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Lutein and Zeaxanthin Isomers Effect on Sleep Quality

Melinda Fernyhough Culver[1], James Bowman[2] and Vijaya Juturu*[1]

[1]*OmniActive Health Technologies Inc. Morristown, USA*

[2]*James P Bowman & Associates LLC, USA*

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***Corresponding author:** Vijaya Juturu, Omni Active Health Technologies Inc, Morristown, New Jersey, USA

Abstract

Purpose: Sleep deprivation can have serious consequences, including, but not limited to, decreased cognitive performance, work productivity, immune function, and increased obesity risk. Macular carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) increase macular pigment and may reduce photo-oxidative stress by blocking blue light and through antioxidant action. This study evaluates the effect consumption of a dietary supplement containing lutein, zeaxanthin, and meso-zeaxanthin for six months on sleep quality using the Pittsburg Sleep Quality Index (PSQI) questionnaire in healthy young adults exposed to daily use of electronic devices and out side activities.

Patients and Methods: This was a double-blind, placebo-controlled randomized (DBPCR) study in 48 healthy young adults (age 18-25 y, males and females, non- smokers, body mass index <27 kg/m^2). Inclusion criteria included daily minimum of 4 h screen time exposure from electronic devices combined with 2-3 h outdoor activity. Subjects were randomly assigned to ingest daily either a placebo (PLA, safflower oil), or 24 mg lutein and Zeaxanthin isomers, L/Zi; 20 mg L/4 mg Zi). Macular pigment optical density (MPOD), serum melatonin, serum lutein and zeaxanthin were analyzed, and sleep quality assessed using the using the PSQI questionnaire. Total sleep scores and sleep subgroup scores at the beginning and the end of the study were recorded and compared between groups. Statistical significance was set at $p < 0.05$.

Results: There was a significant reduction of the overall sleep score of the L/Zi treatment group compared with the placebo group ($p < 0.05$), indicating an improvement in sleep quality. A significant increase in MPOD, serum lutein, and zeaxanthin were observed compared to the placebo treatment ($p < 0.05$). A trend was observed for increased melatonin ($p < 0.1$) in the L/Zi treatment group compared with the placebo group.

Conclusion: The results of the current study show that supplementation with L/Zi had a significant effect on sleep disturbance, daytime dysfunction, medication requirement for sleep, and quality of sleep.

Abbreviations: MDOP: Macular Pigment Optical Density; PSQI: Total Sleep Score; HPLC: High-Performance Liquid Chromatography; PSQI: Pittsburgh Sleep Quality Index; MDOP: Macular Pigment Optical Density; MPOD: Macular Pigment Optical Density

Introduction

An estimated 50–70 million Americans suffer daily from sleep disorders. Billions of dollars are spent each year on sleep-related issues, inclusive of both direct and indirect costs. Sleep quality contributes to the development of chronic conditions and sleeplessness (insomnia) has been associated with diabetes, coronary heart disease, obstructive sleep apnea, arthritis and, muscle pain (myalgia) as well as other chronic diseases [1]. In addition to the health implications, insomnia and sleep deprivation is costly. In fact, it is estimated that lack of sleep costs the U.S. almost 2.3 % of the gross domestic product - more than $400 billion in 2016 [2]. But this value includes only the indirect costs through the loss of productivity; it is the direct treatment costs, such as physician encounters and prescriptions, that make this number conservative.

The Centers for Disease Control has estimated that over one-third of adults in the U.S. get fewer than 7 h of sleep per night. Furthermore, university and college students are likely to have poor sleep quality and fatigue affecting academics, quality of life, and psychological well-being [3]. Lutein and zeaxanthin are two of the most abundant carotenoids present in the diet – they are the pigments responsible for the bright yellow, red, and orange colors of many fruits and vegetables. Lutein and zeaxanthin are isomers that

differ by the location of a single double bond [4]. Supplementation with lutein and zeaxanthin has been shown to increase circulating and tissue levels of these xanthophylls and are potent anti-oxidants that also act as filters of high-energy blue light. Thus, these xanthophylls are reported to be protective against photo-induced oxidative damage, particularly in highly exposed tissues such as the skin and eyes.

The visible light spectrum is composed of wavelengths of light from about 390 nm to 700 nm with short, high energy wavelengths at the lower end and long, low energy at the upper end of the range. Violet - blue light (high-energy blue light) ranges from around 400 – 500 nm and is known to be damaging. Blue light is capable of inducing photo-oxidative damage through generation of ROS and it requires 100 times less energy to cause damage to tissues compared to orange light (590 nm) [5]. The ability of carotenoids, such as lutein, zeaxanthin isomers, β-carotene, and lycopene, to function as blue light filters has been evaluated using a unilamellar liposome model, in vitro [6]. Lutein, zeaxanthin, and meso-zeaxanthin (macular carotenoids) are known to deposit in the macula (yellow spot) of the retina and function to protect the retina at a spot where light is concentrated – the area of visual acuity – through their ability to act as a powerful antioxidant and oxygen singlet quencher. For example, in rhesus monkeys deprived of dietary xanthophyll's during their lifetime, supplementation with either lutein or zeaxanthin at 2.2 mg/kg body weight/day for 22 to 28 weeks resulted in less damage in the fovea following blue light exposure compared to non-supplemented animals [7].

Moreover, the sensitivity to damage in these supplemented animals did not differ from those observed in control animals fed a standard diet throughout their lifetimes. Electronic devices such as smartphones, tablets, computers, and televisions all emit a high amount of blue light. Blue light that is emitted from electronic devices screen can delay the release of melatonin, increase alertness, and reset the body's schedule (circadian rhythm) [8-11]. This can be a particularly big problem for children, teens, and college students causing them to feel sleep-deprived or poorly rested and loss of attention [12-18]. Light from compact fluorescent bulbs and LED also have a large blue light component and can produce similar effects.

One method to combat sleeplessness is using herbal supplements such as valerian root extract or chamomile tea [19-21]. However, these supplements are not without their side effects. For example, Kava has been linked to hepatotoxicity [22]. Another method might be to supplement melatonin. Tart cherry juice concentrate provides an increase in endogenous melatonin that is beneficial in improving sleep quality and might be of benefit in managing disturbed sleep [23]. The ingestion of a Jert valley cherry product may contribute to establishing a high-quality sleep with the advance of age [24]. Other dietary supplements that have been considered include 5-hydroxytryptophan, which potentially gives rise to L-tryptophan, in addition to melatonin itself [25-27]. It is thought these compounds might act through growth-hormone releasing hormone [28]. Despite recent reports that suggest herbal preparations may improve sleep quality, limited controlled data are available. In the present study, we tested the effect of L/Zi dietary supplement containing the active ingredients lutein, zeaxanthin, and meso-zeaxanthin on sleep quality using the PSQI questionnaire.

Material and Methods

Methods

Fifty-one young (18-25 y, M/F), healthy, non-smoking participants were recruited for this randomized, double-masked, placebo-controlled trial. Subjects were randomly assigned into either a supplement group (20 mg L and 4 mg Zi; L/Zi, Lutemax 2020®; n = 35) or a placebo group (PLA; n = 13) for 6 months supplementation. Subjects were requested to avoid carotenoid rich diets including lutein/zeaxanthin isomer rich foods and instructed to follow the dietary restriction list provided during the study period. Subjects were requested to complete the food diaries/records. This study was reviewed and approved by the University of Georgia Institutional Review Board. Informed signed consent was obtained for each subject, and the study adhered to the tenets of the Declaration of Helsinki [ISRCTN #16156382].

Subjects

Potential participants completed a short questionnaire to determine eligibility for the study. Subjects were required to be exposed to blue-light from screen time for a minimum of 4 h/d with an additional requirement of 2-3 h of outside activity/d. These requirements were selected to assure a minimum level of blue light exposure. Additional requirements included at least one or more of the following computer vision symptoms: digital eyestrain, eye fatigue, blurry vision, difficulty focusing, dry and irritated eyes, headaches, and neck and/or back pain. Participants were in good general health, had corrected visual acuity of 20/20 or better, and were not taking medication that may interfere with sleep patterns. The subjects were also screened to ensure the viewing of screens at 3 feet or less and had no current or previous history of ocular pathology. Subjects wearing corrective glasses were not considered for the study primarily because of the potential interference with glare testing from reflection and coating-mediated light absorption of the glass' lenses. Subjects were instructed to maintain their current diet; those that were planning on changing their diet for any reason were excluded from consideration for the trial.

Those persons with a body mass index of 28 or greater were excluded as supplemental lutein may be deposited preferentially in adipose tissue instead of the retina. Due to the potential for saturation, those with a macular pigment optical density (MPOD) of 0.70 or higher were excluded. Subjects were also excluded if they had ocular disease or insufficient visual acuity – a visual acuity of 20/30 corrected was the cutoff for exclusion. Subjects with systemic or chronic diseases (e.g. diabetes), psychiatric medication and any medication to treat a psychiatric condition (e.g. obsessive-compulsive disorder, depression, bipolar disease and schizophrenia) and smokers were excluded. Data were collected on case report forms by the investigators and entered a data base. Subjects were instructed to ingest one pill with a meal (preferably lunch or din-

ner) every day. Compliance was ensured with weekly phone calls and pill counts.

Macular Carotenoid Supplementation

Subjects were randomly assigned to either placebo (n = 13) or MC supplement (L/Zi, n = 35) groups. Pills for each group were identical, brown-colored, soft gelatin capsules. PLA contained only safflower oil without L and Zi. Independent analysis indicated that the active supplement pills (Lutemax 2020®) contained 20 mg of Lutein (L), and 4 mg Zeaxanthin isomers (Zi, zeaxanthin and meso-zeaxanthin), obtained from the extract of dried flowers of Marigold (Tagetes species) supplied by OmniActive Health Technologies Ltd, India.

Macular Pigment Optical Density (MDOP)

Macular pigment optical density was assessed with a non-invasive method previously described by Stringham et al. [29]. In short, subjects are presented with two alternating lights of different wavelengths giving the impression of a flickering disc of light. The subject's task is to adjust the brightness of the two lights until the flicker is perceived to be reduced to a minimum or disappear. MPOD was measured at baseline, 3 months, and 6 months.

Sleep

Sleep quality of participants was assessed by the PSQI. The PSQI is a self-rated questionnaire which measures subjective sleep quality and disturbances over the past month and differentiates between normal and poor sleepers. In this questionnaire, 19 questions are grouped into 7 components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) each having score range from 0 (no difficulty) to 3 (severe difficulty). The questionnaire is scored by tallying the numerical scores in each category. Higher scores are reflective of sleep disorders with a score > 5 indicative of sleep disturbances. The overall PSQI score was calculated and score >5 was considered as disturbed or poor sleep [30]. Sleep questionnaire was administered at baseline, 3 months, and 6 months.

Electronic Device Questionnaire

During each visit (baseline, 3 months, and 6 months), participants completed a short questionnaire asking about the weekly frequency of five outcome variables typically associated with excessive near-field device use: headache, blurry vision, neck strain, eye strain, and eye fatigue. The scoring of the questionnaire was as follows: when symptoms occurred less frequently than once/week but still occurred monthly (e.g. twice/month) then participants were instructed to write down the monthly frequency next to the item. For calculation purposes, a month was considered four weeks; monthly frequency was simply divided by four to yield a weekly value.

Blood Markers

Blood markers (melatonin, lutein, and zeaxanthin) were analyzed at baseline and 6 months. Serum melatonin was assayed using an ELISA assay kit for detection of melatonin in saliva, serum, plasma, and fruit homogenates (ENZO Ultra-Sensitive Melatonin ELISA kit part # ENZ-KIT150-0001). Serum levels of lutein and zeaxanthin were analyzed by high-performance liquid chromatography (HPLC) as previously described. Briefly, sample extractions and analyses were completed under yellow light. Serum proteins were precipitated with an equal volume of ethanol containing an internal standard. After centrifugation, samples were extracted with n-hexane by mixing and centrifugation. Organic layers were pooled and evaporated with nitrogen and re-suspended in the mobile phase. A reversed-phase YMC C [30] column (4.6 250 mm, 5-mm particle size) was used and a volume of 100 mL was injected for each of the serum samples. Detection wavelengths were 447 nm for lutein and 450 nm for total zeaxanthin.

Statistical Analysis

The primary analyses were conducted according to intent-to-treat principles. The statistical power rate $1-\beta$ was set at 0.80; a 20% change in visual performance or physical indicator status in treatment groups, a standard deviation of 20%, and $\alpha = 0.05$ were parameters used for calculation. With the placebo group set at n = 12, the power calculation determined that the treatment group required 30 subjects than needed to detect effects (if present). We recruited additional subjects for the study, assuming some attrition. For each attribute, such as MPOD, serum lutein, serum zeaxanthin, melatonin, total sleep score (PSQI) and sub score categories, the pre/post differences were compared within the treatment groups using a two-sided, two-sample Student's t-test. The effect on other variables of interest was tested using Student's test for all continuous variables and Fisher's exact test for categorical variable. All statistical tests of hypothesis employed a level of significance of $\alpha = 0.05$ and no adjustments were made for the number of tests performed. Analysis was performed using SAS (SAS System for Windows, Version 9.4, SAS Institute, Inc., Cary, N.C., 2002-2008).

Results

Baseline Characteristics

Subject's ages ranged from 18-25 y and included both males and females [PLA: 5/8 and L/Zi: 16/19]. Electronic devices used in both treatments [electronic devices, PLA/L/Zi: 73%/72% used computers, 13.1%/13 used smart phones and 14%/14.7% watching television. No significant differences were observed between groups. This study was conducted in a U.S. population.

Macular Pigment Optical Density (MDOP)

Supplementation of L/Zi significantly increased MPOD compared to PLA group. No significant changes were observed in PLA group (Table 1).

Blood Markers

L/Zi supplementation significantly increased serum lutein and zeaxanthin compared to PLA placebo ($p < 0.05$). Significant decreases in serum lutein were observed in PLA group compared to baseline (-13.8%) but no significant change in zeaxanthin was observed (19.9%; Table 1). L/Zi supplementation increased serum melatonin with a significant trend over baseline ($p < 0.1$) but was

not significantly increased over PLA. No significant changes were observed in PLA group (Table 1).

Sleep

The average PSQI was significantly different at 3 months (60%, $p < 0.05$, Table 1) with a nonsignificant improvement at 6 months (71.43%, $p < 0.1707$) in subjects with L/Zi supplementation compared to PLA. Mean sleep disturbances, latency, day time dysfunction, subjective sleep quality and subjects need meds decreased in L/Zi. Additionally, significant improvements over baseline were noted in the L/Zi supplemented group at 3 months ($p = 0.0006$) and 6 months ($p = 0.0077$, Table 1). Supplementation with L/Zi improved the incidence of sleep disturbances at 3 months (a trend $p<0.1$ over placebo) and 6 months ($p = 0.0016$, $p = 0.0002$) respectively and daytime dysfunction ($p = 0.0700$; $p = 0.0327$, Table 1) over baseline values at 3 and 6 months (Table 1). A significant improvement in the need for sleep medication was observed in L/Zi treatment over placebo at 3 months ($p = 0.0232$) and 6 months ($p = 0.1707$). No significant improvements were noted in placebo over baseline or treatment ($p > 0.05$; Table 1) Compared to baseline, a marked improvement in total sleep quality was observed in the supplementation group at 3 months (60%) and 6 months (71.43%), respectively. Additionally, there was an improvement in sleep disturbances, daytime dysfunction, habitual sleep, efficiency category, subjective sleep quality, and medication requirements of the PSQI questionnaire, with most category scores improving approximately 9-34% after intervention.

Table 1: Mean ± SD of MPOD and PSQI data at baseline and after 3 and 6 mo supplementation.

Details	L/Zi			Placebo		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Mpod	0.38±0.13	0.41±0.14	0.44±0.14**	0.37±0.12	0.37±0.1	0.38±0.12
Melatonin, Ng/Ml	0.169± 0.35		0.853±2.06##	0.998±2.17		1.325±3.56
Serum Lutein	0.18±0.09		3.13±0.70**	0.20±0.17		0.18±0.14*
Serum Zeaxanthin	0.03±0.02		0.46±0.09**	0.04±0.04		0.04±0.03
Sleep Components						
Sleep Duration	0.54±0.66	0.54±0.61	0.51±0.61	0.62±0.65	0.62±0.65	0.54±0.52
Sleep Disturbances	0.86±0.49	0.60±0.55*	0.51±0.61#	0.92±0.49	0.85±0.69	0.85±0.55
Sleep Latency	0.89±0.72	0.83±0.62	0.77±0.65	1.00±0.58	0.85±0.55	0.85±0.55
Daytime Dysfunction	0.69±0.63	0.49±0.51##	0.49±0.56*	0.92±0.76	0.92±0.64	1.00±0.71
Habitual Sleep Efficiency	0.57±0.61	0.60±0.55	0.66±0.64	0.69±0.48	0.85±0.69	0.92±0.49##
Subjective Sleep Quality	0.69±0.47	0.57±0.56	0.54±0.66	0.85±0.55	0.92±0.49	0.77±0.60
Need Meds	0.49±0.98	0.29±0.57**	0.31±0.63	0.38±0.65	0.69±0.75	0.46±0.66
Total Sleep	4.74±2.11	3.89±1.55**	3.80±2.08*	5.46±2.07	5.69±2.69	5.38±2.02

*statistically significant difference from baseline, $p \leq 0.05$

**statistically significant difference over placebo, $p \leq 0.05$

#Trend of significance over placebo, $p<0.1$

##Trend of significant difference from baseline ($p < 0.1$)

Sleep Components based on Pittsburgh Sleep Quality Index (PSQI) Questionnaire.

Table 2: PSQI of subjects at 3 and 6 months of supplementation (change from baseline).

Sleep Components	L/Zi		Placebo		Between-Treatment T-Test (P-Value)	
	3 months	6 months	3 months	6 months	3 months	6 months
Sleep duration	0.00 (>0.5000)	-0.03 (>0.5000)	0 (>0.5000)	-0.08 (0.3370)	0 (>0.5000)	0.05 (>0.5000)
Sleep disturbances	-0.26 (0.0016)*	0.00 -0.34	-0.08 (>0.5000)	-0.08 -0.337	-0.18 -0.313	-0.27 -0.0677
Sleep latency	-0.06 (>0.5000)	-0.08 -0.11	-0.15 -0.4363	-0.15 -0.4363	0.1 (>0.5000)	0.04 (>0.5000)
Daytime dysfunction	-0.20 (0.0700)	-0.15 -0.20	0 (>0.5000)	0.08 (>0.5000)	-0.2 -0.3944	-0.28 -0.1857

Habitual sleep efficiency	0.03 (>0.5000)	0.00 0.09	0.15 -0.4363	0.23 -0.0821	-0.13 (>0.5000)	-0.15 -0.4061
Subjective sleep quality	-0.11 (0.2540)	0.15 -0.14	0.08 -0.337	-0.08 -0.337	-0.19 -0.264	-0.07 (>0.5000)
Need meds	-0.20 (0.0897)	0.08 -0.17	0.31 -0.1039	0.08 -0.337	-0.51 (0.0232)**	-0.25 -0.1708
Total sleep	-0.86 (0.0006)*	-0.94 (0.0077)*	0.23 (>0.5000)	-0.08 (>0.5000)	-1.09 (0.0253)**	-0.87 (0.1707)
*statistically significant difference from baseline ($p \leq 0.05$) **statistically significant difference over placebo ($p \leq 0.05$)						

Discussion

In the current study, supplementation of L/Zi improved MPOD and an increase in MPOD has previously indicated an improvement in visual function. These improvements in vision are likely due to their preferential absorption of high energy short-wave blue light as these xanthophylls protect the macula from damage through their antioxidant and photo-protective activities. Furthermore, the results from the PSQI questionnaire suggest that an improvement in MPOD may also improve sleep patterns. Today, more people than ever before spend time under energy efficient lighting, working in front of computers, interacting with smartphones and watching television – all of which emit high energy blue light. However, electronic devices have been shown to reduce sleep quality and affect visual function and the use of electronic devices and high screen usage independently increase the likelihood of sleep deprivation.

Despite emitting substantially less blue light than natural sunlight, this dramatic rise in electronic usage begins to pose problems. Estimates from population studies indicate that the average American spends more than 10 hours per day viewing screens and this is only increasing [31]. A recent survey reported that 9 out of 10 Americans reported using a technological device in the hour before bed with among those respondents under 30 years old, smartphones were the most popular device. This has led to an alteration of this groups' natural sleep patterns [32]. The most common complaint was a delayed bed time and shorter sleep [33]. One potential reason for this is the blue light that is emitted from these devices and the inhibitory effect it has on melatonin release. The monetary repercussions from sleeplessness are vast and are not only localized to the United States.

Some common foodstuffs have been shown to improve sleep when consumed. For example, the consumption of 2 kiwi fruits 1 h before bedtime daily for 4 weeks significantly increased total sleep time and sleep efficiency as measured by sleep actigraphy in adults with self-reported sleep disorders [34]. Age-related changes in sleep propensity are clearly related to a reduced circadian signal opposing the homeostatic drive for sleep. The high antioxidant capacity of kiwifruit may also reduce oxidative damage and consequently improve sleep quality [34]. The consumption of 8 ounces of tart cherry juice in the morning and nighttime for 2 weeks was associated with a significant reduction in insomnia severity and WASO in adults with chronic insomnia [35]. Tart cherries have also been shown to exhibit anti-inflammatory characteristics that may be beneficial in improving sleep quality [36]. In the current study, we restricted fruits and vegetable rich in macular carotenoids. However, with L/Zi supplementation we observed an improvement in the total sleep at 3 months (60%) and 6 months (71.43%), respectively. One possibility for this might be the blue light filtering action of the macular carotenoids – the absorption of which would allow for production and release of melatonin from the pineal gland.

Moderie et al reported a late circadian phase, a slow build-up of sleep need, and an increased circadian sensitivity to blue light contribute to the complaint of a delayed sleep schedule [37]. Another study combined bright light and melatonin treatment to improve subjective daytime sleepiness, fatigue, and cognitive function over 3 months [38]. Recent studies demonstrate a negative relation between use of technology and sleep, suggesting that recommendations on healthy media use could include restrictions on electronic devices [39-42]. In the current study, subjects were recruited who had a minimum exposure to digital screens of 4 h / day with an additional 2-3 h of daily outside activity. This was done to ensure adequate exposure to blue light (much of which comes from sunlight). Furthermore, 70 % of the subjects in our study reported using multiple electronic devices every day.

At least one physical indices of electronic device use – or so-called computer vision symptoms – were required for this study. This included eyestrain, eye fatigue, blurry vision, difficulty focusing, dry and irritated eyes, headaches, and neck and or back pain. Supplementation with L/Zi increased serum lutein and zeaxanthin, MPOD, and serum melatonin in our study. Since these attributes are somewhat correlated (improvement in one usually means improvement for others), and the results at 3 months are usually correlated to the results at 6 months Macular pigment is composed of the macular carotenoids lutein, zeaxanthin, and meso-zeaxanthin and is mostly present at the nerve fiber and ganglion cell layers of the retina, with peak concentrations in the fovea. It is thought to function as a blue-light filter and antioxidant.

This study was conducted on healthy young individuals without sleep disorders or intake of substances that are known to cause sleep-disorders (e.g. alcohol, smoking). The monitoring of several factors such as daily outside activity and electronic device use (televisions, computers, smart phones, laptops, etc.), physical activity, food intake before and after intervention, as well as lutein and zeax-

anthin serum levels pre and post intervention allowed for determination of the direct impact of L/Zi supplementation on sleep.

There were few limitations of this study. This was a sub-chronic study (6 months) in young healthy subjects, therefore, the long-term effects of L/Zi supplementation on sleep quality is not known. Additionally, the influence of L/Zi supplementation on older people or those with concurrent diseases or sleep pathologies are unknown. It is suggested that additional studies consider larger sample sizes as well as increased intervention period on people with lower intake of macular carotenoids in diet in aging and sleep quality with and without chronic conditions.

Conclusion

These results suggest that supplementation with macular carotenoids (L/Zi) improve overall sleep quality and sleep components such as sleep disturbances, daytime dysfunction, habitual sleep efficiency, subjective sleep quality and need for medications.

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Author Contributions

VJ participated in study design, discussion and coordination, drafted and reviewed the manuscript. MC drafted and reviewed the manuscript. JB performed the statistical analysis. All authors read and approved the final manuscript.

Disclosure

a. Funding: Omni Active Health Technologies Ltd., India.

b. Disclosure: VJ and MC are employees and scientists of Omni Active Health Technologies Inc. NJ USA. The authors report no conflicts of interest in this research work.

c. Ethics approval: This study was approved by the Research Ethics Committee, University of Georgia.

d. ORCID: http://orcid.org/0000-0002-7397-715X

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