Journal of Food and Nutrition Sciences
2020; 8(5): 127-138
http://www.sciencepublishinggroup.com/j/jfns
doi: 10.11648/j.jfns.20200805.12
ISSN: 2330-7285 (Print); ISSN: 2330-7293 (Online)

The Effects of a Multivitamin, Multimineral, and Multiantioxidant Supplement on Cardio-Metabolic Risk Biomarkers: A Cross-Sectional Study

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To cite this article:

Huifeng Jin, Rolando Lorenzo Maddela, Robert Andrew Sinnott. The Effects of a Multivitamin, Multimineral, and Multiantioxidant Supplement on Cardio-Metabolic Risk Biomarkers: A Cross-Sectional Study. *Journal of Food and Nutrition Sciences*. Vol. 8, No. 5, 2020, pp. 127-138. doi: 10.11648/j.jfns.20200805.12

Received: October 7, 2020; **Accepted**: October 22, 2020; **Published**: October 30, 2020

Abstract: Use of dietary supplements like multivitamins/multiminerals (MVMM) and antioxidant nutrients, is a potentially safe and cost-effective alternative to medications. Dietary supplements-induced health promotion is controversial among available studies, and vast majority studies were done with individual or a subset of dietary supplements. In this study we assessed the effect of a blended supplement (CellSentials), formulated with MVMM and rich phytochemicals antioxidants, on multiple cardio-metabolic risk biomarkers. We recruited 56 subjects (age: 58.8 ± 1.6) with over one year consumption of blended supplements. Common cardio-metabolic risk biomarkers were measured, including systolic and diastolic blood pressure (SBP and DBP), plasma glucose (Glu), total cholesterol (TC), triglycerides (TGs), high-density cholesterol (HDL-C)), low-density cholesterol (LDL-C), TC: HDL ratio, oxidative stress markers gamma-glutamyltransferase (GGT), and inflammation markers white blood cell (WBC) count, and C-reactive protein (CRP). They were compared to the age, gender and race-matched Non-Users from the National Health and Nutrition Examination Survey (NHANES) 2007-2014 (n=769, mean age: 55.6 ± 0.5) by multiple linear and logistic regression analyses. Blended supplements users had significantly lower levels of Glucose ($p< 0.001$), TGs ($p<0.001$), and TC: HDL-C ratio ($p<0.001$), higher level of HDL-C ($p=0.008$) as well as lower levels of GGT ($p=0.002$), CRP ($p=0.007$) and WBC ($p=0.002$) than NHANES controls. There were no significant differences in SBP, DBP, TC, LDL-C. Correspondingly, blended supplements users had significantly reduced risks of elevated glucose (OR, 0.21; 95% CI, 0.07 – 0.61), ratio of TC: HDL-C (OR, 0.08; 95% CI, 0.02 – 0.31), TGs levels (OR, 0.07; 95% CI, 0.01 – 0.4), and low HDL-C (OR, 0.23; 95%CI, 0.06 – 0.88). These results demonstrated that blended supplement users had healthier pattern in cardio-metabolic biomarkers than control.

Keywords: Cardio-Metabolic Risk Biomarkers, Oxidative Stress, Inflammation, MVMMs, Antioxidant Nutrients, NHANES, Multiple Regression

1. Introduction

Overweight and obesity epidemics occur widely in the modern world and largely attributed to the unhealthy energy-rich but nutrient-poor dietary pattern as well as physical activity shortage. Obesity drastically increases the incidence of metabolic disorders, including diabetes mellitus, dyslipidemia, and hypertension [1]. Reaven first drew attention to the coexistence of metabolic disorders in overweight people [2]. The World Health Organization has declared that around 39% of world's adults aged 18 years and over were overweight and about 13% were obese in 2016 [3]. If current trends continue, almost half of the world's adult population will be overweight or obese by 2030 [4]. As a result, the overall prevalence of the triple H (high blood pressure, hyperglycemia and hyperlipidemias), which are most prevalent modifiable risk factors for cardiovascular disease, is rising worldwide. Effort has been devoted to reducing the risks by lifestyle changes and drug treatment [5, 6]. Despite clinical benefits of lipid-, glucose- and blood

pressure-lowering medications, there are issues of side effects and intolerance of medications. For example, the incidence of side effects of lipid-lowering medications is estimated to be 5% to 10% [7] and about 2% of patients with dyslipidemia are intolerant of any type of medication [8]. As a potentially safe and cost-effective alternative, dietary supplements use are getting popular and attracting substantial studies [9, 10]. Multivitamins/multiminerals supplements (MVMMs: defined as containing ≥3 vitamins and ≥1 mineral) [11] are the most common type of dietary supplements among adults in the US, followed by the antioxidant nutrients [12], and use is more prevalent among women, older adults, non-Hispanic Whites, and those with higher education and income [13-15]. Additionally, there are growing numbers of supplement products that claim to be beneficial to prevent chronic diseases [16, 17] or for general health and well-being [18]. However, the use of dietary supplements for health promotion is not conclusive [19-24]. Use of dietary supplement have been reported to have impact on cognitive health [25], weight loss [26], obesity [27]. There are also reports that supplementation does not improve cardiovascular outcomes in the general population [11, 28].

Numerous previous studies have demonstrated that inflammation and reactive oxygen species (ROS) are two interplay actors [29] that have important roles in the development and progression of cardiovascular disease [30]. Metabolic syndrome (MetS) is associated with a state of low-grade inflammation, characterized by abnormal pro-inflammatory cytokine production, increased acute-phase reactants, and activation of a network of inflammatory signaling pathways. MetS has also been linked to oxidative stress, a consequence of a reduction in the antioxidant systems and an increase in the production of reactive oxygen species frequently linked to overconsumption of energy in obesity. Dietary intervention may modulate both pro-inflammatory state and oxidative stress status related to MetS, thereby decreasing the cardiovascular risk. Numerous dietary nutrients, have anti-inflammatory and antioxidant activity effects, including vitamin A, C, E, vitamin B6, α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin, selenium, magnesium, zinc, copper, iron, fiber, mono- and polyunsaturated fat [31]; as well as other phytochemicals such as curcuminoids [32], green tea [33], coenzyme CoQ10 [34], α-lipoic acid [35], resveratrol [36], and quercetin [37]. To date, the vast majority of the studies examine the heath-associations of individual or a subset of nutrients/nutraceuticals. Since nutrients/nutraceuticals likely interact and work synergistically in physiological processes, combined MVMM and bioactive phytochemicals are likely to have synergic and stronger effects on inflammation, oxidative stress and metabolic disorders.

In the present study, we sought to assess the effects of a single formulation, CellSentials (CS), a blended MVMM and phytochemicals-antioxidants product manufactured by USANA Health Sciences, Inc., on the critical cardio-metabolic risk factors, oxidative stress markers and inflammation indicators. Our results support a beneficial effect of CellSentials in reducing cardio-metabolic risk factors as well as oxidative stress and inflammation in healthy middle-aged and elderly adults.

2. Materials and Methods

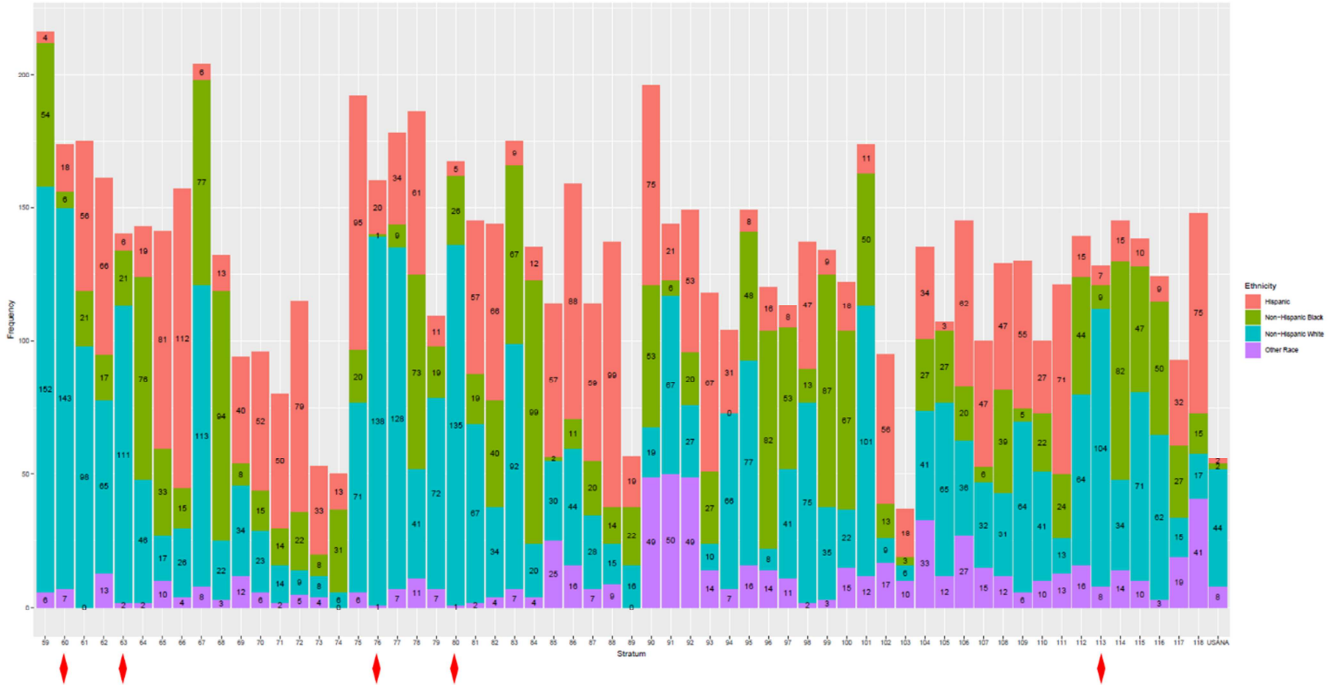
2.1. Study Participants and Data Collection

Consumers of CS supplement for at least one-year were invited to participate in the survey study. 2256 individuals who resided in the US, Canada or Australia, were invited by electronic mail and 188 agreed to participate in the study. Of those, 179 successfully completed the online lifestyle and health status questionnaire including diet, alcohol use, smoking, exercise, lipid-, glucose-, blood pressure-modifying drug usage and current health status information; 168 successfully completed online demographics including age, gender, race/ethnicity, country of birth, education levels, annual household income and pregnancy status at exam; and dietary supplement usage questionnaire including CellSentials, other USANA supplements as well as non-USANA supplements usage; 95 successfully uploaded the most recent physical examination document for the records of their weight, height, blood pressure (SBP and DBP), serum nutrients and biomarkers concentrations including fasting blood glucose and lipid profiles (TC, LDL-C, HDL-C and TGs), as well as inflammation markers C-reactive protein (CRP), white blood cell (WBC) counts, and oxidative stress markers GGT (Gamma-glutamyl transferase). Data collection took place between January and August of 2018. A subset of 87 participants had both questionnaire and examination data. Of those, 31 individuals also consumed non-USANA dietary supplements and were excluded. A final number of 56 participants (designated as "CS Users" hereafter) were used for analysis. The study was reviewed and approved by an independent institutional review board of Aspire (IRB: 2018774) (www.aspire-irb.com, CA), and all participants provided informed consent.

2.2. Non-Users of Supplement from NHANES

The National Health and Nutrition Examination Survey (NHANES) data was used as the source of comparison data for Non-Users of supplements. NHANES is a stratified, multistage probability sample of the civilian non-institutionalized U.S. population, conducted by the National Center for Health Statistics. Started in 2007, NHANES includes detailed information about each nutrient amounts in each dietary supplement, allowing accurate estimated of nutrient intakes from dietary supplements in general. To achieve satisfying statistical reliability, we used combined, multiple year (2007-2014) data for this study. The dietary supplement questionnaire (DSQ) was used to collect detailed information on the participant's use of vitamins, minerals, herbals, and other supplements. The analysis was limited to subjects with data available regarding their use of vitamins and nutritional supplements; those with missing data for dietary supplement use were excluded.

Participants who responded "No" to the question "have you used to take any vitamins, minerals or other dietary supplements in the past month?" were classified as Supplement "Non-Users". Participants who responded "Yes" to the above question were classified as Supplement "Any Users". Since middle-aged persons were more likely to use dietary supplements than young adults [38-40], those younger than 35 years were excluded in this study. In addition, pregnant women were also excluded from this analysis. Further, to match the gender-, age- composition and race- distribution, we selected NHANES 2007-2014 strata with the matched frequency distribution of race/ethnicity (> 75% non-Hispanic white) (Figure 1), men and women without pregnancy, and ≥ 35 years of age, who met supplement non-use criteria.



* Red diamonds represent the race frequency distribution matched stratum: 60, 63, 76, 80 and 113 respectively.

Figure 1. *Frequency distribution of race by each stratum in NHANES 2007-2014 data.*

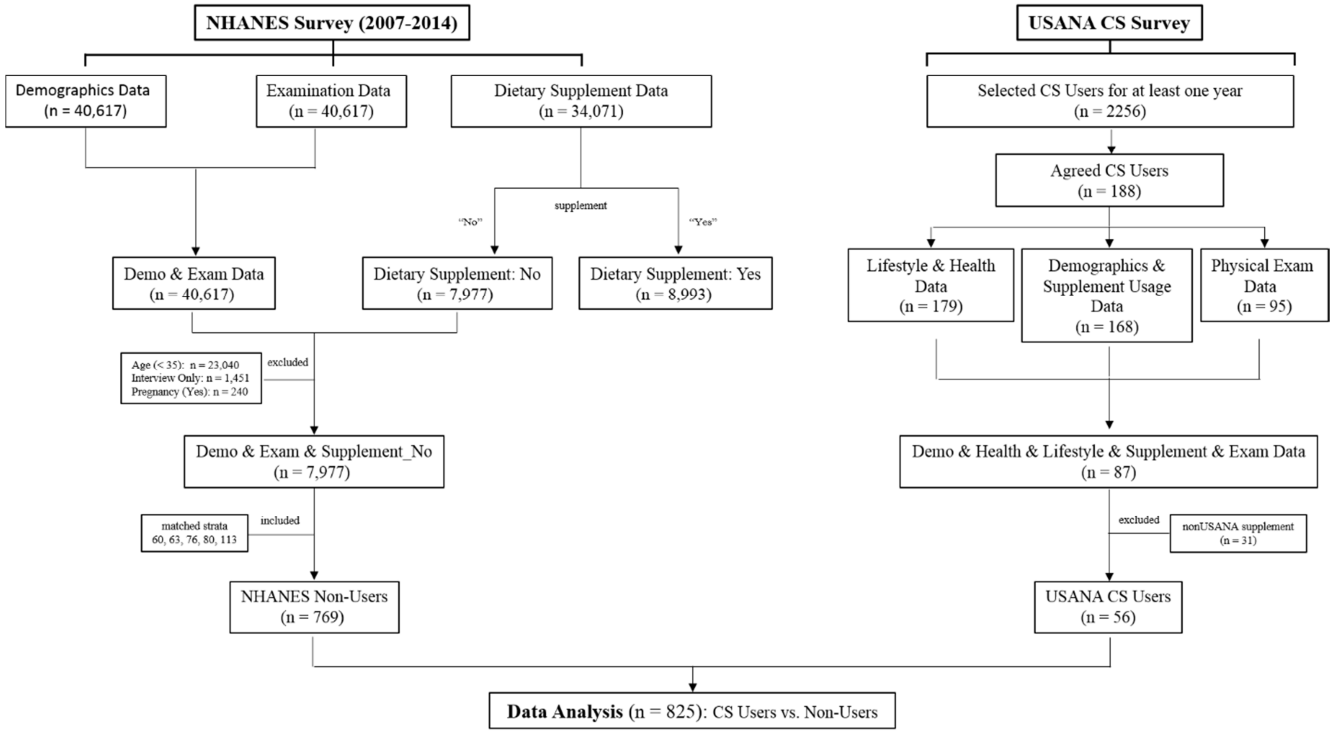


Figure 2. *Flow diagram of participants from USANA CellSentials survey and NHANES 2007-2014 survey.*

We identified 769 NHANES participants in five matched strata who did not consume dietary supplements, and served as the "Non-Users" in the analysis. Figure 2 describes the detailed sample identification and selection process.

2.3. Cardio-metabolic, OS and Inflammation Biomarkers

The following common cardio-metabolic risk factors as well as oxidative stress (OS) and inflammation biomarkers were studied in the current study: fasting blood glucose (Glu), blood lipid profile including total cholesterol (TC), triglycerides (TGs), high-density cholesterol (HDL-C)), low-density cholesterol (LDL-C), systolic/diastolic blood pressure (SBP/DBP); ratio of TC: HDL-C; Gamma-glutamyltransferase (GGT), C-reactive protein (CRP), and white blood cell (WBC) count.

2.4. Definition of the Cardio-metabolic Risk Factors

As commonly used in clinics, elevated blood pressure was defined as >=85 mmHg for diastolic and/or >=130 mmHg for systolic blood pressure or taking antihypertensive medications [41]. Elevated biomarker concentrations were defined as: >=100 mg/dL for fasting plasma glucose or any use of insulin or glucose-lowering drugs; >=200 mg/dL for TC or taking lipid lowering medications; >=130 mg/dL for LDL-cholesterol or taking lipid lowering medications; >=150 mg/dL for TG or taking lipid lowering medications; < 40 mg/dL for HDL-cholesterol for men and < 50 mg/dL for women or taking lipid lowering medications; >=5 for the ratio of TC to HDL-cholesterol, an indicator of dyslipidemia and correlate well with risk of cardiovascular disease [42].

2.5. Statistical Analyses

Data were analyzed using R 3.4.1. We conducted the analyses according to the guidelines recommended by the Centers for Disease Control for analysis of complex NHANES data set accounting for the masked variance and using the proposed weighting methodology [43]. Analyses included descriptive analyses, Pearson correlation tests, multiple linear and logistic regression. The unadjusted differences in means between user groups were tested using a two-sided independent sample t tests. Associations between categorical variables were tested using chi-square tests. Moreover, adjusted differences in means and odds ratios were estimated using multiple linear and logistic regression models, respectively. All P values were 2-sided; $P < 0.05$ was considered statistically significant after Benjamini-Hochberg correction for false discovery rate because of the number of hypotheses being tested.

After combining the USANA CS Users with matched Non-Users from NHANES, data were reweighted. The weights were calculated by combining the 8-year weights using the correct proportion of each, then the weights of the matched 5 strata of Non-Users were calculated by dividing each NHANES Non-User weight by the sum of the NHANES weights of that Non-Users group. Appropriate weights were used from the Mobile Examination Center. The CS Users were assigned a weight of 1. Strata and primary sampling units from NHANES were used for Non-Users group. For the CS Users, a new stratum variable was assigned, and each member of the USANA CS Users group was assigned to a unique primary sampling unit. These adjustments permit more accurate variance estimates and account for stratification factors. Because of skewed distributions of systolic blood pressure, fasting glucose, TC, HDL-C, TGs levels, as well as OS markers (GGT) and inflammation markers (CRP, WBC), ln-transformed values were used to improve normality and geometric means were presented when they were dependent variables. Multiple linear and logistic regression model was employed to examine the systolic/diastolic blood pressure and cardio-metabolic biomarkers concentrations adjusted for age, gender and ethnicity. Considering possible limited sample size for OS and inflammation markers, each potential confounding factor (age, gender and ethnicity) was examined separately in the models. Factors statistically significant at a=0.05 were evaluated in multivariable analysis with forward stepwise selection and covariates significant at a=0.05 were retained. Then correlations between significant markers of OS and inflammation were determined using Pearson's correlation.

3. Results

Ingredient of Cellsentials dietary supplement include multivitamins (vitamin A, C, E, D3, K, B1, B2, B3, B5, B6, B7, B9, B12), antioxidant nutrients (CoQ10, lutein, lycopene, Incelligence Complex with alpha lipoic acid, curcumin, green tea extract, quercetin dihydrate, rutin hesperidin and resveratrol), and core minerals (calcium, iodine, magnesium, zinc, selenium, copper, manganese, chromium, molybdenum, boron, silicon, vanadium, ultra-trace minerals and N-acetyl L-cycteine) (Table 1).

Table 1. *CellSentials Supplement facts list.*

US Vita Antioxidant		
Other ingredients: Microcrystalline Cellulose, Modified Starch, Croscarmellose Sodium, Silicon Dioxide, Ascorbyl Palmitate, Organic Maltodextrin, Vanilla Extract, Organic Sunflower, Lecithin, Organic Palm Olein, Organic Guar Gum.		
Supplement Facts		
Serving size: 2 tablets		
Amount per serving		**%DV**
Vitamin A (as 25% retinyl acetate, and 75% [4500IU] as beta carotene and mixed carotenoids)	6000 IU	120%
Vitamin C (as poly C blend: potassium, calcium, magnesium and zinc ascorbates)	200 mg	330%
Vitamin D3 (as cholecalciferol)	1000 IU	250%
Vitamin E (as D-alpha tocopheryl succinate)	100 IU	330%

US Vita Antioxidant		
Other ingredients: Microcrystalline Cellulose, Modified Starch, Croscarmellose Sodium, Silicon Dioxide, Ascorbyl Palmitate, Organic Maltodextrin, Vanilla Extract, Organic Sunflower, Lecithin, Organic Palm Olein, Organic Guar Gum.		
Supplement Facts		
Serving size: 2 tablets		
Amount per serving		**%DV**
Vitamin K (as K1 [phytonadione] and k2 [mk-7 menaquinone])	270 ug	340%
Vitamin B1 (as thiamin HCL)	15 mg	1000%
Vitamin B2 (as riboflavin)	15 mg	880%
Niacin (as niacinamide and niacin)	20 mg	100%
Vitamin B6 (as pyridoxine HCL)	16 mg	800%
Folate (as folic acid)	300 ug	80%
Vitamin B12 (as cyanocoalamin)	100 ug	1670%
Biotin	150 ug	50%
Pantothenic aci (as D-calcium pantothenate)	45 mg	450%
Mixed tocopherols (D-gamma, D-delta, D-beta tocopherol)	40 mg	†
Incelligence™ complex		
Alpha lipoic acid	50 mg	
Meriva bioavailable curcumin complex [curcuma longa l., root]	36 mg	
Green tea extract [camellia sinensis hunt., leaves]	35 mg	
Quercetin dihydrate	30 mg	
Rutin	20 mg	
Hesperidin [citrus spp. L., fruit]	20 mg	
Resveratrol	20 mg	
Olivol [olive fruit extract, olea europaea l., fruit]	15 mg	
Inositol	64 mg	†
Choline bitartrate	125 mg	†
Coenzyme Q10	6 mg	†
Lutein (tagetes erecta l., flower)	300 ug	†
Lycopene	500 ug	†

US Core Minerals		
Other ingredients: Microcrystalline Cellulose, Modified Starch, Croscarmellose Sodium, Ascorbyl Palmitate, Organic Maltodextrin, Pregelatinized Starch, Silicon Dioxide, Vanilla Extract, Organic Sunflower, Lecithin, Organic Palm Olein, Organic Guar Gum.		
Supplement Facts		
Serving size: 2 tablets		
Amount Per Serving		**%DV**
Vitamin C (as magnesium ascorbate and calcium ascorbate)	300 mg	500%
Calcium (as calcium citrate and calcium ascorbate)	112.5 mg	10%
Iodine (as potassium iodide)	250 ug	170%
Magnesium (as magnesium citrate and magnesium ascorbate)	112.5 mg	30%
Zinc (as zinc citrate)	10 mg	70%
Selenium (as L-selenomethionine and sodium selenite)	100 ug	140%
Copper (as copper gluconate)	1 mg	50%
Manganese (as manganese gluconate)	1 mg	50%
Chromium (as chromium polynicotinate)	150 ug	130%
Molybdenum (as molybdenum citrate)	25 ug	35%
Boron (as boron citrate)	1500 ug	†
Silicon (as calcium silicate)	2 mg	†
Vanadium (as vanadium citrate)	20 ug	†
Ultra trace minerals	1500 ug	†
N-acetyl L-cysteine	80 mg	†

† Daily Values not established.

Significant differences by user groups were found for gender, ethnicity and self-reported health status with more older-aged white females taking CS supplement. ($p < 0.001$) (Table 2). The CS users are marginally statistically older than Non-users ($p=0.055$). Also 91% USANA CS Users reported that they are healthy ($p < 0.001$). As shown in Table 2, mean biomarker values for CS users were significantly lower in SBP (119.1 vs. 127.4 mm Hg (-6.5%)), glucose (98.6 vs. 113.9 mg/dL (-13.4%)), TGs (122.4 vs. 161.5 mg/dL (-24.2%)), TC: HDL-C ratio (3.8 vs. 4.5 (-15.6%)) and higher in HDL-C (60.5 vs. 49.4 mg/dL (22.5%) compared to NHANES Non-Users. In addition, CS Users are higher in TC (212.5 vs. 200.3 mg/dL (6.1%)) than NHANES Non-users. There were no significant differences in DBP (72.9 vs. 72.2 (mm Hg) (1%)) and LDL-C (127.2 vs. 117.9 mg/dL (7.9%)).

Table 2. *Participant characteristics by dietary supplement use.*

	Overall	USANA CS Users	NHANES Non-Users	p Value
Participants	825	56	769	
Age (mean ± SE)	55.82 ± 0.48	58.83 ± 1.58	55.6 ± 0.5	0.055
Gender (% Female)	0.47	0.73	0.45	< 0.001
Ethnicity (%)				< 0.001
Hispanic	0.07	0.04	0.07	
Non-Hispanic Black	0.08	0.04	0.08	
Non-Hispanic White	0.82	0.79	0.82	
Other Race	0.03	0.14	0.02	
Health Status (%)				< 0.001
Excellent or Very Good	0.36	0.91	0.32	
Non-Fair or Poor	0.22	0.04	0.23	
Good	0.34	0.05	0.36	
Don't Know	0.08	0.00	0.09	
Systolic blood pressure (mmHg) (mean ± SE)	127.17 ± 0.71 (n=736)	119.12 ± 2.96 (n=24)	127.44 ± 0.73 (n=712)	0.011
Diastolic Blood Pressure (mm Hg) (mean ± SE)	72.26 ± 0.47 (n=736)	72.92 ± 1.9 (n=24)	72.24 ± 0.48 (n=712)	0.731
Glucose (mg/dL) (mean ± SE)	112.48 ± 1.99 (n=401)	98.6 ± 5.81 (n=36)	113.85 ± 2.1 (n=365)	0.018
Total Cholesterol (mg/dL)(mean ± SE)	200.88 ± 1.57 (n=764)	212.46 ± 5.31 (n=39)	200.26 ± 1.62 (n=725)	0.033
LDL Cholesterol (mg/dL) (mean ± SE)	118.7 ± 1.82 (n=384)	127.16 ± 4.43 (n=35)	117.85 ± 1.95 (n=349)	0.060
HDL Cholesterol (mg/dL) (mean ± SE)	49.86 ± 0.59 (n=760)	60.48 ± 3.18 (n=35)	49.35 ± 0.59 (n=725)	0.001
Triglycerides (mg/dL) (mean ± SE)	157.87 ± 6.19 (n=399)	122.39 ± 11.84 (n=37)	161.5 ± 6.69 (n=362)	0.006
Ratio of TC: HDL (mean ± SE)	4.42 ± 0.07 (n=760)	3.75 ± 0.19 (n=35)	4.45 ± 0.07 (n=725)	< 0.001

Next, adjusted mean differences of blood pressure and each biomarkers as well as their risk estimates (odds ratios) were calculated using multiple linear and logistic regression. The CS users showed significant decrease in geometric mean concentrations of fasting blood glucose ($p < 0.001$), TGs ($p < 0.001$) and mean of ratio of TC: HDL ($p < 0.001$), and significant increase in geometric mean concentration of HDL-C ($p=0.008$) compared to Non-users. However, there was no significant difference between two groups in levels of SBP, DBP and TC after Benjamini-Hochberg adjusted comparisons (Figure 3).

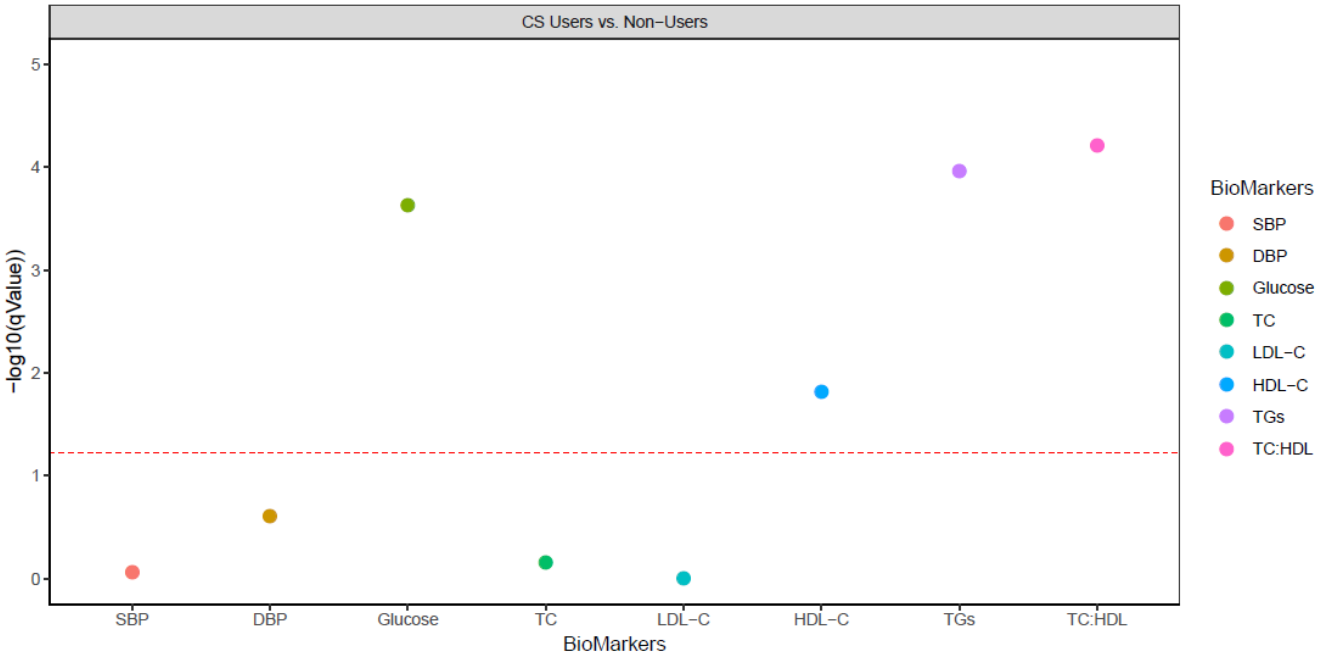


Figure 3. *Adjusted multiple linear regression methods to assess the associations of each cardio-metabolic risk factor with CellSentials use. The x axis represents cardio-metabolic risk factors; qValue represents p value after Benjamini-Hochberg adjusted comparisons, y axis represents –log10 (qValue) of each cardio-metabolic risk factor analysis. Red dashed line represents the cutoff statistical significance after Benjamini-Hochberg False Discovery Threshold at P=0.05 comparison. Dots above the red dashed line represent statistically significance.*

Adjusted risk estimates for elevated blood pressure and elevated concentrations of serum biomarkers are reported in Table 3. Correspondingly, CS Users had significantly reduced risks of elevated blood glucose (OR, 0.21; 95% CI, 0.07 - 0.61), ratio of TC: HDL-C (OR, 0.08; 95% CI, 0.02 - 0.31), TGs levels (OR, 0.07; 95% CI, 0.01 - 0.4), and significantly reduced risk of low HDL-C (OR, 0.23; 95%CI, 0.06 - 0.88). Risks of elevated BP, TC and LDL-C did not significantly

differ from Non-Users.

Table 3. *Risk of elevated cardio-metabolic factor levels by supplement user group.*

Outcome	Cases: n (%)	OR	95% CI
Elevated blood pressure (systolic ≥130 mm Hg, or diastolic ≥85 mmHg)			
CS Users	6/(25)	0.42	(0.05 - 3.22)
Non-Users	424/(59.6)	1.00	
Elevated fasting glucose (≥ 100 mg/dL)			
CS Users	9/(25)	0.21	(0.07 - 0.61) **
Non-Users	235/(64.4)	1.00	
Total cholesterol (>200 mg/dL)			
CS Users	26/(66.7)	0.39	(0.11 - 1.34)
Non-Users	438/(60.4)	1.00	
LDL-cholesterol (>130 mg/dL)			
CS Users	17/(48.6)	0.48	(0.18 - 1.3)
Non-Users	179/(51.3)	1.00	
HDL-cholesterol (<40 mg/dL for males, <50 mg/dL for females)			
CS Users	8/(22.9)	0.23	(0.06 - 0.88) *
Non-Users	376/(51.9)	1.00	
Triglycerides (≥150 mg/dL)			
CS Users	12/(32.4)	0.07	(0.01 - 0.4) **
Non-Users	184/(50.8)	1.00	
Ratio of total cholesterol to HDL-cholesterol (≥ 5)			
CS Users	7/(20)	0.08	(0.02 - 0.31) ***
Non-Users	324/(44.7)	1.00	

Adjusted odds ratios with 95% confidence interval of each cardio-metabolic risk factor by CS Users with Non-Users as a reference using multiple logistic regression analysis.
* P < 0.05; ** P < 0.01; *** P < 0.001.
CI, confidence interval; OR, odds ratio.

Lastly, we investigated relationships between CS supplementation and markers of OS and inflammation. After adjusting for relevant covariates, CS supplementation was associated with a decrease in CRP, GGT and WBC. The most striking inverse association was observed for the oxidative stress marker GGT, where CS supplementation was associated with a 47.7% decrease in blood GGT concentration (16.111 ± 1.273 vs. 30.799 ± 0.859 U/L, p=0.002). Additionally, CS supplementation was associated with a 25.2% and a 19.2% decrease in total WBC count (5.694 ± 0.29 vs. 7.617 ± 0.11 K/uL, p=0.002) and serum concentrations of CRP (0.366 ± 0.21 vs. 0.453 ± 0.03 mg/dL, p=0.007) respectively. (Figure 4). Next we calculated the Pearson correlation coefficients between significant OS marker GGT and significant inflammation markers CRP and WBC to test the correlations between OS and inflammation. GGT levels show a both positive correlation with increasing markers of inflammation CRP levels (r=0.31, p < 0.001) and WBC count (as a general parameter of the immune system state) (r=0.2, p < 0.001).

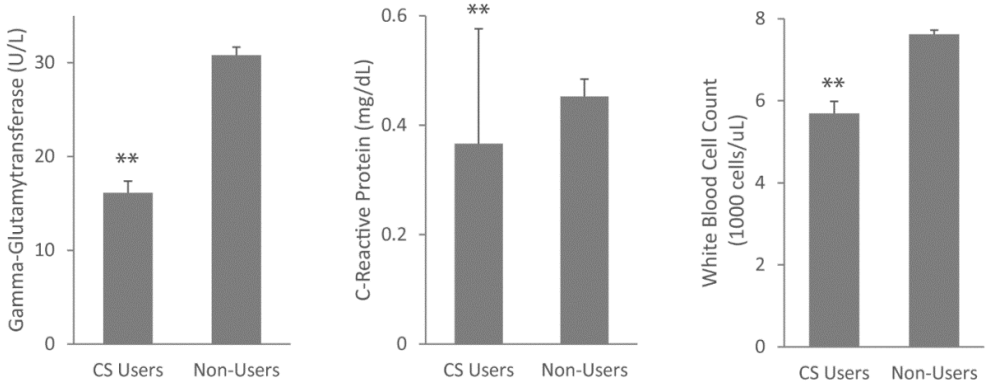


Figure 4. *Serum levels of gamma-glutamyl transferase (GGT), C-reactive protein (CRP) and white blood cell (WBC) count between CS supplement use and NHANES "Non-Users". **P < 0.01.*

4. Discussion

Overall, the results showed that CS supplement users were more likely to be older, female, White, which was consistent with the reports of US populations examined in the NHANES [14, 15]. Importantly, we found that individuals who use dietary supplements are healthier in the present study (Table 2). The CS users were observed to have significantly lower levels in glucose, TGs and ratio of TC: HDL-C as well as higher levels in HDL-C, with lower risk of elevated glucose, TGs, ratio of TC: HDL-C and reduced

HDL-C levels adjusted for age, gender and race. In addition, OS markers GGT values and inflammation markers CRP and WBC were observed to be lower in CS users.

The use of alternative therapies like herbs and dietary supplements is very common among hypertensive, diabetic (hyperglycaemic) and hyperlipidemic patients all over the globe [44]. In vitro and in vivo studies have shown that vitamins/minerals and phytochemicals have important roles in improving insulin sensitivity, insulin production/action, as well as carbohydrate, lipid and protein metabolisms, which collectively lead to the control of the excessive oxidative stress and pancreatic beta-cell dysfunction [31, 45, 46]. Vitamins, minerals and phytochemicals also promote the enhancement of endothelial function and the reduced production of growth factors such as angiotensin and endothelins, all of which are associated with the control of hypertension, hyperglycemia and hyperlipidemia [47-52].

We found that CS supplement use was associated with lower TGs and higher HDL-C concentrations with significantly lower risk of an elevated ratio of TC: HDL-C in supplement users (Tables 2 and 3, Figure 3). These results support common practice of using fish oil, vitamin E [53], vitamin D [54], vitamin B6 and B12 [55], folate [56], niacin [57], magnesium [58], zinc [59], chromium and biotin [60, 61], calcium and iron [62], selenium [63] and CoQ10 [64], in the dietary intervention of blood lipid profile.

Dietary MVMM have been shown to reduce blood pressure [65]. Dietary folate and vitamin C, as well as plasma ascorbic acid, have been found to be inversely associated with blood pressure in observational studies [66, 67]. Multiple nutrition components have been reported to be effective at lowering blood pressure including vitamin C [68], -D [54], -E [69], -B6 [70], -B12, folate [71, 72], niacin [73], thiamine [74], riboflavin [75], magnesium [58], iron [76], calcium [77] and CoQ10 [78]. Consistently, in the present study, significant reduction of SBP was observed in unadjusted analysis (119.12 ± 2.96 vs. 127.44 ± 0.73 mmHg, p=0.011) (Table 2). However, no significant reduction in risk of elevated BP was observed after controlling for age, gender and race (OR, 0.42; 95% CI, 0.05 – 3.22) (Table 3). It is possible that the non-significant result is due to the small sample size (only 24 participants have SBP/DBP values in the CS user group in the present study) and the resulting large variation.

The study showed significant lower levels of glucose as well as correspondingly lower risk of elevated glucose level in USANA CS users (Tables 2 and 3, Figure 3). This is consistent with previous studies that showing folate [79], vitamin E [80], -C [81], -B6 [82], -B12 [83], niacin [84], thiamine [85], magnesium [58], chromium [60], zinc [86] and copper [87, 88] have some beneficial effects on insulin action, glycaemic control and endothelial function. Notably, a meta-analysis of 18 trials with 21,081 subjects reported that folate supplementation significantly decreased glucose level [79].

CS supplement is rich in antioxidant nutrients including vitamins C and E, CoQ10, lutein, lycopene, alpha lipoic acid, curcumin, green tea extract, quercetin dihydrate, rutin hesperidin and resveratrol. Cardiometabolic diseases are closely-associated with oxidative stress and inflammation. As expected, we were able to show that CS supplementation significantly reduced serum GGT, the oxidative stress biomarker, and CRP level and WBC counts, two inflammation markers (Figure 4) GGT is a transferase that catalyzes the transfer of gamma-glutamyl functional groups. It plays a key role in the synthesis and degradation of glutathione (GSH), which is the most abundant thiol in animal cells and is critical in preventing damage to cellular components caused by reactive oxygen species (ROS) such as free radicals and peroxides. Evidences from previous studies suggests that GGT levels correlate positively with cardiovascular risk factors such as CRP and inversely with antioxidant levels [89, 90]. The function of serum CRP (C-reactive protein) is to bind to the lysophosphatidylcholine on the surface of dying/degenerating cells, activating the complement system to promote phagocytosis by macrophages. Recent researches have established that elevated basal levels of CRP are associated with various risks of cardiometabolic diseases.

Our study did not address the mechanisms of how antioxidant nutrients may decrease oxidative stress and inflammation, but numerous previous studies have established that there are multiple ways. Antioxidants, including lipoic acid, carotenoids, lutein, lycopene, vitamin C, vitamin E, and flavonoids, can directly bind to ROS and terminate free radical chain reactions, thus protect DNA, protein, and lipids from ROS attacks and subsequent oxidative stress. Antioxidant nutrients and their metabolites, may also be capable of regulating antioxidant enzymes activities therefore balance of oxidation-reduction reaction. For example, curcumin can induce and increase antioxidant enzymes activities including glutathione peroxidase and glutathione S-transferase. Further, antioxidant nutrients can regulate pro-inflammation cell signaling pathways. An important target is nuclear factor kappa B (NF-kB) and IkB kinase and downstream inflammatory cytokine/chemokine signaling pathways that can be inhibited by curcumin, CoQ10, and catechins [32, 34, 91].

The study has limitations. The datasets relied on self-reported measures of dietary supplement use, which is subject to recall bias, and over or under reporting. Second, although the present study adjusted for some potential confounding variables, residual confounding or confounding from unknown or unmeasured factors cannot be completely excluded. The results could be confounded by unmeasured biological and genetic factors. Third, due to the most recent physical examination document was used for biomarkers in the present study, the examination time and location/center varied, therefore, there are fewer samples available for analysis for these biomarker outcome measures, in addition, there was no access to other commonly used serum antioxidants such as vitamin C and E. Studies with greater sample sizes may prove more informative. Fourth, this is a cross-sectional observation, therefore the reported

associations, cannot presume causality. Further studies are needed to confirm the effectiveness of the product, as well as understand the biological mechanisms underlying the observed associations.

5. Conclusion

The findings from the present study demonstrate that blended dietary multivitamins/multiminerals and antioxidants nutrients supplement improve cardio-metabolic biomarker levels and is associated with lower risk of hyperglycemia and hyperlipidemia. Further studies using well-designed longitudinal cohort studies and randomized placebo-controlled trials, are warranted to provide stronger evidence and establish causal inference.

Abbreviations

MVMM (multivitamins/multiminerals), CS (CellSentials), systolic and diastolic (SBP and DBP), glucose (Glu), total cholesterol (TC), triglycerides (TGs), high-density cholesterol (HDL-C), low-density cholesterol (LDL-C), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), white blood cells (WBC), OS (Oxidative Stress), National Health and Nutrition Examination Survey (NHANES)

Author Contributions

H. J., R. L. M. and R. A. S. conceived and designed the study. H. J. analyzed the data. H. J. wrote the manuscript. H. J. and R. L. M. edited the manuscript. All authors have read and approved the final manuscript.

Funding

This research is funded by USANA Health Sciences, Inc.

Conflicts of Interest

H. J., R. L. M. and R. A. S. are employed by USANA Health Sciences, Inc. The authors declare that they have no competing interests.

Acknowledgements

We thank Marie Mullen for her assistance in performing the survey.

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