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Dietary Supplementation For Prevention And Treatment Of Noncommunicable Diseases In Southeast Asia: A Selective Review

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Abstract: ***Southeast Asia has undergone momentous changes in the last 50 years. Average life expectancy in the region reached 71 years in 2013, socioeconomic status is rising (although great disparities persist between and within countries), and almost half of Southeast Asians now live in urban areas, a figure expected to increase to 64% by the year 2050. Laudable successes in preventing and treating infectious diseases have caused public health efforts to shift toward addressing the growing impact of noncommunicable diseases (NCDs), the most important of which are cardiovascular disease, chronic obstructive pulmonary disease, cancer, and diabetes. Rising life expectancy will increase the burden of such diseases, and increases in affluence and urbanization in the region are responsible in part for deterioration in the quality of local diets, a critical factor in the development of NCDs. Although encouraging consumption of a healthful diet will be useful in preventing NCDs, it is unlikely that public education campaigns will suffice to persuade at-risk individuals to satisfactorily modify their dietary behaviors. Thus, other alternatives for health maintenance and NCD prevention should be investigated. This review discusses recent research on selected dietary supplements that might be useful in preventing and treating NCDs.***

I. INTRODUCTION

Southeast (SE) Asia is a diverse and rapidly changing region of the world. Life expectancy at birth in the region has increased from an average of 55 years in 1970 to 71 years in 2013, and the current overall population of about 621 million is expected to grow to 833 million by 2050, an increase of 34% [1]. Socioeconomic status is increasing throughout SE Asia but varies greatly by country. In 2014, the estimated gross domestic product (GDP) based on purchasing-power-parity per capita GDP in current international dollars ranged from 3,263 dollars in Cambodia to 82,762 dollars in Singapore, a greater than 25-fold difference [2]. After Africa, Asia is the most rapidly urbanizing area of the world. In SE Asia the percentage of people living in an urbanized area rose from 32% in 1990 to 47% in 2014 and is expected to increase to 64% in 2050. Urbanization is likely to be particularly rapid in Indonesia, the Lao People's Democratic Republic, and Thailand [3].

SE Asia is in the midst of an epidemic increase in noncommunicable diseases (NCDs) [4]. The most important NCD types are cardiovascular disease (CVD), cancer, chronic pulmonary disease, and diabetes, but the classification includes many other conditions, such as hypertension, chronic kidney disease, osteoarthritis, and dementia. A number of factors are responsible for the rise in NCDs. Successes in combating infectious diseases and the resulting increase in life expectancy throughout the region have increased the numbers of individuals affected by NCDs, as most such conditions are related to aging. In addition, increasing affluence and urbanization in SE Asia are responsible in part for declining dietary quality, an important modifiable risk factor for NCDs [5]. Worrying dietary trends in urban SE Asian populations include high intakes of salt and sugar, greater reliance on convenience food, and low intakes of fresh vegetables and fruits [4,6].

In light of the trends associated with growing affluence, urbanization, and increased life expectancy in SE Asia, might dietary supplementation with micronutrients, phytochemicals, and other nutrients decrease disability and death due to NCDs among vulnerable populations? If so, what supplements have the greatest potential to prevent or treat diseases associated with the above trends in SE Asian populations? This report will review the known and potential benefits of selected micronutrients (vitamins and minerals) and other nutrients (essential fatty acids, phytochemicals, herbs, amino acid derivatives) in preventing and treating NCDs in urban SE Asian populations. When available, studies of SE Asian populations will be discussed. If such studies are unavailable or of poor quality, observational and clinical evidence from other regions will be presented. Although most current evidence regarding the effects of supplementation on NCDs pertains to CVD and cancer, this review will also present noteworthy research findings on other important NCDs, such as diabetes, Alzheimer disease, and osteoarthritis.

II. VITAMINS: KNOWN FUNCTIONS AND RECENT RESEARCH

Vitamins are organic compounds that are vital in maintaining the normal metabolic functions of the body. The B vitamins and vitamin C are water-soluble; vitamins A, D, E, and K are fat-soluble. Table 1 shows the principal functions and important sources of these vitamins.

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TABLE I. FUNCTIONS AND SOURCES OF VITAMINS [7]

Vitamin	Functions	Selected sources
Water-soluble vitamins		
Vitamin B_1 (thiamin)	Involved in energy transformation; contributes to normal functioning of heart and nervous system	Beef, brewer's yeast, legumes, nuts, oats, pork, rice, seeds, wheat, whole-grain cereals, some fruits, dairy products
Vitamin B_2 (riboflavin)	Has role in energy metabolism; helps maintain red blood cells, vision, skin, and mucous membranes; contributes to normal function of nervous system; protects cells from oxidative stress	Dairy products, eggs, enriched cereals and grains, meats, liver, and green vegetables
Vitamin B_3 (niacin)	Necessary for oxidation-reduction reactions and energy-producing reactions; contributes to normal functioning of nervous system and maintenance of mucous membranes and skin	Vegetables, fruits, grains, meats, milk, and eggs
Vitamin B_5 (pantothenic acid)	Required for synthesis of coenzyme A; contributes to energy production, metabolism of steroid hormones, vitamin D, and some neurotransmitters; helps maintain mental performance	Whole-grain cereals, legumes, eggs, meat, avocado, and yogurt
Vitamin B_6 (pyridoxine)	Contributes to energy production, immune function, metabolism of homocysteine, protein, and glycogen, and regulation of hormone activity	Cereal grains, legumes, vegetables such as carrots, spinach, peas, and potatoes, milk, cheese, eggs, fish, liver, meat, and flour
Vitamin B_7 (biotin)	Cofactor for 4 carboxylases; contributes to energy production, maintenance of hair, skin, and mucous membranes, regulation of gene expression, and macronutrient metabolism	Egg yolk, liver, and some vegetables
Vitamin B_9 (folate)	Necessary for metabolism of nucleic acids and amino acids, hematopoiesis, amino acid synthesis, homocysteine metabolism, cell division, and maternal tissue growth during pregnancy	Cereals, baked goods, leafy vegetables, okra, asparagus, some fruits, legumes, yeast, mushrooms, organ meat, orange juice, and tomato juice
Vitamin B_{12} (cobalamin)	Functions as a coenzyme; has roles in energy production, hematopoiesis, maintenance of neurologic, psychologic, and immune function, and cell division	Fish, shellfish, meat, eggs, and dairy products
Vitamin C (ascorbic acid)	Antioxidant; cofactor in synthesis of carnitine, thyroxin, norepinephrine, dopamine, and tryptophan	Citrus fruits and juices; vegetables
Fat-soluble vitamins		
Vitamin A	Essential for vision, cell specialization, growth, reproduction, bone development, and immune system	Beef liver, kidney, eggs, dairy products (retinoids); dark or yellow vegetables, carrots, tree nuts (carotenoids)
Vitamin D	Important in bone development, growth, and maintenance, absorption and utilization of calcium and phosphorus, serum calcium homeostasis, and muscle function	Fish, eggs, fortified milk, cod liver oil; sun exposure
Vitamin E	Antioxidant that protects cell membranes	Eggs, fortified cereals, fruit, green leafy vegetables, meat, nuts, nut oils, poultry, vegetable oils, argan oil, olive oil, wheat germ oil, whole grains
Vitamin K	Essential in coagulation and bone mineralization	Green leafy vegetables, vegetable oils, oats, potatoes, tomatoes, asparagus, butter, margarine, milk, carrots, corn, most fruits; intestinal flora

A. *Benefits of Selected Vitamins in Preventing NCDs*

Vitamin D: Vitamin D is essential for the maintenance of bones and teeth and normal calcium absorption, and its potential role in CVD, cancer, and diabetes has generated considerable interest. Although the results of research efforts have not yet yielded conclusive recommendations regarding vitamin D supplementation, a recent meta-analysis of individual participant data found significant inverse

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associations of 25-hydroxyvitamin D concentration (25(OH)D; the most frequently measured metabolite of vitamin D) with all-cause mortality (risk ratio [RR] of the bottom vs. the top quintile of 25(OH)D concentration, 1.57; 95% confidence interval [CI], 1.36–1.81) and cardiovascular mortality (RR, 1.41; 95% CI, 1.18–1.68), and with cancer mortality among persons with a history of cancer (RR, 1.70; 95% CI, 1.00–2.88) [8]. In addition, a meta-analysis of 10 randomized, controlled trials published during 2009–2014 found that vitamin D supplementation was associated with a significant 10.3-nmol/L decrease in circulating high-sensitivity C-reactive protein (hs-CRP) concentration, a marker of inflammation and predictor of CVD [9]. A systematic review and meta-analysis of observational cohort and randomized intervention studies of the effects of circulating and supplemental vitamin D reported that primary-prevention observational studies showed moderate but significant inverse associations of circulating vitamin D concentration with risks of all-cause mortality (RR, 1.35; 95% CI, 1.22–1.49), CVD mortality (RR, 1.35; 95% CI, 1.13–1.61), cancer mortality (RR, 1.14; 95% CI, 1.01–1.29), and non-vascular, non-cancer mortality (RR, 1.30; 95% CI, 1.07–1.59). The authors concede that observational studies cannot conclusively demonstrate whether observed associations with outcomes are direct or indirect. However, in their analysis of randomized controlled trials investigating vitamin D supplementation, stratified by type of supplementation, the authors found that vitamin D3 was associated with an 11% reduction in mortality [10].

Global years lived with disability attributable to Alzheimer disease is increasing rapidly [11]. Some observational evidence indicates that vitamin D status has effects on cognitive status. In their study of 1658 US adults, Littlejohns et al. reported that the multivariate-adjusted hazard ratios for participants with severely deficient (<25 nmol/L) and deficient (≥25 to <50 nmol/L) 25(OH)D concentrations were 2.25 (95% CI, 1.23–4.13) and 1.53 (95% CI, 1.06–2.21) for all-cause dementia and 2.22 (95% CI, 1.02–4.83) and 1.69 (95% CI, 1.06–2.69) for incident Alzheimer disease, as compared with participants with sufficient concentrations (>50 nmol/L) [12]. A summit of international experts, "Vitamin D and Cognition in Older Adults," concluded that a 25(OH)D concentration less than 74.9 nmol/L and inefficient utilization of vitamin D increase the risks of cognitive decline and Alzheimer disease and its related disorders in adults aged 65 years or older and may affect disease presentation [13].

These findings may be relevant for SE Asian populations with vitamin D deficiency. A review of vitamin D status in SE Asia found that being young, being female, residing in an urban area, and being less physically active were predictors of low vitamin D status among SE Asians [14]. Moy et al. reported that approximately 70% of a sample of 380 university employees of Malay ethnicity living in Kuala Lumpur, Malaysia, had insufficient (<50 nmol/L) vitamin D concentrations [15]. Vitamin D status was determined in 412 of 485 elderly Singaporeans admitted to hospital for hip fracture during a 1-year period. Mean vitamin D level was 47.7 nmol/L; 57.5% had vitamin D deficiency (vitamin D level, <49.9 nmol/L), 34.5% had vitamin D insufficiency (52.4–72.4 nmol/L), and only 8% had normal vitamin D levels (>74.9 nmol/L). The proportion of patients with vitamin D deficiency was 90.5% in Malays, 61.1% in Indians, and 55% in Chinese [16]. A study of 219 Singaporeans with pre-dialysis chronic kidney disease found that 83% did not have a sufficient 25(OH)D concentration and that Malay race was a predictor of vitamin D deficiency (<74.9 nmol/L) in univariate and multivariate logistic regression analyses [17]. The authors hypothesized that the ethnic difference in vitamin D deficiency was due to the darker skin color (i.e., greater amount of melanin) of Malays and/or cultural/lifestyle differences, e.g., the tendency of Malay women to wear clothing that covers most of their skin. It is likely that populations that share these characteristics have a similar risk for vitamin D deficiency.

Vitamin C: Vitamin C has long been of interest to researchers and the general public, most notably for its purported effectiveness against the common cold. Vitamin C levels have not been extensively studied in SE Asia; however, evidence from the region and other countries suggests that suboptimal vitamin C concentration is a concern, particularly among elderly adults and smokers [18-20]. Although there is little change in the blood concentration of vitamin C when daily intake is greater than 100 mg per day, individuals who consume less than this might benefit from increased intake [21]. A meta-analysis of the effects of vitamin C on stroke found that dietary vitamin C intake and circulating vitamin C concentration were significantly associated with stroke risk. The summary relative risk of stroke for the highest versus the lowest category was 0.81 (95% CI, 0.74–0.90) for dietary vitamin C intake and 0.62 (95% CI, 0.49–0.79) for circulating vitamin C [21].

In a meta-analysis of randomized controlled trials of the effects of vitamin C supplementation on blood pressure, Juraschek and colleagues found significant reductions of −3.84 mm Hg (95% CI, 25.29–22.38 mm Hg; P <0.01) in systolic blood pressure and −1.48 mm Hg (95% CI, 22.86–20.10 mm Hg; P = 0.04) in diastolic blood pressure [22]. Vitamin C might also have a protective effect against gastric adenocarcinoma. An analysis of participants in the prospective General Population Nutrition Intervention Trial found that prediagnostic plasma vitamin C concentration was inversely associated with subsequent risk of incident gastric adenocarcinoma in a high-risk Chinese population [23]. The authors hypothesized that the antioxidant action of vitamin C protects cells from oxidative DNA damage, inhibits *N*-nitroso compound formation, and/or limits the toxicity of reactive oxidative species produced by *Helicobacter pylori* infection.

Vitamin K: Vitamin K occurs in two natural active forms: phylloquinone (vitamin K1), which is found in green leafy vegetables and vegetable oils, and menaquinone (vitamin K2), which is present in intestinal bacteria and fermented foods. In addition to its effects on coagulation and bone metabolism, vitamin K appears to have important roles in cancer development and atherosclerotic disease [24-26]. A prospective cohort analysis of 7216 participants in the Prevención con Dieta Mediterránea (PREDIMED) study found that, after adjustment for potential confounders, energy-adjusted baseline dietary phylloquinone intake was significantly inversely associated with cancer mortality (hazard ratio [HR] for the highest vs. the lowest quartile of intake, 0.54; 95% CI, 0.30–0.96) and all-cause mortality (HR, 0.64; 95% CI, 0.45–0.90). In addition, longitudinal analysis showed that participants who increased their

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phylloquinone or menaquinone intake during follow-up had lower risks of cancer mortality (HR, 0.64; 95% CI, 0.43–0.95 and HR, 0.41; 95% CI: 0.26–0.64; respectively) and all-cause mortality (HR, 0.57; 95% CI: 0.44–0.73; and HR, 0.55; 95% CI: 0.42–0.73; respectively), as compared with participants who did not increase their intake [25]. In a recent review of observational and clinical studies of the association of vitamin K status and vascular calcification, which can progress to vascular occlusion, the authors concluded that evidence from observational population-based studies suggests that menaquinone intake is more important than phylloquinone intake in protecting against vascular calcification [27].

The role of vitamin K in bone metabolism has stimulated research on its associations with osteoporosis and osteoarthritis, an increasingly important cause of global years lived with disability [11]. The effectiveness of menaquinone therapy for postmenopausal osteoporosis was investigated in a review of randomized controlled trials conducted in Japan, China, and Indonesia. The author concluded that treatment with menatetrenone (a synthetic form of menaquinone) had positive effects on bone mineral density and fracture incidence [28]. This supports the results of a similar, earlier study, which showed that menatetrenone improved bone mineral content and bone geometry at critical sites and helped maintain femoral neck bone strength, as determined by dual-energy X-ray absorptiometry, in postmenopausal non-osteoporotic women during a 3-year observation period [29].

Knee arthritis is a leading cause of lower-extremity disability. The association of vitamin K with new-onset radiographic knee osteoarthritis and early osteoarthritic changes on magnetic resonance imaging was investigated in 1180 older adults in the United States. As compared with no deficiency, subclinical vitamin K deficiency (plasma phylloquinone level <0.5 nM) was associated with significantly increased risks of incident radiographic knee osteoarthritis (RR, 1.56; 95% CI, 1.08–2.25) and cartilage lesions (RR 2.39; 95% CI, 1.05–5.40) 30 months after baseline assessment [30].

III. Minerals: Known Functions and Recent Research

Minerals are required for a wide range of life functions and are typically classified as major or trace minerals. Table 2 shows minerals available as dietary supplements and their principal functions and sources.

Table II. Functions and Sources of Selected Minerals [7]

Mineral	Functions	Selected sources
Major minerals		
Calcium	Important in maintenance of bones and teeth, muscle contractility, responses to hormones and neurotransmitters, and blood clot formation	Dairy products, dark, leafy greens, sardines, clams, oysters, dried beans, amaranth, legumes, broccoli, dried fruits, seaweed
Magnesium	Has roles in muscle function, energy production, development and maintenance of bones and teeth, regulation of ion channels, neurotransmission, cell signaling, and protein synthesis	Green vegetables, beans, nuts, shellfish, soya flour, whole grains
Phosphorus	Contributes to skeletal tissue development, energy storage and transfer, formation of nucleic acids, and acid–base balance	Meat, poultry, fish, eggs, milk, dairy products
Potassium	Important in functioning of muscle and nervous system and in maintaining normal blood pressure	Potatoes, fruits, berries, vegetables, dairy products (excluding cheese), nuts
Trace minerals		
Chromium	Believed to potentiate action of insulin and thus has role in maintaining blood glucose levels	Whole grains, pulses, some vegetables, liver, processed meats, ready-to-eat cereals, spices, beer
Copper	Cofactor for a number of enzymes; has roles in immune function, energy metabolism, protection against oxidative stress, nervous system function, and iron transport	Vegetables, legumes, nuts, grains, fruits, shellfish, avocado, beef, and animal organs such as liver and kidneys
Iodine	Essential for synthesis of thyroid hormones, which are important in digestion, metabolism, bone growth, and development, and cardiovascular and gastrointestinal health	Meat, poultry, milk, eggs, dairy products (depends on amount of iodine in local soil, fertilizer use, and irrigation methods)
Iron	Forms part of several proteins, thereby contributing to red blood cell formation, hemoglobin synthesis, and other functions	Heme iron—meat, fish, poultry; nonheme iron—beans, lentils, flours, cereals, grain products
Manganese	Contributes to bone development, connective tissue synthesis, and energy production; component of antioxidant manganese superoxide dismutase	Milk, eggs, cereal, date palm, corn flour, carob flour, mussels, leafy and non-leafy vegetables

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Molybdenum	Has role in metabolism of sulfur-containing amino acids	Legumes, leafy vegetables, liver, dairy products
Selenium	Important in synthesis of antioxidant proteins; contributes to immune function, spermatogenesis, and thyroid function	Cereals, meat, oysters, tuna, poultry
Zinc	Contributes to immune function, sexual maturation, gene expression, fertility, reproduction	Beef, pork, shellfish, peanuts, legumes

A. Benefits of Selected Minerals in Preventing NCDs

***Zinc*:** Zinc is required for the activity of more than 300 enzymes and more than 1000 transcription factors. Zinc status and zinc deficiency have not been adequately studied by means of nationally representative surveys in low-income countries, because of financial and logistic difficulties, as well as the small number of validated biomarkers. A study that attempted to assess zinc intake by analyzing data on the amount of total and absorbable zinc in national food supplies concluded that SE Asia was among the regions with the highest risk of inadequate zinc intake [31]. These results support earlier findings indicating that more than 25% of the population of Southeast Asia is at risk for inadequate zinc intake [32].

A moderate zinc deficiency can adversely affect growth (stunting), appetite, the skin, wound healing, mental acuity, and the immune and neurologic systems [33]. However, studies by Prasad and colleagues showed that even a mild zinc deficiency has adverse biochemical, immunologic, and clinical effects, e.g., hyperammonemia and adverse effects on testosterone level, sperm count, lean body mass, and the activity of thymulin, natural killer cells, and T helper cells [34-36].

With respect to NCDs, zinc assists in regulating blood glucose and thus has an important role in diabetes. In a study of 82,297 US women, the RR of type 2 diabetes in the highest quintile as compared with the lowest quintile was 0.90 (95% CI, 0.82–0.99) for total zinc intake and 0.92 (95% CI, 0.84–1.00) for dietary zinc intake from food sources [37]. A meta-analysis of randomized placebo-controlled supplementation trials investigated the effect of zinc supplementation on fasting blood glucose, glycated hemoglobin (HbA1c), serum insulin, and serum zinc concentrations and found a small but significant decrease in fasting glucose concentration (−0.19 ± 0.08 mmol/L, P = 0.013) and a nonsignificant reduction in HbA1c (−0.64 ± 0.36%, P = 0.072) after zinc supplementation [38]. Reductions in fasting glucose were greater in obese persons and those with diabetes. The authors concluded that increased zinc intake had modest positive effects on cardiometabolic risk factors in persons with diabetes.

Iron: Although the burden of iron-deficiency anemia has recently considerably declined in SE Asia, prevalence remains unacceptably high in the region. The estimated prevalence in SE Asia in 2010 was approximately 17% among females and 12% among males [39]. Iron-deficiency anemia appears to have effects on cognitive performance, energy levels, and productivity [40]. When severe, it increases the risks of preterm labor, low birthweight, and child and maternal mortality [39]. A systematic review of 14 studies assessing the effects of iron supplementation on cognition found evidence that iron supplementation improved attention and concentration in adolescents and women at all baseline levels of iron status over periods ranging from 8 to 17 weeks [41]. Few studies have investigated the effects of anemia among elderly adults. A meta-analysis of the relationship of cognitive decline and dementia in the elderly with anemia and hemoglobin level was able to identify only three studies that satisfied the search criteria, two of which could be combined into a meta-analysis. Anemia was associated with a significant increase in the risk of incident dementia (pooled HR, 1.94; 95% CI, 1.32–2.87) [42].

IV. MINERALS: OTHER NUTRIENTS

Ensuring optimal intakes of vitamins and minerals is essential for maintaining good health and preventing NCDs. However, numerous other substances are beneficial for health and should be assessed in relation to disease prevention and treatment. This section highlights a few of the thousands of potentially beneficial nutrients, phytochemicals, and herbs that have been identified. The conclusions reached should be regarded as provisional, as only a small number of these substances have been carefully investigated and very few of those have been studied in SE Asian populations.

A. Fatty Acids

Fish Oil/Krill Oil: The benefits of fish oil consumption on NCDs have been much discussed, often in the context of the perceived need to reduce the ratio of omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) in the diet of populations with high intakes of vegetable oils [43]. Earlier epidemiologic and clinical trials showed persons at risk of coronary heart disease benefited from consuming omega-3 PUFAs. However, the findings of more recent studies have been less conclusive. Some researchers hypothesize that the failure of recent trials and meta-analyses to show a convincing benefit for fish oil is due to flaws in the studies and enrollment of individuals receiving optimal medical therapy, which reduces the number of CVD events and thus complicates identification of differences between treatment groups [44]. The evidence for a beneficial effect of fish oil on joint pain is clearer. A meta-analysis of 17 randomized, controlled trials of the analgesic effects of omega-3 PUFA supplementation for inflammatory joint pain in patients with rheumatoid arthritis or joint pain related to inflammatory bowel disease or dysmenorrhea found that supplementation improved pain outcomes after 3 months, particularly in relation to patient-assessed pain, duration of morning stiffness, number of painful and/or tender joints, and use of nonsteroidal anti-inflammatory drugs [45]. Among the other reported effects of increased omega-3 PUFA intake, the potential beneficial effect on mood in depressed individuals appears promising [46].

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Fish consume a diet abundant in the omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Krill consume a diet similarly rich in EPA and DHA, and krill oil, which also contains the promising carotenoid antioxidant astaxanthin, has emerged as an alternative to fish oil. Antarctic krill (*Euphausia superba*) are a common source of krill oil, and some studies have found that krill oil might be better than fish oil at delivering EPA and DHA [47]. In a randomized, double-blind, parallel-arm trial, Maki and colleagues randomly assigned obese adults to receive 2 g/day of krill oil, menhaden (fish) oil, or control (olive) oil for 4 weeks [48]. Increases in plasma EPA and DHA concentrations were significantly greater (P <0.001) in participants receiving krill oil (178.4 ± 38.7 and 90.2 ± 40.3 μmol/L, respectively) and menhaden oil (131.8 ± 28.0 and 149.9 ± 30.4 μmol/L, respectively), as compared with the control group (2.9 ± 13.8 and −1.1 ± 32.4 μmol/L, respectively). Krill oil supplementation was well tolerated and had no adverse effects. In a prospective randomized study of the effects of krill oil on total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol in patients with hyperlipidemia, reductions in glucose, total cholesterol, triglycerides, and LDL cholesterol, and the increase in HDL cholesterol, were greater among participants receiving 1 to 3 g krill oil per day than in those receiving fish oil or placebo [49]. Moreover, a maintenance dose of 500 mg krill oil was sufficient for long-term regulation of blood lipids.

B. Phytochemicals

Astaxanthin: Astaxanthin is a carotenoid that is abundant in marine organisms and provides the reddish color to salmon and cooked shellfish. It functions as an antioxidant and may protect against inflammation, ultraviolet damage to the skin, carcinogenesis, stomach ulcer caused by *H. pylori* infection, and aging and age-related diseases. In addition, astaxanthin promotes the health of body organs, including the heart, liver, and eyes [50,51].

In a placebo-controlled trial, 61 non-obese Japanese adults aged 25 to 60 years who had a fasting serum triglyceride concentration of 1.36 to 2.26 mmol/L, but no diabetes or hypertension, were given an astaxanthin dose of 0, 6, 12, or 18 mg/day for 12 weeks. Triglyceride concentration decreased, and HDL cholesterol significantly increased. Multiple-comparison testing revealed that the 12 and 18 mg/day doses significantly reduced triglycerides and that the 6 and 12 mg/day doses significantly increased HDL cholesterol [52].

C. Amino Acid Derivatives

Chondroitin Sulfate/Glucosamine: Osteoarthritis is the most common cause of disability in older adults. Fransen et al. examined osteoarthritis prevalence in Asia and concluded that the prevalence of knee pain and symptomatic knee osteoarthritis is high among older adults in rural and urban areas [53]. The increase in life expectancy among SE Asians will likely increase the prevalence of ostearthritis in the region. Chondroitin sulfate and glucosamine occur naturally in the body and are widely used, alone and together, as dietary supplements in the treatment of osteoarthritis. A multicenter, double-blind, placebo- and celecoxib-controlled study—the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)—evaluated the efficacy and safety of glucosamine and chondroitin sulfate as a treatment for knee pain from osteoarthritis [54]. Although the drugs did not reduce pain in the overall group of individuals with knee osteoarthritis, exploratory analyses indicated that the combination of glucosamine and chondroitin sulfate might be effective in a subgroup of patients with moderate-to-severe knee pain.

A later double-blind, randomized, placebo-controlled clinical trial with a 2-year follow-up period studied 605 adults aged 45 to 75 years. The participants were randomized to receive either glucosamine sulfate 1500 mg, chondroitin sulfate 800 mg, both dietary supplements, or matching placebo capsules. After adjustment for factors associated with structural disease progression, participants who received combination treatment with glucosamine and chondroitin sulfate had significantly less joint space narrowing at 2 years than did those receiving a placebo (0.12 mm vs 0.22 mm, respectively; P = 0.046). The authors surmised that the difference would be of considerable clinical importance if this reduction were to persist over a longer interval (10–15 years) [55].

D. Herbs

Ginseng: Ginseng has a long history as a health supplement in Asia. Extracts of ginseng have been used for their purported effects on inflammation, diabetes, and cancer and for their antioxidant and immunity-enhancing effects. A recent 4-week, randomized, double-blind, placebo-controlled trial of the effects of supplementation with fermented red ginseng on fasting and postprandial plasma glucose profiles during meal tolerance tests found significant reductions in fasting glucose level, from 6.5 ± 0.5 to 6.1 ± 0.6 mmol/L (P = 0.039), and postprandial plasma glucose, from 9.3 ± 2.2 to 7.7 ± 1.9 mmol/L (P <0.001), in the participants receiving ginseng [56]. In addition, the 2-h postprandial insulin level at 4 weeks was significantly higher in the participants receiving ginseng than in the placebo group.

Ginseng is frequently used as a treatment for fatigue, a common complaint among older adults [57]. Medical disorders characterized by chronic fatigue, such as idiopathic chronic fatigue and chronic fatigue syndrome, can have a substantial impact on quality of life. Fatigue is also a common symptom of NCDs, including CVD, cancer, and osteoarthritis [58]. In a randomized, double-blind, placebo-controlled trial, Kim et al. assessed the anti-fatigue effects of *Panax ginseng* C.A. Meyer by asking individuals with idiopathic chronic fatigue to report their fatigue on a self-rating numeric scale (NRS) and a visual analogue scale (VAS) [59]. Mental NRS score significantly decreased after *P. ginseng* administration (20.4 ± 5.0 to 15.1 ± 6.5 [95% CI, 2.3–8.2] for 1 g; 20.7 ± 6.3 to 13.8 ± 6.2 [95% CI, −0.1 to 4.2] for 2 g), as compared with the placebo group (20.9 ± 4.5 to 18.8 ± 2.9; 95% CI, 4.1–9.9) (P <0.01). Administration of *P. ginseng* 2 g significantly reduced VAS score (7.3 ± 1.3 to 4.4 ± 1.8; 95% CI, 0.7–1.8), as compared

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with placebo (7.1 ± 1.0 to 5.8 ± 1.3; 95% CI, 2.2–3.7) (P <0.01).

A systematic review of randomized clinical studies concluded that ginseng appeared to have benefits, notably for Alzheimer disease, colon cancer, exercise capacity, and erectile dysfunction, although the authors cautioned that high-quality, larger-scale, randomized, controlled trials would be necessary in order to confirm these findings [60].

Tea: Leaves harvested from the plant *Camillia sinesis* are used to make the three main types of tea: green, black, and oolong. Green tea is rich in phenolics, including flavanols and associated compounds. Among the many constituents of tea leaves, the most important flavanic polyphenols in green tea are (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). Black tea contains tearubigins and theaflavins [61]. Tea is the second most frequently consumed beverage in the world and has been studied for its effects on cancer, blood pressure, and CVD. A review of laboratory and human studies of the effects of liquid tea and tea extracts in cancer chemoprevention described current data regarding these effects as considerable and growing, although there remains a need for additional human intervention trials [62].

In a double-blind placebo-controlled study, 60 men with high-grade prostate intraepithelial neoplasia, who were thus at increased risk of developing prostate cancer, were given green tea catechins (GTCs). The GTCs had a chemoprevention efficacy of 90%: only one of the 30 men who received 600 mg of GTCs per day developed prostate cancer, as compared with nine of the 30 men in the placebo group (P <0.01) [63]. A follow-up analysis published 1 year later by the same group showed that the difference in the number of prostate cancer diagnoses between groups remained significant at 19 to 23 months after GTC treatment [64]. These results indicate that GTCs might be effective for chemopreventive treatment of precancerous tissues.

A review of the effects of green and black tea on primary prevention of CVD [65] found that black tea was associated with statistically significant reductions in LDL cholesterol (mean difference [MD], −0.43 mmol/L; 95% CI, −0.56 to −0.31 mmol/L), systolic blood pressure (MD, −1.85 mm Hg; 95% CI, −3.21 to −0.48 mm Hg), and diastolic blood pressure (MD, −1.27 mm Hg; 95% CI, −3.06 to 0.53 mm Hg) over 6 months. Green tea was associated with significant reductions in total cholesterol (MD, −0.62 mmol/L; 95% CI, −0.77 to −0.46 mmol/L), LDL cholesterol (MD, −0.64 mmol/L; 95% CI, −0.77 to −0.52 mmol/L), systolic blood pressure (MD, −3.18 mm Hg; 95% CI −5.25 to −1.11 mm Hg), and diastolic blood pressure (MD, −3.42 mm Hg; 95% CI, −4.54 to −2.30 mm Hg). The authors concluded that, although there was insufficient evidence for conclusive recommendations, tea appears to have beneficial effects on CVD risk factors.

V. NCDs: The Scope of the Problem

A. NCD Trends in SE Asia

In the 11 countries of SE Asia (Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Viet Nam), the total number of deaths from NCDs is projected to be more than 3.0 million in 2015 and 4.8 million in 2030 [66]. Of the deaths in 2015, approximately 1.4 million will be from CVD, 630,000 from cancer, and 230,000 from diabetes, all of which are diseases closely associated with diet. In 2012, NCDs were estimated to account for 61% of total disability-adjusted life years (i.e., years of lost "healthy" life) in persons aged 15 to 59 years and 82% of disability-adjusted life years in those aged 60 years or older [67]. These values are expected to increase to 74% and 89%, respectively, by 2030 [4]. Much of the mortality and disability burden falls on individuals of working age, and the costs are therefore considerable for their families and society. The problem of premature death is particularly serious in the Philippines, where the probability of dying from one of the four main NCDs between the ages of 30 and 70 years is 28% [68]. NCDs also have an appreciable impact on quality of life in SE Asia. A study of Malaysians aged 55 years or older reported that those with more than one NCD had diminished health-related quality of life [69]. The link between diet and NCDs was highlighted in an analysis of risk factors related to the burden of disease and injury, which found that 13 of the top 20 risk factors in SE Asia in 2010 were at least partially related to diet and that the impact on the global disease burden of many diet-related risk factors—e.g., high blood pressure, low fruit intake, high body mass index, high fasting plasma glucose—had substantially increased since 1990 [70].

B. Dietary Trends in SE Asia

A number of indices are used to describe daily micronutrient intakes that are considered sufficient to satisfy the health requirements of a predetermined proportion of the target population. Dietary Reference Values (DRVs) and Estimated Average Requirements (EARs) specify how much of a nutrient is required in order to meet the needs of 50% of the healthy subjects in a specific population subgroup. Dietary Reference Intakes (DRIs) and Recommended Dietary Allowances (RDAs) specify how much of a nutrient is required in order to meet the needs of nearly all healthy subjects (97%–98%; the mean plus two standard deviations) in a specific population subgroup. An attempt to harmonize RDAs for SE Asia (SEA-RDAs) yielded a working document that provided SEA-RDAs for most micronutrients [71]. However, the prevalences of micronutrient deficiencies in SE Asia, particularly in adults, have not been adequately investigated.

Several countries develop and distribute dietary guidelines. In the United States, the 2015 Dietary Guidelines Advisory Committee submitted its recommendations to the US Department of Health and Human Services and the US Department of Agriculture. Their report stresses the value of "dietary patterns that are rich in vegetables, fruit, whole grains, seafood, legumes, and nuts; moderate in low- and non-fat dairy products and alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and beverages and refined grains" [72]. In SE Asia, the guidelines of the Singapore Health Promotion Board call for

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greater dietary variety and increased consumption of whole grains, fruit, and vegetables, reduced intakes of fat (especially saturated fat), salt, and sugar-sweetened beverages, and moderation of alcohol intake [73]. Guidelines from other countries in the region vary in their recommendations regarding dietary fat, salt, and sugar but agree on the need for a varied diet and increased intake of plant foods.

The analysis of risk factors related to the burden of disease and injury reported that "diet low in fruit", "diet high in sodium", and "diet low in vegetables" were among the top 10 risk factors in SE Asia and were the most important explicitly diet-related risk factors [70]. These findings confirm the results of previous studies, which reported low intakes of fruit and vegetables and high sodium consumption in SE Asia [74-76]. In a review of salt intake in six SE Asian countries, nearly all the included studies reported that total sodium consumption exceeded the recommended limit of 2 g per day (>5 g of salt per day) [77]. In a 2011 study of Singaporeans aged 18 to 79 years, mean sodium intake, as measured by 24-h urine collection (the gold standard for such evaluation), was 3.78 g for men and 2.80 g for women [78]. Regarding fruit and vegetable intake, World Health Survey data from five selected SE Asian countries revealed insufficient fruit and vegetable consumption (<5 servings per day) in more than 80% of residents in each of the countries in 2003 [4]. More than a decade later, the situation appears even worse. A recent analysis of fruit and vegetable intake among students in low-, middle-, and high-income countries found that 86.1% of students in Indonesia, the Lao People's Democratic Republic, the Philippines, Singapore, and Thailand ate fewer than five servings of fruit and vegetables per day and that 71% ate one or no servings per day [74].

VI. Preventing NCDs

The Director-General of the World Health Organization (WHO) has described the worldwide increase in NCDs as "a slow-motion disaster" [79]. Although the WHO and governments in SE Asia understand the impact of NCDs, and have made substantial efforts to address modifiable risk factors such as tobacco use, excessive alcohol intake, high salt intake, low fruit/vegetable consumption, low physical activity, and overweight/obesity [5], the evidence suggests that, while tobacco control measures have been successful in some countries, other risk factors are less tractable, particularly in countries with limited resources for public health interventions. A central problem in addressing the rapid increase in NCDs is that health systems in most developing countries focus on providing acute care and are thus inadequate for preventing and treating chronic diseases [79]. Other barriers to NCD prevention are the lack of access to fresh fruit and vegetables in many urban areas and the concomitant increased availability of processed and convenience food, which tends to be calorie-dense and high in salt and refined sugar [80].

The premise of this review is that, in the SE Asian context of a rapidly increasing NCD burden, inadequate health care resources, and diminished access to healthful food, all potential possibilities for NCD prevention should be considered, including the use of dietary supplements. Unfortunately, studies of the effects of micronutrients on NCD prevention have mostly investigated populations in high-income countries, and few high-quality studies have analyzed the effects of phytochemicals and herbs on NCDs. Findings of studies from developed countries cannot be generalized to populations in low- and middle-income countries because, in addition to the obvious ethnic and socioeconomic differences, study participants in developed countries are likely to be better nourished and to have access to the highest standard of medical care. The potential beneficial effects of dietary supplements may prove to be more apparent in populations with a higher disease burden attributable to nutritional deficiencies and less access to advanced care. There is thus an urgent need for studies of micronutrients, phytochemicals, herbs, and other nutrients in populations that have nutritional deficiencies and lack access to health care for prevention and management of NCDs.

VII. Concluding Recommendations

SE Asia is undergoing rapid economic, demographic, and epidemiologic changes. An important effect of these changes is the nutrition transition, namely, the increased consumption of convenience foods—including ultra-processed foods and street food (which displace healthful foods in the diet)—increased intakes of salt and refined sugars, and decreased consumption of fruits and vegetables. The fundamental problem is that, while most people are aware that this nutrition pattern is unhealthy, they are unable or unwilling to make the dietary changes that might protect them against NCDs. Several factors have been cited to explain the dissemination and persistence of unhealthy dietary behaviors, including the decreased availability of healthful food (e.g., the disappearance of traditional wet markets), the aggressive marketing efforts of transnational food companies, and, not least, the hyper-palatability, convenience, durability, and low cost (in terms of total energy consumed) of ultra-processed foods [81]. To lessen the burden of NCDs, public health authorities should continue to provide information on healthy lifestyles and augment successful interventions, such as food fortification programs. However, those involved in nutrition research and clinical prevention and treatment of NCDs must be willing to consider additional options for the substantial number of individuals who fall short of optimal nutrition.

The present review has examined some of the benefits associated with circulating levels of and supplementation with selected nutrients. Taken as a whole, the findings indicate that dietary supplements may have a role in NCD prevention and treatment, particularly among individuals with suboptimal micronutrient intakes. Current research findings and the author's clinical experience suggest that a number of measures are prudent at this time. Individuals at risk of vitamin D deficiency (e.g., those who spend the day indoors or get little sun exposure when outdoors) should consider taking a vitamin D supplement. In addition, evidence indicates that many SE Asians have suboptimal vitamin C levels. At-risk individuals, i.e., elderly adults, smokers, and those who consume limited amounts of fruits

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and vegetables, might benefit from supplementing with vitamin C. The Western diet—which is increasingly prevalent in SE Asia—is characterized by a high ratio of omega-6 to omega-3 PUFAs. Pre-industrial populations had a ratio of less than 4:1, whereas the ratio in the Western diet is typically greater than 15:1. A high ratio is associated with CVD, cancer, osteoporosis, and autoimmune and inflammatory diseases [82]. The ratio of omega-6 to omega-3 PUFAs consumed can be decreased by taking a fish oil or krill oil supplement or by consuming less vegetable oil—ideally both. An increased intake of omega-3 PUFAs is also beneficial in lowering triglycerides [83]—which increase with consumption of refined carbohydrates and processed food—and may help in alleviating depression [46]. This review described some of the health benefits of ginseng and tea, which can be consumed as dietary supplements or infusions, and, although the present evidence is limited, ongoing research will likely identify other herbal compounds and phytochemicals that are useful in disease prevention and treatment. Finally, a multi-vitamin/multi-mineral supplement may offer important benefits as a convenient form of broad protection against nutritional deficiencies, particularly in populations that have high prevalences of these deficiencies. The cost and safety profile of such a supplement would likely be highly favorable when assessed in relation to the benefits of preventing or delaying the diminished quality of life, loss of productivity, disability, and mortality associated with NCDs.

Conflicts of Interest

At the time of drafting this manuscript, Dr Leslie Tay was a paid consultant of PGT Healthcare, licensed distributors of Swisse brand of Vitamins, Minerals & Supplements. Dr Tay received an unrestricted grant from PGT Healthcare and supervised the development, drafting, revision of article and approved the final article of submission independently.

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REFERENCES

[1] Population Reference Bureau. 2014 World Population Data Sheet.

[2] International Monetary Fund. World Economic and Financial Surveys. World Economic Outlook Database. Available online: https://www.imf.org/external/pubs/ft/weo/2015/01/weodata/index.aspx (accessed on 18 October 2015).

[3] United Nations, Department of Economic and Social Affairs, Population Division (2014). World Urbanization Prospects: The 2014 Revision, Highlights (st/esa/ser.A/352).

[4] Dans A, Ng N, Varghese C, Tai ES, Firestone R, Bonita R. The rise of chronic non-communicable diseases in southeast Asia: time for action. *Lancet*. 2011;377(9766):680-689.

[5] WHO. Global Status Report on Noncommunicable Disease 2014.

[6] Kanungsukkasem U, Ng N, Van Minh H, et al. Fruit and vegetable consumption in rural adults population in INDEPTH HDSS sites in Asia. *Glob Health Action*. 2009;2(0):2.

[7] Gropper SS, Smith JL. *Advanced Nutrition and Human Metabolism*. 6th ed. Belmont, OH: Cengage Learning; 2012.

[8] Schöttker B, Jorde R, Peasey A, et al; Consortium on Health and Ageing: Network of Cohorts in Europe and the United States. Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. *BMJ*. 2014;348(jun17 16):g3656.

[9] Chen N, Wan Z, Han SF, Li BY, Zhang ZL, Qin LQ. Effect of vitamin D supplementation on the level of circulating high-sensitivity C-reactive protein: a meta-analysis of randomized controlled trials. *Nutrients*. 2014;6(6):2206-2216.

[10] Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014,348:g1903.

[11] Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the global burden of disease study 2013. *Lancet*. 2015.

[12] Littlejohns TJ, Henley WE, Lang IA, et al. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*. 2014;83(10):920-928.

[13] Annweiler C, Dursun E, Féron F, et al. 'Vitamin D and cognition in older adults': updated international recommendations. *J Intern Med*. 2015;277(1):45-57.

[14] Nimitphong H, Holick MF. Vitamin D status and sun exposure in southeast Asia. *Dermatoendocrinol*. 2013;5(1):34-37.

[15] Moy FM, Bulgiba A. High prevalence of vitamin D insufficiency and its association with obesity and metabolic syndrome among Malay adults in Kuala Lumpur, Malaysia. *BMC Public Health*. 2011;11(1):735.

[16] Ramason R, Selvaganapathi N, Ismail NH, Wong WC, Rajamoney GN, Chong MS. Prevalence of vitamin d deficiency in patients with hip fracture seen in an orthogeriatric service in sunny singapore. *Geriatr Orthop Surg Rehabil*. 2014;5(2):82-86.

[17] Loh ZY, Yap CW, Vathsala A, How P. Clinical and demographic predictors for vitamin D deficiency in multiethnic Asian patients with chronic kidney disease. *Clin Kidney J*. 2012;5(4):303-308.

[18] Cahill L, Corey PN, El-Sohemy A. Vitamin C deficiency in a population of young Canadian adults. *Am J Epidemiol*. 2009;170(4):464-471.

DOI: 10.18535/ijmsci/v2i10.07

[19] Ravindran RD, Vashist P, Gupta SK, et al. Prevalence and risk factors for vitamin C deficiency in north and south India: a two centre population based study in people aged 60 years and over. *PLoS One*. 2011;6(12):e28588.

[20] Torheim LE, Ferguson EL, Penrose K, Arimond M. Women in resource-poor settings are at risk of inadequate intakes of multiple micronutrients. *J Nutr*. 2010;140(11):2051S-2058S.

[21] Chen GC, Lu DB, Pang Z, Liu QF. Vitamin C intake, circulating vitamin C and risk of stroke: a meta-analysis of prospective studies. *J Am Heart Assoc*. 2013;2(6):e000329.

[22] Juraschek SP, Guallar E, Appel LJ, Miller ER III. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2012;95(5):1079-1088.

[23] Lam TK, Freedman ND, Fan JH, et al. Prediagnostic plasma vitamin C and risk of gastric adenocarcinoma and esophageal squamous cell carcinoma in a Chinese population. *Am J Clin Nutr*. 2013;98(5):1289-1297.

[24] Apalset EM, Gjesdal CG, Eide GE, Tell GS. Intake of vitamin K1 and K2 and risk of hip fractures: The Hordaland Health Study. *Bone*. 2011;49(5):990-995.

[25] Juanola-Falgarona M, Salas-Salvadó J, Martínez-González MA, et al. Dietary intake of vitamin K is inversely associated with mortality risk. *J Nutr*. 2014;144(5):743-750.

[26] Lamson DW, Plaza SM. The anticancer effects of vitamin K. *Altern Med Rev*. 2003;8(3):303-318.

[27] Shea MK, Holden RM. Vitamin K status and vascular calcification: evidence from observational and clinical studies. *Adv Nutr*. 2012;3(2):158-1

[28] Iwamoto J. Vitamin K_2 therapy for postmenopausal osteoporosis. *Nutrients*. 2014;6(5):1971-1980.

[29] Knapen MH, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos Int*. 2007;18(7):963-972.

[30] Misra D, Booth SL, Tolstykh I, et al. Vitamin K deficiency is associated with incident knee osteoarthritis. *Am J Med*. 2013;126(3):243-248.

[31] Wessells KR, Brown KH. Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. *PLoS One*. 2012;7(11):e50568.

[32] Brown KH, Rivera JA, Bhutta Z, et al; International Zinc Nutrition Consultative Group (IZiNCG). International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull*. 2004;25(1)(suppl 2):S99-S203.

[33] Prasad AS. Discovery of human zinc deficiency: its impact on human health and disease. *Adv Nutr*. 2013;4(2):176-190.

[34] Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am J Physiol*. 1997;272(6 Pt 1):E1002-E1007.

[35] Beck FW, Kaplan J, Fine N, Handschu W, Prasad AS. Decreased expression of CD73 (ecto-5′-nucleotidase) in the CD8+ subset is associated with zinc deficiency in human patients. *J Lab Clin Med*. 1997;130(2):147-156.

[36] Prasad AS, Meftah S, Abdallah J, et al. Serum thymulin in human zinc deficiency. *J Clin Invest*. 1988;82(4):1202-1210.

[37] Sun Q, van Dam RM, Willett WC, Hu FB. Prospective study of zinc intake and risk of type 2 diabetes in women. *Diabetes Care*. 2009;32(4):629-634.

[38] Capdor J, Foster M, Petocz P, Samman S. Zinc and glycemic control: a meta-analysis of randomised placebo controlled supplementation trials in humans. *J Trace Elem Med Biol*. 2013;27(2):137-142.

[39] Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615-624.

[40] McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. *Am J Clin Nutr*. 2007;85(4):931-945.

[41] Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. *Nutr J*. 2010;9(1):4.

[42] Peters R, Burch L, Warner J, Beckett N, Poulter R, Bulpitt C. Haemoglobin, anaemia, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr*. 2008;8(1):18.

[43] Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106(21):2747-2757.

[44] Asfandyar K, Niazi JJD. Explaining the recent fish oil trial "failures". *Journal of Glycomics & Lipidomics* 2013,03.

[45] Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain*. 2007;129(1-2):210-223.

[46] Giles GE, Mahoney CR, Kanarek RB. Omega-3 fatty acids influence mood in healthy and depressed individuals. *Nutr Rev*. 2013;71(11):727-741.

[47] Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A. Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations--a comparative bioavailability study of fish oil vs. krill oil. *Lipids Health Dis*. 2011;10(1):145.

DOI: 10.18535/ijmsci/v2i10.07

[48] Maki KC, Reeves MS, Farmer M, et al. Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women. *Nutr Res*. 2009;29(9):609-615.

[49] Bunea R, El Farrah K, Deutsch L. Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. *Altern Med Rev*. 2004;9(4):420-428.

[50] Barros MP, Poppe SC, Bondan EF. Neuroprotective properties of the marine carotenoid astaxanthin and omega-3 fatty acids, and perspectives for the natural combination of both in krill oil. *Nutrients*. 2014;6(3):1293-1317.

[51] Guerin M, Huntley ME, Olaizola M. Haematococcus astaxanthin: applications for human health and nutrition. *Trends Biotechnol*. 2003;21(5):210-216.

[52] Yoshida H, Yanai H, Ito K, et al. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. *Atherosclerosis*. 2010;209(2):520-523.

[53] Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in Asia. *Int J Rheum Dis*. 2011;14(2):113-121.

[54] Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med*. 2006;354(8):795-808.

[55] Fransen M, Agaliotis M, Nairn L, et al; LEGS study collaborative group. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis*. 2015;74(5):851-858.

[56] Oh MR, Park SH, Kim SY, et al. Postprandial glucose-lowering effects of fermented red ginseng in subjects with impaired fasting glucose or type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *BMC Complement Altern Med*. 2014;14(1):237.

[57] Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res*. 2004;56(2):157-170.

[58] Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*. 2013;80(4):409-416.

[59] Kim HG, Cho JH, Yoo SR, et al. Antifatigue effects of Panax ginseng C.A. Meyer: a randomised, double-blind, placebo-controlled trial. *PLoS One*. 2013;8(4):e61271.

[60] Choi J, Kim TH, Choi TY, Lee MS. Ginseng for health care: a systematic review of randomized controlled trials in Korean literature. *PLoS One*. 2013;8(4):e59978.

[61] Tejero J, Gayoso S, Caro I, et al. Comparative analysis of the antioxidant and free-radical scavenging activities of different water-soluble extracts of green, black and oolong tea samples. *Food Nutr Sci*. 2014;05(22):2157-2166.

[62] Lambert JD. Does tea prevent cancer? Evidence from laboratory and human intervention studies. *Am J Clin Nutr*. 2013;98(6)(suppl):1667S-1675S.

[63] Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res*. 2006;66(2):1234-12

[64] Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. *Eur Urol*. 2008;54(2):472-473.

[65] Hartley L, Flowers N, Holmes J, et al. Green and black tea for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;6:CD009934.

[66] WHO. Projections of Mortality and Causes of Death, 2015 and 2030. Available online: http://www.who.int/healthinfo/global_burden_disease/projections/en/ (accessed on 20 August 2015).

[67] WHO. Global Health Estimates. Available online: http://www.who.int/healthinfo/global_burden_disease/en/ (accessed on 20 August 2015).

[68] WHO. Noncommunicable Diseases Country Profiles 2014. Philippines. Available online: http://www.who.int/nmh/countries/phl_en.pdf?ua=1 (accessed on 20 August 2015).

[69] Sazlina SG, Zaiton A, Nor Afiah MZ, Hayati KS. Predictors of health related quality of life in older people with non-communicable diseases attending three primary care clinics in Malaysia. *J Nutr Health Aging*. 2012;16(5):498-502.

[70] Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-2260.

[71] International Life Sciences Institute-Southeast Asia Region. Recommended Dietary Allowances (RDA) Harmonization in Southeast Asia. Singapore: International Life Sciences Institute (ILSI) Monograph Series: 2005.

[72] The 2015 Dietary Guidelines Advisory Committee. Scientific Report of the 2015 Dietary Guidelines Advisory Committee.

[73] Singapore Health Promotion Board. Food-based Dietary Guidelines for Adults. Available online: http://www.hpb.gov.sg/HOPPortal/health-article/2758 (accessed on 20 August 2015).

[74] Peltzer K, Pengpid S. Correlates of healthy fruit and vegetable diet in students in low, middle and high income countries. *Int J Public Health*. 2015;60(1):79-90.

[75] Peltzer K, Pengpid S. Fruits and vegetables consumption and associated factors among in-school

DOI: 10.18535/ijmsci/v2i10.07

adolescents in five Southeast Asian countries. *Int J Environ Res Public Health*. 2012;9(10):3575-3587.

[76] Mozaffarian D, Fahimi S, Singh GM, et al; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371(7):624-634.

[77] Batcagan-Abueg AP, Lee JJ, Chan P, Rebello SA, Amarra MS. Salt intakes and salt reduction initiatives in Southeast Asia: a review. *Asia Pac J Clin Nutr*. 2013;22(4):490-504.

[78] Singapore: Salt Intake Study, 2010. Available online: http://www.worldactiononsalt.com/worldaction/asia/75286.pdf (accessed on 20 August 2015).

[79] Council on Foreign Relations. The Emerging Crisis: Noncommunicable Diseases. Available online: http://www.cfr.org/diseases-noncommunicable/NCDs-interactive/p33802?cid=otr-marketing_use-NCDs_interactive/#!/ (accessed on 20 August 2015).

[80] Monteiro CA. *C.G., Levy RB, Claro RM, Moubarac J-C. Ultra-processing. The big issue for nutrition, disease, health, well-being.* [commentary] World Nutrition; 2012:3.

[81] Moodie R, Stuckler D, Monteiro C, et al; Lancet NCD Action Group. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. 2013;381(9867):670-679.

[82] Simopoulos AP. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. *Biomed Pharmacother*. 2006;60(9):502-507.

[83] Weintraub H. Update on marine omega-3 fatty acids: management of dyslipidemia and current omega-3 treatment options. *Atherosclerosis*. 2013;230(2):381-389.

DOI: 10.18535/ijmsci/v2i10.07