] In this period, young adults aged 18-24 years have demographic diversity, unpredictability of future. As they transition out of their parents' home, they are open to

various possibilities, taking partial responsibility of independent living, but still leaving other responsibility to their parents, college authorities, or other adults. Eighteen to twenty-four year olds are also distinct since they explore new behaviors, beliefs, and thoughts that will help them shape themselves into the person that they want to become. Due to changes in their residential status, school attendance, work status, and romance relationship, they may see themselves as neither adolescents nor adults, but somehow in between. They pursue self-sufficiency and are in transition to adults who accept their own responsibility, make independent decisions, and become financially independent. Young adults in the age of 18-24 years are both biologically and socially different from adolescents aged 10-18 years or adults aged over 24 year. They are different from adolescents who take few responsibilities in the society or adults who take more responsibilities and have normative behaviors. Additionally, young adults are more likely to be exposed to dangerous behaviors and have worse health conditions in multiple areas. [2, 3] The suicide death rate among young adults aged 20-24 years was 13.6 per 100,000 people, while among adolescents aged 15-19 years was 7.5 per 100,000 people. Therefore, young adults have a higher rate of depression and suicide. [2] In this case, young adulthood in the age of 18-24 years is a distinct period of time to shape their life-long healthy eating behaviors and to prevent them from potential mental health disorders. Therefore, we need to focus on these individuals.

1.2 Psychosocial Health

1.2.1 Anxiety Symptoms

When people are faced with a final exam, a job interview, or a meeting with their boss, they might temporarily feel panic. However, the feeling with an anxiety disorder can last for

days, months, or even years and can be hard to eliminate. [4] The symptoms of anxiety, worry, panic, fear, or embarrassment interrupt people's study, work, or ability to communicate with other people. People with anxiety symptoms may have difficulty keeping a healthy social relationship due to the antisocial behaviors caused by the chronic feelings. [4]

From 2001 to 2003, approximately 19.1% of American adults aged 18 years and older experienced anxiety disorders; among these, an estimated 22.3% of adults aged 18-29 years had anxiety disorder. [5] Compared to males, the prevalence of anxiety disorder in females is higher in American adults. [5]

1.2.2 Depression

Depression is often comorbid with anxiety. [6] The symptoms of depression include sad and anxious mood; hopelessness, guilt, worthlessness, or helplessness; and irritability. [7] People with depressive symptoms also show less or no interest in hobbies and activities and may be non-energetic or restless. The symptoms may influence their work and life due to issues with concentrating, remembering, and sleeping; change in appetite and/or weight; thoughts or attempts of death or suicide; and physical pain with unknown reasons. Notably, it is the most common mental illness among college students in the United States. [6] In 2016, about 16.2 million (6.7%) adults suffered major depressive episodes; among these, 10.9% of the adults aged 18-25 years underwent major depressive episodes. [8] Interestingly, the prevalence in females is also higher for American adults compared to males, [8] which is similar to the prevalence of anxiety disorder. This may be due to a personality difference or some men's unwillingness to show vulnerability and seek help, resulting in under-diagnosis.

1.2.3 Impulsivity/Dysregulation

Impulsivity and dysregulation also often come with anxiety disorder and depression among adolescents. [7] However, the mechanism and nature of the impairments still require further clarification. Chamorro et al. [9] investigated the impulsivity rate in more than 30 thousand adults in the United States, and they found that 17% of the sample had impulsivity impairment, indicating that impulsivity was prevalent, especially in men and younger people; also, the impulsivity rate among participants aged 18-29 years was 21.67% (data for only 18-24 year olds not reported). Although there are several definitions of impulsivity, major factors that contribute to impulsivity are motor (engaging in actions without enough thinking), inattention, and non-planning. [10] Moreover, brain injuries such as frontal lobe lesion may cause impulsive behaviors as well. [10]

On the other hand, dysregulation is an indicator of irritation and less attention. While impulsivity is positively associated with several mental health disorders and even suicide, [9] dysregulation is related to risky behaviors such as eating disorders. [11]

1.2.4 Self-esteem

Self-esteem is one's attitude of himself/herself, [12] and even though self-esteem is interior, it can be impacted by role models or by peers. [13] Self-efficacy is an individual's belief that he/she is able to manage tasks. [13] Self-esteem and self-efficacy play a major role in people's achievement in goals, missions, and challenges. [13] Yorra [13] investigated the level of self-efficacy and self-esteem in 399 third-year pharmacy students whose grade point averages (GPAs) were equal to or higher than 3.0 in the New England area in the US. He found that the school that students attended and the hours that students got paid were

significantly correlated to self-esteem level. Also, self-esteem is usually correlated to body image among young adults. [14, 15] Skorek et al. [15] examined the relationship between personalities (conscientiousness, emotional stability, extraversion, agreeableness, openness), body esteem level, and self-esteem level among undergraduate students in Central California. They found that female participants had lower emotional stability and body esteem than males. Higher personality stability was associated with higher self-esteem and higher body satisfaction. The findings indicate that gender, personality, and body image may affect individuals' self-esteem.

1.3 Risk Factors for Psychological Impairments

1.3.1 Excess Body Weight

Anxiety, depression, impulsivity/dysregulation, and low self-esteem is associated with excess weight, [4, 9, 11, 14, 15] excess weight may be a risk factor for poor mental health. People who have a body mass index (BMI) of 25-29.9 are classified as overweight and those who have a BMI of 30 and above are classified as obese. [16] Obesity affects 78.6 million people, which is equal to 33% of the population in the United States, and it is predicted to increase to 50% by 2030. [17] In Arkansas, 20.7% of young adults (18-25 year olds) and 34.6% of adults (20 years old and older) had obesity in 2015. [18] Moreover, excess weight is associated to poor mental health outcomes such as depression, low self-esteem, peer victimization, and poor quality of life. [19]

1.3.2 Nutrient Deficiencies

While excess weight may contribute to poor mental health, deficiency in vitamins and minerals is another risk factor. [20] Vitamins function as coenzymes and antioxidants to prevent

damage in the brain.[12] For example, the B vitamins, a group of water-soluble micronutrients, play an important role in cognition and brain function. Pyridoxine (vitamin B6), folate (vitamin B9), and cobalamin (vitamin B12) influence blood homocysteine (a sulphur-containing amino acid) level. Some mechanisms that result in an increase of mental illness outcomes are also associated with elevated homocysteine.[20] Pyridoxine occurs naturally in the form that exists in food, in additional use, or in dietary supplements. The natural forms are pyridoxine, pyridoxal, pyridoxamine, and respective 5'-phosphate esters. Pyridoxal 5'-phosphate is the active form of pyridoxine that serves as a carbonyl-reactive coenzyme in many reactions of amino acid metabolism.[20-22] Among those metabolic pathways, there is one pathway that lowers homocysteine levels.

Also, pyridoxine facilitates the formation of epinephrine, norepinephrine, serotonin, and γ-amino butyric acid (GABA).[12] They are all neurotransmitters in the central nervous system. Moreover, it assists in the synthesis of taurine that concentrates in the brain and in the conversion of tryptophan to niacin by kynureninase.[12]

Second, folate is a kind of vitamin that is involved in various metabolic pathways such as deoxyribonucleic acid (DNA) synthesis, methylation, and methionine regeneration.[13] It is commonly used to lower cases of neural tube defects in infants. In addition, it is used in 1-carbon metabolism by tetrahydrofolate (THF) to maintain proper *S*-adenosylmethionine (SAM) level.[20] THF receives and donates methyl groups, and methionine synthase requires it, together with cobalamin, to attach a methyl group to homocysteine, so that SAM is formed. Typically, since this pathway keeps the SAM level stable, homocysteine can be removed by it, so that a damaging effect on brain function is prevented. SAM serves as the methyl group

donor in several methylation reactions and causes oxidative stress through several mechanisms. [13]

Furthermore, cobalamin has two forms of coenzymes, methylcobalamin and deoxyadenosylcobalamin, serving the enzymes called methionine synthase and methylmalonyl-CoA mutase. [20] Cobalamin deficiency causes folate being trapped in the methyl-5 form and reduction of DNA synthesis, which may influence brain function.

On the other hand, pyridoxine, folate, and cobalamin prevent oxidation by reducing oxidative stress resulting from mechanisms that involve SAM [13, 20]; antioxidants prevent oxidation, a damage that is caused by oxygen and produces free radicals and other reactive oxygen species. [20] However, our brain is too vulnerable to defend against oxidation due to lipid-rich and metabolically active mechanisms without a powerful system for antioxidation; therefore, antioxidants play a critical role to protect the brain. [20] Vitamins A, C, and E are powerful dietary antioxidants that can prevent cytotoxicity due to free radicals, sweep out reactive oxygen species, and upregulate enzyme activity of antioxidants. Specifically, vitamin C provides an electron and acts as an oxidant to terminate the free radical chain reaction and becomes a vital defender for the brain due to high levels of vitamin C in the plasma of cerebrospinal fluid and the brain. [23] Vitamin C also renovates radical removal of vitamin E. [24] Moreover, α-tocopherol, a type of vitamin E, is typically the main format in the brain, and neurological disease will happen if people lack it. Furthermore, vitamins E and A prevent lipid peroxidation, which is paramount for membrane conservation. [23]

Additionally, minerals influence brain function and mood in multiple ways. For example, when neurotransmitters dopamine, serotonin, and norepinephrine react with

oxygen, iron and copper ions release; after that, free radicals catalyze and cause damage to the brain. [20] Furthermore, dietary magnesium, copper, and zinc act as cofactors of enzymes that prevent damage from oxidative stress. [20] Magnesium is involved in multiple metabolic pathways, so normal function of the nervous system and release of neurotransmitters are dependent on magnesium. [25] Copper is the cofactor of an antioxidant enzyme copper, zinc superoxide dismutase (CuZnSOD). [26] Meanwhile, zinc plays a role for many enzymes that maintain brain zinc homeostasis. [27] Some underlying pathways have been investigated; however, some remain unclear.

Therefore, micronutrient deficiency may associate with poor psychological health. Given critical roles of vitamins and minerals in brain function, brain development, DNA synthesis, and mood, MVM supplements may have a positive effect on mood improvement. However, the actual effect is still a debate. Evidence shows that MVM supplements could help decrease antagonistic and violent behaviors in children and adults. [28] Additionally, evidence from a meta-analysis suggests that MVM supplementation reduced levels of stress, psychiatric symptoms, anxiety, confusion and fatigue, but not depression. [29]

2 Existing Studies of MVM Use and Psychological Health among Adults

Several human intervention studies have tested whether MVM supplements may improve psychological outcomes among adults aged 18 years and above. However, others suggested that MVM supplements have no significant effect on mental health improvement. Among those, some are randomized, placebo-controlled trials, while some are pretest-posttest studies.

2.1 Randomized, Double-Blind, Placebo-Controlled Design

2.11 Swisse Vit® Supplement

Harris et al. [30] hypothesized that the MVM supplement would improve symptoms of depression. In this study, 50 healthy male participants who were 50-69 years old were provided with a supplement called Swisse Men's Ultivite® which had multivitamins, herbal extracts, and minerals, or a placebo for 8 weeks. Data were collected through General Health Questionnaire (GHQ), Depression Anxiety Stress Scale (DASS), as well as Perceived Stress Scale (PSS), Profile of Mood States (PMS), and Visual Analog Mood Scales (VAMS). They found that there was a significant difference for GHQ scores between treatment and placebo-controlled groups; particularly, the alternative from baseline in the treatment group was higher than placebo-controlled group. Also, a statistically significant treatment effect across the intervention was discovered for the total DASS score but not for any subscales (depression, anxiety, and stress). Moreover, the MVM group had a more positive score change in alert scores on VAMS. Finally, they concluded that there was a tendency for better performance in the multivitamin-mineral supplement group. [30]

Pipingas et al. [31] also investigated the effect of Swisse Ultivite® on mood. One hundred and thirty-eight healthy young adults aged 20-50 years participated in this study for 16 weeks. However, males were provided the formula for men and females were provided the one for women. The findings showed no significant difference on the scores of the General Health Questionnaire (GHQ), Profile of Mood States (POMS), Pennebaker Inventory of Limbic Languidness (PILL), Chadler Fatigue Scale (CFS), Bond-Lader Visual Analogue Scales (VAS) between the MVM supplement group and the placebo-controlled group. However, compared

to the placebo-controlled group, MVM tended to reduce the score in the subscales of VAS (significant in stress, anxiety, and physical fatigue). During weeks 1-4, the rates of VAS stress scale and anxiety scale in the MVM group were significantly lower than the placebo-controlled group. During both weeks 5-8 and weeks 9-12, VAS physical fatigue rating was significantly less in the MVM supplement group in comparison to the placebo-controlled group. [31]

Meanwhile, Sarris et al. [32] analyzed the qualitative data from 114 participants in this study. Participants were asked about positive and negative experiences after taking the supplement. The positive experiences included domains such as general mental benefit; improved concentration, attention, and/or memory; increased calmness or relaxation; better mood and emotional state; general physical benefit; improved sleep; more energetic or alert; better health or immunity; dermatological benefit; and increased/better appetite. The negative experiences included impaired concentration or attention, being stressed or anxious, more moody emotions, impaired sleep, being more fatigued or drowsy, poorer health or immunity, upper gastrointestinal complaints, indigestion or nausea, dermatological complaints, gynecological effect, and unintended weight gain. The supplement group reported at least one positive experience such as energy and mental alertness as well as increase in mood and emotional wellbeing. Also, the supplement had no major adverse effects. [32]

After that, Macpherson et al. [33] investigated the effect of Swisse Women's 50+ Ultivite® on the mood and cognition of 76 healthy women aged 50-75 years. Mood was assessed by the Depression Axiety Stress Scale (DASS); State Trait Anxiety Inventory (STAI)-State Anxiety Scale; Bond-Lader Visual Analogue Scale (VAS); Stress, Anxiety, Concentration,

Physical Fatigue and Mental Fatigue Visual Analogue Scales. They also examined cognitive effects using the Swinburne University computerized cognitive assessment battery, including a series of tasks related to reaction time, stroop test, recognition memory, and working memory. The results showed that the MVM supplement benefited mood 1-2 hours after consumption. The rating of overall mood on DASS improved and this effect seems to be due to stress reduction. On VAS, the supplement was associated with decreased rating of stress and increased rating of calmness. [33]

2.12 Berocca® Supplement

The supplement Berocca® contains B vitamins, vitamin C, calcium, magnesium, and zinc. Compared to Swisse Vit®, it did not have vitamin D3 or herbal extracts.

Carroll et al. [34] examined the possible mental effect of a MVM supplement using Berocca®. Eighty men aged 18-42 years were provided with the supplement or a placebo for 28 days. Data were collected using the assessments including the GHQ, PSS, Hospital Anxiety and Depression Scale (HADS), a physical symptom checklist, and a dietary questionnaire. Plasma zinc concentration was also assessed. Moreover, participants completed the general rating scales for anxiety, depression, tension, tiredness, and inability to concentrate (basically indicated 1 for not at all and 7 for very). Also, they self-reported the effect of the MVM. The findings indicated that the MVM supplement was associated with psychological state improvement, reductions in anxiety, less perceived stress, rating of less tired and better concentrations, and less physical or somatic symptoms. [34]

Another double-center study also used Berocca® by Schlebusch et al. [35] to investigate its effect on mood improvement. Three hundred participants aged 18-65 years completed a

stress symptom checklist as well as a biographical questionnaire, the Hamilton Anxiety Rating Scale (HARS), the Psychological General Well-being Schedule (PGWS), the Visual Analogue Scale (VAS), and Berocca Stress Index (BSI). Also, collateral information from participants' close relatives was obtained, and participants completed the daily patient diary. Participants were provided the MVM supplement or a placebo for 30 days. Schlebusch et al.[35] found that there were no differences between the MVM supplement and placebo-controlled groups regarding demographics and stress scores at baseline. However, both the scores of the two groups improved between baseline and the end of treatment. In subgroups of 18-44 and 45-65 year olds, gender and ethnicity showed no significant impact on the overall study outcome. However, the score improvement on BSI, HARS, PGWS, and VAS was statistically significant. Also, the difference of scores was greater in MVM supplement group compared to the placebo-controlled group. Importantly, this beneficial effect lasted for the whole day. [35]

Kennedy et al. [36] examined the effect of Berocca® on mood and cognition with 215 men aged 30-55 years for 33 days. The Profile of Mood States (POMS), the Perceived Stress Scale (PSS), the General Health Questionnaire (GHQ), the Bond-Lader Mood Scales, and the Energy Visual Analogue Scales (VAS) were used to measure the status of mood. Meanwhile, participants were asked to complete a series of tasks including serial subtractions, rapid visual information processing task, subjective mental fatigue scale, stroop task, and Wisconsin card sort task to measure the cognitive function. The results showed that in the MVM supplement group participants consumed more vegetables and fruits than those in the placebo-controlled group. Also, participants in the MVM supplement group rated lower subjective stress (PSS scores) and increased vigor (physical strength and good health;

POMS subscale) compared to placebo-controlled group. If vegetable and fruit consumption was considered, the score in GHQ significantly decreased. Moreover, the serial threes correct rate in the serial subtractions significantly increased, while the mental tiredness significantly decreased. This indicated that participants' cognition and memory improved. Within the previous study, Kennedy et al. [36] also investigated the effect using a mobile phone assessment in the prior 4 weeks. The findings indicated increased alertness in the evening after a 14-day intervention and the increased alertness throughout daytime after a 28-day intervention. Furthermore, the mental stamina and concentration rate in the VAS increased after work with the improved overall physical stamina rate. [36]

Recently, White et al. [37] used a different Berocca® that contained more thiamine than the former one to examine its potential beneficial effect on mood in young adults. Fifty-five participants aged 18-40 years took the daily supplement for 28 days. Participants completed the Profile of Mood States (POMS), Perceived Stress Scale-10 (PSS), Visual Analogue Mood Scales (VAS), State-Trait Anxiety Inventory (STAI) Meanwhile, blood samples were collected to further examine the level of serum vitamin B6, folate, vitamin B12, homocysteine (Hcy), and high sensitivity C-reactive protein. The results suggested that compared to placebo-controlled group, MVM supplement consumption lowered serum Hcy level and increased vitamin B6 and vitamin B12. Also, MVM supplementation was associated with lower depression-dejection scores, but not associated with change in cognitive assessment.[37] Overall, the findings from the five articles above indicate that the MVM supplement Berocca® may have a positive effect on mood in adults. Also, it might improve people's performance in work and study.

2.13 Other Supplements

In 1995, Benton et al. [38] conducted a study to investigate the influence of a vitamin supplement on cognitive function. The supplement contained 9 vitamins including thiamin, riboflavin, and pyridoxine and the dose was 10 times of the recommended dietary allowance (RDA). Two hundred and nine participants aged 17-27 years were provided with the supplement or a placebo for 12 months. Also, a series of psychometric tests were administered. Moreover, blood was collected to analyze serum vitamin A and vitamin E levels as well as plasma ascorbic acid concentration, among others. The findings suggested that vitamin status was correlated with cognitive functioning in both females and males. The correlation was more obvious after 12 months than after 3 months. Furthermore, the correlation was more significant in females than in males. In this study, Benton et al. [38] also examined the effect of the supplement (9 vitamins; 10 times of RDA) on mood. The Profile of Mood States (POMS) and the General Health Questionnaire (GHQ) were used to measure the mood of participants. The results indicated that a high dose of vitamins may have a long-term positive effect on women's mood. [38]

Similarly, Haskell et al. [39] published another article in 2010 investigating the effect of MVM supplementation using Supradyn® on fatigue and cognitive function in healthy women. Two hundred and sixteen females aged 25-50 years participated in this study taking the supplement or a placebo for 3 months. Haskell et al. [39] used various measurements and cognitive testing tasks as well as physiological assays to collect data. The results showed reduced tiredness measured in the Visual Analogue Scales (VAS) and increased math score as well as increased accuracy of performance in Stroop Color-Word and speed of memory

searching in the MVM group. In contrast, there was no significant beneficial effect on improvement of fatigue and mood. [39]

Also, Gosney et al. [40] in 2008 explored the association between MVM supplementation and depression and anxiety symptoms among elderly people. Seventy-three healthy elder people from 11 nursing homes were treated with a MVM supplement or a placebo for 8 weeks. Both the supplements and placebos were supplied by a company called Recip AB, Sweden. Data were assessed by the Montgomery-Asberg Depression Rating Scale (MASRS), and Hospital Anxiety and Depression Scale (HADS). Gosney et al. [40] found that in the MVM group the scores on the depression subscale of HADS tended to decrease, while the scores on the anxiety subscale of HADS tended to significantly reduce in the placebo-controlled group. Also, participants with severe depression showed an increase in selenium level and a decrease in depression. The results only indicated that selenium might ameliorate depressive symptoms in older population. [40]

Additionally, in 2013 Lewis et al. [41] investigated the relationship between a vitamin B-complex supplement called Max Stress and people's mental health. Sixty depressive adults over 18 years old had the supplement for 60 days. Participants completed the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), and the assessment related to quality of life and physical activity level at baseline, and after 30 and 60 days. The findings suggested that Max Stress can decrease depressive and anxiety symptoms as well as improve quality of life in adults with depression. [41] Notably, the beneficial effect tended to be short-term and continuously decrease over the study period.

Moreover, Kennedy et al. [42] examined the effect of a nutrient enriched breakfast bar which contained α-Linolenic acid, L-tyrosine, L-theanine, vitamins, minerals and 21.5 mg of caffeine on mental health among healthy young adults. Ninety-five participants took the breakfast bar or a placebo for 8 weeks. Cognitive function was measured by multiple tasks including the cognitive demand battery (CDB) using the Computerised Mental Performance Assessment System (COMPASS); at the same time, mood was measured by the Depression, Anxiety and Stress Scales (DASS). The consumption of the nutrient-enriched breakfast bar had an acute effect on improvement of cognitive impairments (attention, working and episodic memory as well as executive function). Also, alertness was significantly and acutely improved due to the nutrient enriched breakfast bar. However, there was no chronic effect on cognitive or mood improvement. [42]

Furthermore, Evans et al. [43] conducted a study to investigate the effect of a beverage called Zeal Wellness on mood. The beverage contained various compounds such as vitamins and minerals as well as rice, bran, fruit, and vegetable extracts. Ninety-nine participants with moderate stress aged 18-65 years drank one dose or two doses of the beverage or a placebo for 4 weeks. Participants completed the Profile of Mood States (POMS) to measure the mood status at screening, baseline, and days 8, 15, and 29; meanwhile, blood samples were collected. After analyzing the Profile of Mood States-Total Mood Disturbance (POMS-TMD) score and blood samples, Evans et al. [43] found that, compared to the combined placebo and 1-dose daily beverage group, POMS-TMD scores and anger-hostility mood symptoms significantly decreased in the 2-dose daily beverage group. Also, the POMS iceberg profile shifted to a healthy profile. [43] Therefore, this beverage had beneficial effects on mental health.

2.2 Pretest-posttest Design

Participants usually report positive or negative results based on their own bias. This may influence the results away from the truth. Therefore, without a control group, pretest-posttest study design has a risk of providing false positive or false negative results, and is considered a relatively weaker study design.

Kimball et al. [44] investigated the relationship between MVM supplement and mood. More than 10,000 participants aged 18-95 years were provided Vital 2 Platinum for an average of 12 months. The Vital 2 Platinum contained omega-3 fatty acids (EPA and DHA), vitamin C, vitamin B_{12}, probiotics, and vitamin D_3 drops. Questionnaires such as the European Quality of Life Five Dimensions (EQ-5D) and the Targeted Symptoms List (TSL) were used and BMI and serum vitamin D and vitamin B_{12} level were examined. The results suggested that participants who had either severe/extreme or no/slight/moderate depression and anxiety reported improvement in depression and anxiety. Also, vitamin D intake and physical activities were significantly associated with improvement in depression and anxiety.[44] Therefore, nutritional supplementation may be beneficial to people who suffer from depression and anxiety on improvement of moods.

Also, Han et al. [45] examined the effect of a MVM beverage called Lifelong Vitality Pack on mood. Sixteen participants with average age of 42 years were given Lifelong Vitality Pack containing multivitamins, multiminerals, herbal, and an omega-3 fatty acids supplement infused with essential oils for 2 months. Blood samples were used to examine biomarkers related to cardiovascular health, antioxidant status, inflammation, and blood glucose regulation. Also, participants completed a 16-item survey to assess physical and mental

health. The results showed that HDL cholesterol, LDL/HDL cholesterol ratio, fasting insulin, homocysteine, serum vitamin E, EPA, and the arachidonic acid (AA)/EPA ratio were improved after 2-month supplementation. Moreover, there was a significant improvement on back and muscle pain, cold and flu incidence, anxiety, frustration, and irritation as well as mental clarity, energy, motivation, control, balance, and happiness. [45]

3 Summary and Recommendation

Despite the critical weakness in the study design for pretest-posttest studies, [44, 45] other randomized, double-blind, placebo-controlled studies above provide some interesting results. However, they still have limitations. First, participants' ages widely ranged in most studies. The widest age range was from 18 to 65 years old. [43] However, young adults aged 18-24 year are at a unique developmental stage. [3] They are physically and socially different from adults aged over 24 years as we discussed above. Also, the MVM supplements which participants consumed in these studies were different. Some supplements contained not only vitamins and minerals, but also herbal extracts, plant extracts, fatty acids, amino acids, etc. Two had a high concentration of vitamins which human beings do not regularly take. [38, 41] Moreover, the lengths of intervention varied. The lengths were from 28 days to 12 months. Furthermore, weight is mostly absent in those studies. Weight is associated with mental health as discussed above. Therefore, the attention to overweight/obese status may be required in future studies. Given the importance of investigating the effect of MVM on young adults' mood, we utilized the supplement that has the same components as Berocca® (only containing vitamins and minerals) and examined its effect on improvement of: anxiety,

depression, impulsivity/dysregulation, and low self-esteem among healthy young adults. Our objectives were 1) to investigate whether a 30-day MVM supplementation using supplements containing only vitamins and minerals improves mental health in young adults; 2) to examine the effect of supplementation in overweight/obese group. Our hypotheses were 1) our MVM supplementation will decrease symptoms of anxiety, depression, dysregulation, and low self-esteem in young adults; 2) our MVM supplementation will decrease symptoms of anxiety, depression, dysregulation, and low self-esteem in young adults in overweight/obese BMI group.

Chapter 2

5 Methods

5.1 Participants and Randomization

This study was approved by the University of Arkansas Institutional Review Board for human subject research (Approval #1709073942), and each participant signed informed consent form before enrolling in the study. We promoted the study through flyers at a mid-south public university beginning in October 2018 and ending in May 2019.

This study was a randomized, double-blind, placebo-controlled trial. There were 272 potential participants, but 121 of them failed to meet the inclusion criteria, and 20 of them were eligible but never enrolled. One hundred and thirty-one participants were enrolled at baseline. We measured their height and weight, and stratified them into two groups by BMI. One group had participants with normal BMI (18.5-24.9), and the other group had participants with overweight/obese BMI (≥25). Those who were underweight (BMI<18.5) were ineligible for our study. We further randomly assigned participants to take a MVM supplement or a placebo for 30 days. Participants completed questionnaires regarding mental health-related outcomes at baseline and on Day 30. Participants who were U.S. citizens were compensated a total of $100 in the parent study given incrementally when each questionnaire required by the parent study was completed. The compensation schedule was that participants received $10 after the completion of questionnaires at baseline, $15 after the completion of questionnaires on Day 2, $20 after the completion of questionnaires on Day 3, $25 after the completion of questionnaires on Day 15, and finally $30 after the completion of questionnaires on Day 30. The incremental approach was chosen to promote compliance retention. Due to university payment policy and tax policy, participants who were non-citizens

were paid in total at the end of the study. They needed to be taxed at 30% of the $100.

5.2 Inclusion and Exclusion Criteria

Inclusion criteria included 18-24 years old; full-time or part-time students, or at least working part-time; and willing to avoid taking other supplements during the study. Exclusion criteria included underweight; diagnosis with malabsorption or related gastrointestinal disease such as Crohn's disease or inflammatory bowel disease; diagnosis with diseases related to impaired liver or renal function; diagnosis with a mental illness; taking prescription medications related to mental illnesses. We determined potential participants' eligibility through a phone screening and scheduled their study timeline on their consenting day.

5.3 Supplement

The supplement contained the same components as the supplement Berocca®. It had 15 mg thiamin (vitamin B_1), 15 mg riboflavin (vitamin B_2), 50 mg nicotinamide (vitamin B_3), 23 mg pantothenic acid (vitamin B_5), 10 mg pyridoxine hydrochloride (vitamin B_6), 10 µg methylcobalamin (vitamin B_{12}), 500mg Vitamin C, 150µg biotin, 400µg folic acid, 100 mg calcium, 100 mg magnesium, and 10 mg zinc. Participants took the supplement or a placebo daily for 30 days. Both the supplement and placebo were provided by a local compounding pharmacy.

5.4 Assessment

Participants completed questionnaires through Qualtrics at baseline and on Day 30. The questionnaires included demographic questions, Beck Anxiety Inventory (BAI), Center for Epidemiologic Studies Depression Scale (CES-D), Abbreviated Dysreglation Inventory

(ADI), and a single item for self-esteem (SISE). On Day 30, participants completed questionnaires after they took the active supplement or a placebo in the morning.

5.41 Participants' demographic characteristics

Participants completed a short demographic survey asking about their age, gender, student full- or part-time status, year in college, highest level of education completed, students' employment status, geographic living location, highest level of education students' mother completed, highest level of education students' father completed, and food security. The survey included questions such as "What is your age in years?", "What is your gender?", "Are you a full-time or part-time student?", "What year are you in college?", "What is your highest level of education completed?", "What is your employment status?", "What is your geographic living location?", "What is the highest level of education your mother completed?", and "What is the highest level of education your father completed?" U.S. Household Food Security Survey Module: Six-Item Short Form Economic Research Service, USDA was used to assess participants' food security level. [46] A higher score indicated higher food security. Also, food security status has three categories of "high or marginal food security", "low food security", and "very low food security". A study of Gulliford et al. [47] revealed item-score correlations of the scale were from 0.52 to 0.79 and revealed a good Cronbach's $\alpha = 0.87$. Participants provided this demographic information at baseline. The remaining questionnaires were completed at all time points.

5.42 Beck Anxiety Inventory (BAI)

The BAI is a brief measure of anxiety symptomology developed to discriminate between anxiety and depression with a 21-item self-reported questionnaire assessing

symptoms related to mental disorders such as nervousness, dizziness, inability to relax, etc.[48] The questionnaire asked how much participants have been bothered by anxiety symptom listed below during the past week, including today. The answers included “numbness or tingling”, “terrified or afraid”, “hands trembling”, etc. [48] The score was calculated by summary of each item. A score of 0-21 indicated a low level of anxiety; a score of 22-35 indicated a moderate level of anxiety; a score of 36 and above indicated potentially concerning levels of anxiety. Items on the inventory have good internal consistency (α= 0.92) and test-retest reliability (α= 0.75). The items are correlated with the revised Hamilton Anxiety Rating Scale (0.51) and correlate with the Hamilton Depression Rating Scale (0.25). [48]

5.43 Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a 20-item self-reported measure of characteristic attitudes and symptoms of depression developed by National Institute of Mental Health. The CES-D is correlated with other depression measures and has high internal consistency (α= 0.90). [49] The questionnaire asked participants to indicate how often they have felt or behaved the way listed below during the last week. The answers included “I was bothered by things that usually don't bother me.”, “I had trouble keeping my mind on what I was doing.”, “I felt depressed.”, etc. [49] The score was summed, and a higher score indicated the presence of more symptomatology.

5.44 Abbreviated Dysregulation Inventory (ADI)

The ADI is a 30-item self-reported measure of aspects of temperament and behavior. The scores of scale reflected three aspects of dysregulation: behavioral dysregulation (BD), cognitive dysregulation (CD), and emotional dysregulation (ED). [50] It was rated on a 4-point

scale. “0” indicated “Never True”, and “3” indicated “Always True”. [50] The scores were summed in each subscales, and a higher score indicated the presence of more symptomatology. Items on BD and ED have good internal consistency (behavioral dysregulation α= 0.87, emotional dysregulation α= 0.87). [51, 52] Evidence also revealed good validity of ADI items. [51-53]

5.45 Single Item for Self-Esteem (SISE)

The single item for self-esteem (SISE) was a question asked if participants had high self-esteem and was rated on 5 points from strongly agree to strongly disagree. Evidence showed that the SISE is as valid and reliable as a scale. [54] It can be an alternative to the Rosenberg Self-Esteem Scale (RSE) in adults. [54]

5.46 Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA 24® 2016)

The ASA 24® 2016 is developed by the National Cancer Institute. Participants provided dietary information over the previous day through the online system. They completed the system each time with the survey. The 24-hour dietary recalls were collected so that caffeine, fruit, and vegetable intake could be controlled for in data analyses due to their potential influence on mental health and the effect of the supplementation on mental health. [55, 56] Participants’ caffeine intake was recorded in the unit of mg. Participants’ fruit and vegetable intakes were recorded in the unit of cup eq./day. Fruits intake included total intact fruits (whole or cut) and fruit juices. Vegetables intake included total dark green, red and orange, starchy, legumes, and other vegetables.

5.5 Statistical Analysis

Data were analyzed by SPSS 24 (IBM Inc., Chicago, IL, USA). We used chi-square

and independent sample t-test to test if characteristics of participants were equal. Also, we used repeated measures ANCOVA to examine the change between mean differences of scores from BAI, CES-D, ADI, and SISE in college-age young adults before and after the intervention. Box's test of equality of covariance matrices tested the assumption that the covariance matrices were equal ($p > 0.01$), and Levene's test of equality of error variances tested if variances between the groups were equal ($p > 0.05$). First, in order to examine the overall effects of supplementation on mental health-related outcomes, we considered score changes of BAI, CES-D, ADI, and SISE from baseline to Day 30 as within-subject factors, and participants' treatment/placebo group as a between-subject factor. This analysis tested if there was an overall effect period. Data were adjusted by covariates such as gender, BMI, food security score, caffeine intake, and fruits and vegetables intake. After that, in order to examine the effect of supplementation in participants with excess weight, we selected overweight/obese BMI group. We considered score changes of mental health-related outcomes from Day 0 to Day 30 as within-subject factors and participants' treatment/placebo group as a between-subject factor. Data were adjusted by the same covariates, except BMI. Since our hypotheses were directional, a one-tailed p-value less than 0.05 was considered significant. Partial η^2 represented the effect size (small: 0.01, medium: 0.06, large: 0.14). A small effect size means that where a real effect, while a large effect size shows a big enough and consistent enough effect. [57] Within subject results indicated whether there were differences within the placebo-controlled group from baseline to Day 30 or whether there were differences within the MVM supplementation group from baseline to Day 30. Between subject results indicated whether there were differences between the placebo-controlled

group and the MVM supplementation group pre- and post-intervention.

The prevalence of anxiety in females is higher than males. So is the prevalence of depression and self-esteem. The majority of our sample was women (n=131; 80.15%). Therefore, gender was taken into consideration a covariate. As we previously discussed, excess weight may be a risk factor for poor mental health. Thus, participants' BMI was also a covariate we adjusted. Food security level may affect people's food choice and eating habits. Food insecurity is usually linked to hunger and may influence growth and health status. [58] In our study, more than 80% of participants had no food insecurity problems. Nontheless, we included this variable in the analysis. Fruit and vegetable intake is another covariate that we adjusted for in the analysis because intake of raw fruits and vegetables was related to less depressive symptoms, higher positive mood, and higher life satisfaction. [55] Moreover, evidence suggests that 200-250 mg caffeine intake elevates mood, but higher doses (>600 mg) may increase anxiety level. [56] Hence, we also adjusted for caffeine intake.

Chapter 3

6 Results

The preliminary data were from October 2018 to May 2019. There were 131 participants at baseline. Among those, 103 participants completed all of the questionnaires for anxiety, and 102 completed all of the questionnaires for depression, dysregulation, and self-esteem level.

6.1 Demographic Characteristics

Means and standard deviations are presented in Table 1 for participants' age, body mass index (BMI) at baseline. The sample (n=131) was compromised of 80.15% females and 19.85% males with a mean age of 20.59 years (SD=1.77). There were 69 participants in MVM supplementation group and 62 in placebo-controlled group with the overall mean BMI of 25.92 (SD=6.21). The mean BMI in MVM supplementation group was 25.87 (SD=6.01), and the mean BMI of placebo-controlled group was 25.97 (SD=6.48). The mean age of MVM supplementation group was 20.70 years (SD=1.76), while the mean age of placebo-controlled group was 20.53 years (SD=1.79). Characteristics of the study sample (e.g., gender, year in college, etc.) are shown in Table 2. Most of the participants (n=129; 86.81%) were college students. Similarly, more than 80% of the participants lived in urban areas (n=131; 86.26%) or had high or marginal food security (n=126; 84.13%). More than half of the participants' mother or father had a bachelor's or higher degree (n=131; mother: 62.6%; father: 58.78%). Generally, the supplementation group and placebo-controlled group had no difference in age, BMI, gender, year in college, living location, food security status, and

participants' parents' education level using independent sample t-test and chi square ($p>0.05$). This suggests that the two groups were well matched.

Table 1 Means, Standard Deviations of Participants' Age and BMI and T-Tests Comparing MVM Supplementation Group and Placebo-Controlled Group.

Variable	Total Sample		MVM		Placebo		t
	N	Mean (SD*)	N	Mean (SD*)	N	Mean (SD*)	
Age	131	20.59(1.77)	69	20.70(1.76)	62	20.53(1.79)	-0.526
BMI (m/kg2)	131	25.92(6.21)	69	25.87(6.01)	62	25.97(6.48)	0.092

* SD, Standard deviation

Table 2 Sample Size and Percentage in Participants' Gender, Year in College, Living Location, Food Security Status, and Parents' Education Level with Chi-Square Comparing MVM Supplementation Group and Placebo-Controlled Group.

Variable	N Total Sample			Category	N in Each Category			χ^2
	Total	MVM	Placebo		Total	MVM	Placebo	
Gender	131	69	62	Male	26 (19.85%)	14 (20.29%)	12 (19.35%)	0.018
				Female	105 (80.15%)	55 (79.71%)	50 (80.65%)	
Year in college	129	68	61	Freshman/ Sophomore	51 (39.52%)	25 (36.77%)	26 (42.62%)	4.100
				Junior/Senior	61 (47.29%)	34 (50.00%)	27 (44.26%)	
				Graduate student	16 (12.40%)	8 (11.76%)	8 (13.12%)	
				Not a college student	1 (0.79%)	1 (1.47%)	0	
Location	131	69	62	Urban	113 (86.26%)	58 (84.06%)	55 (88.71%)	0.596
				Rural	18 (13.74%)	11 (15.94%)	7 (11.29%)	
Food security	126	64	62	High or marginal	106 (84.13%)	54 (84.38%)	52 (83.87%)	9.575
				Low	14 (11.11%)	5 (7.81%)	9 (14.52%)	
				Very low	6 (4.76%)	5 (7.81%)	1 (1.61%)	

Table 2 (Cont.)

Variable	N Total Sample			Category	N in Each Category			χ^2
	Total	MVM	Placebo		Total	MVM	Placebo	
Mother's education	131	69	62	Up to high school	26 (19.84%)	13 (18.84%)	13 (20.97%)	2.106
				Some post high school training	23 (17.56%)	13 (18.84%)	10 (16.13%)	
				College graduate	59 (45.04%)	31 (44.93%)	28 (45.16%)	
				Master's degree or higher	23 (17.56%)	12 (17.39%)	11 (17.74%)	
Father's education	131	69	62	Up to high school	31 (23.66%)	16 (23.18%)	15 (24.19%)	10.245
				Some post high school training	23 (17.56%)	13 (18.84%)	10 (16.13%)	
				College graduate	43 (32.83%)	20 (28.99%)	23 (37.10%)	
				Master's degree or higher	34 (25.95%)	20 (28.99%)	14 (22.58%)	

6.2 Descriptive Statistics of Unadjusted Pre- and Post-Intervention Outcomes

One hundred and three participants completed all the anxiety questionnaires, and 102 participants completed all questionnaires testing symptoms of depression, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, and self-esteem level. There were 53 participants in MVM supplementation group and 50 participants in placebo-controlled group regarding completion of BAI, whereas 53 participants in MVM supplementation group and 49 participants in placebo-controlled group completed CES-D, ADI (BD, CD, ED), and

SISE. Unadjusted means and standard deviations of score changes for mental health-related assessments from baseline to the last day of the intervention are indicated in Table 3. In overweight/obese BMI group, 44 participants completed questionnaires for anxiety symptom, depressive symptom, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, and self-esteem level. There were 21 participants in MVM supplementation group and 23 participants in placebo-controlled group completed BAI, CES-D, ADI (BD, CD, ED), and SISE. Presented in Table 4 are the unadjusted means and standard deviations of score changes for assessments on Day 0 and Day 30 in overweight/obese BMI group.

Table 3 Means, and Standard Deviations of Scores in BAI, CES-D, ADI (BD, CD, and ED), and SISE at Baseline and on Day 30.

Assessment		Group	N	Baseline Mean* (SD**)	Day 30 Mean* (SD)
BAI		MVM	53	1.09 (0.30)	1.02 (0.14)
		Placebo	50	1.06 (0.24)	1.02 (0.14)
CES-D		MVM	53	9.42 (3.86)	7.81 (3.96)
		Placebo	49	8.65 (2.95)	6.39 (3.38)
ADI	BD	MVM	53	6.60 (5.39)	5.34 (6.00)
		Placebo	49	6.82 (4.52)	4.90 (4.11)
	CD	MVM	53	21.21 (5.74)	21.19 (5.82)
		Placebo	49	21.10 (5.34)	20.14 (7.92)
	ED	MVM	53	5.08 (4.41)	3.38 (4.02)
		Placebo	49	5.27 (3.86)	2.90 (2.76)
SISE		MVM	53	1.38 (0.95)	1.11 (0.89)
		Placebo	49	1.12 (0.78)	0.92 (0.73)

* Unadjusted mean

** SD, Standard deviation

Table 4 Means, and Standard Deviations of Scores in BAI, CES-D, ADI (BD, CD, and ED), and SISE at Baseline and on Day 30 in Overweight/Obese BMI Group.

Assessment	Group	N	Baseline Mean* (SD**)	Day 30 Mean (SD)
BAI	MVM	21	1.24 (0.44)	1.05 (0.22)
	Placebo	23	1.09 (0.29)	1.04 (0.21)

Table 4 (Cont.)

Assessment		Group	N	Baseline Mean* (SD**)	Day 30 Mean (SD)
CES-D		MVM	21	10.48 (4.55)	9.10 (4.98)
		Placebo	23	9.17 (2.62)	6.48 (3.38)
ADI	BD	MVM	21	7.86 (6.37)	7.43 (7.49)
		Placebo	23	7.09 (4.78)	4.96 (2.85)
	CD	MVM	21	20.52 (6.05)	19.61 (6.00)
		Placebo	23	20.52 (6.05)	18.43 (7.35)
	ED	MVM	21	6.48 (5.13)	4.52 (5.09)
		Placebo	23	5.78 (4.39)	3.00 (2.65)
SISE		MVM	21	1.71 (1.01)	1.62 (0.92)
		Placebo	23	1.39 (0.78)	1.26 (0.69)

* Unadjusted means

** SD, Standard deviation

6.3 Effects of MVM Supplementation on Mental Health-Related Outcomes

Shown in Table 5 are the mean and standard deviation of scores of BAI, CES-D, ADI (BD, CD, and ED), and SISE pre- and post-intervention after controlling for covariates such as gender, BMI, food security score, as well as caffeine, fruit, and vegetable intakes with p-values of within- and between-subject comparisons. Within subject results indicated the effect of supplementation within the placebo-controlled group from baseline to Day 30 or the effect of supplementation within the MVM supplementation group from baseline to Day 30. Between subject results indicated the effect of supplementation between the placebo-controlled group and the MVM supplementation group from baseline to Day 30.

6.31 Effects within MVM Supplementation Group or Placebo-Controlled Group

Box's test of equality of covariance matrices showed no violation of assumption ($p>0.01$). Concerning within-subject results, there was a difference within MVM supplementation group in depression from baseline to the last day of intervention while controlling for gender, BMI, food security score, as well as fruits, vegetables, and caffeine intake. There was also a difference within placebo-controlled group from baseline to Day 30

in depression. F (1, 90) = 3.43, p= 0.03, partial η^2= 0.04. However, there was no difference within MVM supplementation group or within placebo-controlled group from baseline to Day 30 in terms of anxiety, F(1, 91)= 1.03, p= 0.16, partial η^2= 0.11; behavioral dysregulation, F(1, 90)= 2.58, p= 0.06, partial η^2= 0.03; cognitive dysregulation, F(1, 90)= 0.02, p= 0.44, partial η^2< 0.01; emotional dysregulation, F(1, 90)= 0.01, p= 0.47, partial η^2< 0.01; or self-esteem level, F(1, 90)= 1.24, p= 0.13, partial η^2= 0.01. There was a medium effect size within MVM supplementation group or within placebo-controlled group in anxiety (partial η^2= 0.11). There were also small effect sizes in behavioral dysregulation (partial η^2= 0.03) and self-esteem level (partial η^2= 0.01).

6.32 Effects between MVM Supplementation Group and Placebo-Controlled Group

With respect to between-subject results, Levene's test of equality of error variances showed no violation of assumption (p> 0.05) except for cognitive dysregulation on Day 30 ($F_{Day\ 30}$= 4.23, $p_{Day\ 30}$= 0.04). There was a difference between MVM supplementation group and placebo-controlled group from baseline to Day 30 after controlling for gender, BMI, food security score and intake of fruits, vegetables, and caffeine in terms of depression, F(1, 90)= 4.11, p= 0.02, partial η^2= 0.04. There was no difference for anxiety, F(1, 91)= 0.30, p= 0.29, partial η^2< 0.01; behavioral dysregulation, F(1, 90)= 0.05, p= 0.41, partial η^2< 0.01; cognitive dysregulation, F(1, 90)= 0.02, p= 0.44, partial η^2< 0.01; emotional dysregulation, F(1, 90)= 0.07, p= 0.39, partial η^2< 0.01; and self-esteem level, F(1, 90)= 2.44, p= 0.06, partial η^2= 0.03. There was a small effect size in self-esteem level (partial η^2= 0.03) between MVM supplementation group and placebo-controlled group.

Table 5 Adjusted* Means, Standard Deviation of Scores in BAI, CES-D, ADI (BD, CD, and ED), and SISE Pre- and Post-Intervention with P Value Showing the Significance within MVM Supplementation Groups or Placebo-Controlled Group or Between MVM Supplementation Groups and Placebo-Controlled Group and with Partial η^2 Showing the Effect Size within MVM Supplementation Groups or Placebo-Controlled Group or Between MVM Supplementation Groups and Placebo-Controlled Group.

Assessment		Group	N	Baseline $Mean_{adj}$ (SD**)	Day 30 $Mean_{adj}$ (SD)	P_w #	Partial η^2_w Δ	P_b §	Partial η^2_b ◎
BAI		MVM	53	1.09 (0.30)	1.02 (0.14)	0.16	0.11£	0.29	<0.01
		Placebo	50	1.06 (0.24)	1.02 (0.14)				
CES-D		MVM	53	9.42 (3.86)	7.81 (3.96)	0.03†	0.04€	0.02†	0.04€
		Placebo	49	8.65 (2.95)	6.39 (3.38)				
ADI	BD	MVM	53	6.60 (5.39)	5.34 (6.00)	0.06	0.03€	0.41	<0.01
		Placebo	49	6.82 (4.52)	4.90 (4.11)				
	CD	MVM	53	21.21 (5.74)	21.19 (5.82)	0.44	<0.01	0.44	<0.01
		Placebo	49	21.10 (5.34)	20.14 (7.92)				
	ED	MVM	53	5.08 (4.41)	3.38 (4.02)	0.47	<0.01	0.39	<0.01
		Placebo	49	5.27 (3.86)	2.90 (2.76)				
SISE		MVM	53	1.38 (0.95)	1.11 (0.89)	0.13	0.01€	0.06	0.03€
		Placebo	49	1.12 (0.78)	0.92 (0.73)				

* Adjusted for gender, BMI, food security score, caffeine intake, and fruit and vegetable intakes.

** SD, Standard deviation

† P<0.05

P_w showing the significance within MVM supplementation groups or placebo-controlled group.

Δ Partial η^2_w showing the effect size within MVM supplementation groups or placebo-controlled group.

§ P_b showing the significance between MVM supplementation groups and placebo-controlled group.

◎ Partial η^2_b showing the effect size between MVM supplementation groups or placebo-controlled group.

€ Partial η^2 showing small effect

£ Partial η^2 showing medium effect

6.4 Effects of MVM Supplementation in Overweight/Obese BMI Group

Indicated in Table 6 are the means and standard deviations of BAI, CES-D, ADI (BD, CD, and ED), and SISE pre- and post- intervention in overweight/obese BMI groups after adjusting for gender, food security score, caffeine intake, and fruit and vegetable intake with

one-tailed p-values of within- and between-subject. Within subject results indicated the effect of supplementation in overweight/obese BMI group within the placebo-controlled group from baseline to Day 30 or the effect of supplementation within the MVM supplementation group from baseline to Day 30. Between subject results indicated the effect of supplementation in overweight/obese BMI group between the placebo-controlled group and the MVM supplementation group from baseline to Day 30.

6.41 Effects within MVM Supplementation Group or Placebo-Controlled Group in Overweight/Obese BMI Group

With reference to within-subject results, Box's test of equality of covariance matrices showed no violation of assumptions ($p > 0.01$) except for behavioral dysregulation (Box's $M = 20.56$, $F = 6.50$, $p < 0.01$). There was no difference within MVM supplementation group or placebo-controlled group from Day 0 to Day 30 in overweight/obese BMI group while controlling for gender, food security score, as well as fruits, vegetables, and caffeine intake regarding anxiety, $F(1, 34) = 2.52$, $p = 0.06$, partial $\eta^2 = 0.07$; depression, $F(1, 34) = 2.68$, $p = 0.06$, partial $\eta^2 = 0.07$; behavioral dysregulation, $F(1, 34) = 0.03$, $p = 0.43$, partial $\eta^2 < 0.01$; cognitive dysregulation, $F(1, 34) = 2.61$, $p = 0.06$, partial $\eta^2 = 0.07$; emotional dysregulation, $F(1, 34) = 0.11$, $p = 0.37$, partial $\eta^2 < 0.01$; or self-esteem level, $F(1, 34) = 0.12$, $p = 0.37$, partial $\eta^2 < 0.01$. There were medium effect sizes in anxiety, depression, and cognitive dysregulation within MVM supplementation or within placebo-controlled group in overweight/obese BMI group (partial $\eta^2 = 0.07$).

6.42 Effects between MVM Supplementation Group and Placebo-Controlled Group in Overweight/Obese BMI Group

With respect to between-subject results, Levene's test of equality of error variances showed no violation of assumptions ($p > 0.05$) except for baseline anxiety, $F_{baseline} = 5.33$, $p_{baseline} = 0.03$, behavioral dysregulation on Day 30, $F_{Day\ 30} = 5.37$, $p_{Day\ 30} = 0.03$, and cognitive dysregulation on Day 30, $F_{Day\ 30} = 4.43$, $p_{Day\ 30} = 0.04$. There was no statistically significant difference between MVM supplementation group and placebo-controlled group from baseline to Day 30 in overweight/obese BMI group after controlling for gender, food security score and intake of fruits, vegetables, and caffeine in terms of anxiety, $F(1, 34) = 0.46$, $p = 0.25$, partial $\eta^2 = 0.01$; depression, $F(1, 34) = 2.45$, $p = 0.06$, partial $\eta^2 = 0.07$; behavioral dysregulation, $F(1, 34) = 0.70$, $p = 0.21$, partial $\eta^2 = 0.02$; cognitive dysregulation, $F(1, 34) = 0.21$, $p = 0.33$, partial $\eta^2 = 0.01$; emotional dysregulation, $F(1, 34) = 0.51$, $p = 0.24$, partial $\eta^2 = 0.02$; or self-esteem level, $F(1, 34) = 1.46$, $p = 0.12$, partial $\eta^2 = 0.04$. There was a medium effect size in depression between MVM supplementation and placebo-controlled group in overweight/obese BMI group (partial $\eta^2 = 0.07$). Also, there were small effect sizes in anxiety (partial $\eta^2 = 0.01$), behavioral dysregulation (partial $\eta^2 = 0.02$), cognitive dysregulation (partial $\eta^2 = 0.01$), emotional dysregulation (partial $\eta^2 = 0.02$), and self-esteem level (partial $\eta^2 = 0.04$) between MVM supplementation and placebo-controlled group in overweight/obese BMI group.

Table 6 Adjusted* Means, Standard Deviation of Scores in BAI, CES-D, ADI (BD, CD, and ED), and SISE Pre- and Post-Intervention in Overweight/Obese BMI Group with P Value Showing the Significance within MVM Supplementation Groups or Placebo-Controlled Group or Between MVM Supplementation Groups and Placebo-Controlled Group and with Partial η^2 Showing the Effect Size within MVM Supplementation Groups or Placebo-Controlled Group or Between MVM Supplementation Groups and Placebo-Controlled Group.

Assessment		Group	N	Baseline $Mean_{adj}$ (SD**)	Day 30 $Mean_{adj}$ (SD)	P_w #	Partial η^2_w Δ	P_b §	Partial η^2_b ◎
BAI		MVM	21	1.24 (0.44)	1.05 (0.22)	0.06	0.07£	0.25	0.01€
		Placebo	23	1.09 (0.29)	1.04 (0.21)				
CES-D		MVM	21	10.48 (4.55)	9.10 (4.98)	0.06	0.07£	0.06	0.07£
		Placebo	23	9.17 (2.62)	6.48 (3.38)				
ADI	BD	MVM	21	7.86 (6.37)	7.43 (7.49)	0.43	<0.01	0.21	0.02€
		Placebo	23	7.09 (4.78)	4.96 (2.85)				
	CD	MVM	21	20.52 (6.05)	19.62 (6.00)	0.06	0.07£	0.33	0.01€
		Placebo	23	19.91 (5.58)	18.43 (7.35)				
	ED	MVM	21	6.48 (5.13)	4.52 (5.09)	0.37	<0.01	0.24	0.02€
		Placebo	23	5.78 (4.39)	3.00 (2.65)				
SISE		MVM	21	1.71 (1.00)	1.62 (0.92)	0.37	<0.01	0.12	0.04€
		Placebo	23	1.39 (0.78)	1.26 (0.69)				

* Adjusted for gender, food security score, caffeine intake, and fruit and vegetable intakes.

** SD, Standard deviation

P_w showing the significance within MVM supplementation groups or placebo-controlled group in overweight/obese BMI group.

Δ Partial η^2_w showing the effect size within MVM supplementation groups or placebo-controlled group in overweight/obese BMI group.

§ P_b showing the significance between MVM supplementation groups and placebo-controlled group in overweight/obese BMI group.

◎ Partial η^2_b showing the effect size between MVM supplementation groups or placebo-controlled group in overweight/obese BMI group.

€ Partial η^2 showing small effect

£ Partial η^2 showing medium effect

Chapter 4

7 Discussion

7.1 The MVM Supplementation will Decrease Symptoms of Depression in Young Adults.

In the current study using the MVM supplement in participants aged 18-24 years, few differences were found in the MVM supplementation group in symptoms of anxiety, depression, dysregulation, or self-esteem level compared to placebo-controlled group. While controlling for gender, BMI, food security score, and intake of caffeine, fruits, and vegetables, there was a difference in score changes in depression within MVM supplementation group or within placebo-controlled group ($p= 0.03$). There was also a difference in score changes in depression between MVM supplementation group and placebo-controlled group ($p= 0.02$). Therefore, our MVM supplementation may reduce depressive symptoms in young adults. We found no difference in the score changes in MVM supplementation group or placebo-controlled group in anxiety, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, and self-esteem level ($p> 0.05$). There was no difference in score changes between MVM supplementation group and placebo-controlled group in anxiety, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, and self-esteem level ($p> 0.05$) either. However, when looking closer to the effect size, the results showed a medium effect size within MVM supplementation group or within placebo-controlled group in anxiety (partial $\eta^2= 0.11$). The results also showed small effect sizes in behavioral dysregulation (partial $\eta^2= 0.03$) and self-esteem level (partial $\eta^2= 0.01$). Between MVM supplementation group and placebo-controlled group, the results also showed a small effect size in self-esteem level (partial $\eta^2= 0.03$). A small effect size means that where a real effect,

while a large effect size shows a big enough and consistent enough effect. [57] Therefore, our MVM supplementation tends to lower the rates of anxiety, behavioral dysregulation, and self-esteem level within the MVM supplementation group or within the placebo-controlled group and tends to lower the rate of self-esteem level in MVM supplementation group compared to placebo-controlled group. However, lack of statistical significance may be due to our small sample size or the way we conducted the analysis.

7.2 The MVM Supplementation Tends to Decrease Symptoms of Anxiety, Depression, Dysregulation, and Self-Esteem Level in Overweight/Obese BMI Group in Young Adults.

Studies in young adults specific to examination of psychological impairments such as anxiety, depression, self-esteem level, dysregulation, and poor body image are sparse. Therefore, the mechanism by which weight status affects mental health remains unknown. In our current study, there was no difference in changes of anxiety, depression, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, or self-esteem level within MVM supplementation group or within placebo-controlled group from baseline to Day 30 in overweight/obese BMI group ($p > 0.05$) with adjustment for gender, food security score, and intake of caffeine, fruits, and vegetables. There was no difference in MVM supplementation group in changes of anxiety, depression, behavioral dysregulation, cognitive dysregulation, emotional dysregulation, or self-esteem level compared to placebo-controlled group ($p > 0.05$) either in overweight/obese BMI group. When we looked at effect size, we found medium effect sizes in anxiety, depression, and cognitive dysregulation within MVM supplementation or within placebo-controlled group in overweight/obese BMI group (partial $\eta^2 = 0.07$).

Compared to placebo-controlled group, there was a medium effect size in depression in MVM supplementation group in overweight/obese BMI group (partial η^2= 0.07). Also, there were small effect sizes in anxiety (partial η^2= 0.01), behavioral dysregulation (partial η^2= 0.02), cognitive dysregulation (partial η^2= 0.01), emotional dysregulation (partial η^2= 0.02), and self-esteem level (partial η^2= 0.04) in MVM supplementation group in overweight/obese BMI group in comparison to placebo-controlled group. A small effect size means that where a real effect, while a large effect size shows a big enough and consistent enough effect. [57] Therefore, our MVM supplementation tends to reduce the rates of anxiety, depression, and cognitive dysregulation within MVM supplementation group or placebo-controlled group. Also, the MVM supplementation tends to decrease symptoms of behavioral dysregulation, emotional dysregulation, and self-esteem level in the supplementation group compared to the placebo-controlled group. However, lack of statistical significance may be due to our small sample size or the way we conducted the analysis.

7.3 Comparison with Previous Studies

The lack of effect is in contrast to what Carroll et al. [34] found in a 28-day study, which was that Berocca® was associated with anxiety reduction. The lack of beneficial effect is also in contrast to the findings from the 30-day study of Schlebusch et al. [35] that Berocca® decreased symptoms of anxiety and stress and improved psychological general well-being. Moreover, lack of effect is also in contrast to the results from other previous studies using Berocca®. Kennedy et al. [36] suggested that a 33-day supplementation lowered stress and tiredness and improved alertness and physical health in comparison to placebo-controlled group. This discrepancy between our study and previous studies may be due to various

participants' characteristics. Carroll et al. [34] recruited male participants aged 18-42 years. Participants in the study by Schlebusch et al. [35] were 18-65 years of age, even if they had an age subgroup of 18-44 year olds. Male participants aged 30-55 years were in the study of Kennedy et al. [36] Thus, the age range of participants in these studies of 18-65 years old was broad whereas our study was more focused and investigated emerging adults aged 18-24 years. Varying sample sizes may also contribute to the discrepancy from our findings to previous work. The sample sizes in the studies of Schlebusch et al. [35] and Kennedy et al. [36] were more than 200. Another possibility for the difference in outcomes is the difference in instruments used to assess mental health. The questionnaires in the previous studies used to detect participants' physical and mental health were the General Health Questionnaire (GHQ), Hospital Anxiety and Depression Scale (HADS), Profile of Mood States (POMS), Visual Analogue Mood Scales (VAS), and State-Trait Anxiety Inventory (STAI). We in our current study used Beck Anxiety Inventory (BAI), Center for Epidemiologic Studies Depression Scale (CES-D), Abbreviated Dysregulation Inventory (ADI), and a single item for self-esteem level (SISE). A final possible explanation for no effect observed in our study is a potential placebo effect, where participants in the placebo group had improvement simply because they thought they were taking the active supplement.

Lewis et al. [41] used a B-complex supplement for 60 days. They also used BAI and Beck Depression Inventory (BDI) as an assessment to determine anxiety level. They found beneficial effects of decreased symptoms of anxiety and depression. [41] This may indicate that B vitamins contribute to our mental health. However, their participants were depressive adults, not healthy adults as in our study. The similar result was found in the 28-day study of White et

al. [37], which was that Berocca® supplementation decreased depressive symptoms. This may also show the role of vitamins and minerals in our brain biochemistry to decrease depressive symptoms and improve mental health in healthy people.

Our findings also seemed close to what Pipingas et al. [31] found, which was that MVM supplementation had few positive effects on mood. However, there were differences in our methodologies. The length of their study was 16 weeks, which was 4 times longer than ours. Also, the supplement they used contained botanicals such as Korean ginseng, Ginkgo Biloba, Chamomile, and green tea; evidence suggests that botanicals may have beneficial effects on mood. Moreover, men and women were given different supplements with slightly different doses of vitamins and minerals. Lastly, the age range of their participants was 20-50 years old rather than our participants of 18-24 years old. Therefore, the dissimilarity in length of the intervention, in supplement content, and in participants' characteristics may influence the effect of MVM supplementation on mental health.

7.3 Strengths/Limitations and Future Directions

Our first strength is that we focused specifically on young adults aged 18-24 years who are at a distinct developmental stage. [3] As they graduate from high school and experience various changes in love, work, and worldviews, it is likely that new environment influences their characteristics, behaviors, and mental health. [3] Also, depression is the most common problem in American college students, [6] which may develop suicide. Therefore, we paid particular attention to this population. Also, weight status may influence one's self-esteem level and then influence his/her mental health. Thus, we adjusted BMI as a covariate and investigated the effect of our supplementation on mental health in young adults

in overweight/obese BMI group. Another strength of our study is that the supplement we used contained only vitamins and minerals while some supplements other studies used contained botanical ingredients or caffeine, which may itself influence our mood or may influence the effect of the supplementation on mood. Finally, we recorded participants' caffeine, fruit, and vegetable intake via ASA 24-h dietary recall and adjusted the intake in analysis for controlling the confounding effect from caffeine, fruits, and vegetables that participants had. This is also a strength. However, the study has limitations. We did not ask participants' race in our current study. However, different races and cultures may have various mental health-related outcomes. Also, the compliance might be influenced since participants self-reported if they took the supplement. It is likely that they forgot to take the supplement but still reported that they took it. Thus, objective biological assessments such as blood or urine sample may provide a better way to check the compliance and a more comprehensive testing methodology. Moreover, some of the results showed good effect sizes instead of statistical significance. This may be because our sample size was relatively small. The insufficient sample size may result in type II error which gives us false negative results. Therefore, further studies may consider the method with a combination of biological tests and self-report questionnaires. Also, race should be a characteristic that will be asked in future studies. Lastly, future studies with a larger sample size are in warranted.

Chapter 5

8 Conclusion

There was a significant difference in score changes of depression within MVM supplementation group or within placebo-controlled group from baseline to Day 30. Also, a difference was found between MVM supplementation group and placebo-controlled group from baseline to Day 30 in depression. Therefore, our MVM supplementation may have beneficial effects in depression in young adults. It may also improve young adults' quality of life in terms of depression. There was no difference in score changes of anxiety, dysregulation, or self-esteem level within MVM supplementation group or within placebo-controlled group from baseline to Day 30. There was no difference in anxiety, depression, dysregulation, or self-esteem level in overweight/obese BMI group from baseline to Day 30. However, our MVM supplementation tends to have beneficial effects in anxiety, depression, dysregulation, and self-esteem level according to moderate effect sizes. Future studies are warranted to clarify the conflicting results and should take into consideration improvements in study design such as a question about race, objective biological assessment, and a larger sample size.

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Appendix Research protocol approval letter

UNIVERSITY OF ARKANSAS

To:	Jennifer Nicole Becnel HOEC 210
From:	Douglas James Adams, Chair IRB Committee
Date:	04/24/2018
Action:	**Expedited Approval**
Action Date:	04/24/2018
Protocol #:	1709073942
Study Title:	Effects of Multivitamin-Mineral Supplementation on Psychological and Physical Health in Young Adults with Excess Weight and of Healthy Weight
Expiration Date:	04/10/2019
Last Approval Date:	

The above-referenced protocol has been approved following expedited review by the IRB Committee that oversees research with human subjects.

If the research involves collaboration with another institution then the research cannot commence until the Committee receives written notification of approval from the collaborating institution's IRB.

It is the Principal Investigator's responsibility to obtain review and continued approval before the expiration date.

Protocols are approved for a maximum period of one year. You may not continue any research activity beyond the expiration date without Committee approval. Please submit continuation requests early enough to allow sufficient time for review. Failure to receive approval for continuation before the expiration date will result in the automatic suspension of the approval of this protocol. Information collected following suspension is unapproved research and cannot be reported or published as research data. If you do not wish continued approval, please notify the Committee of the study closure.

Adverse Events: Any serious or unexpected adverse event must be reported to the IRB Committee within 48 hours. All other adverse events should be reported within 10 working days.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, study personnel, or number of participants, please submit an amendment to the IRB. All changes must be approved by the IRB Committee before they can be initiated.

You must maintain a research file for at least 3 years after completion of the study. This file should include all correspondence with the IRB Committee, original signed consent forms, and study data.

cc: Sabrina Trudo, Investigator
Ryan W Grant, Key Personnel
Natalie Miller, Key Personnel
Taylor Michelle Peabody, Key Personnel
Ya-Hsuan Chang, Key Personnel