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Plasma vitamin profiles and their associations with metabolic health and mental wellbeing in midlife Asian women

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Vitamins play an essential role in a variety of metabolic pathways involved in energy metabolism and neuronal function and hence, contribute to metabolic, mental and overall health and wellbeing. Women become more susceptible to vitamin deficiencies when transitioning into midlife due to changes in hormonal levels, nutrition, and lifestyle. These factors can potentially predispose them to changes in physical and mental health. The objective of this study is to examine associations between vitamins and health outcomes, including metabolic, mental and muscle health, among Asian women. Women were from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) a prospective longitudinal cohort study. The study measurements were performed in 662 women at postnatal 8–8.5 years study visits at a mean age of 39.9 years. Plasma vitamin concentrations were measured using liquid chromatography-tandem mass spectrometry (A, D, E, K, B) and microbiological assays (B12 and folate). Body mass index (BMI), blood pressure, fasting and post-oral glucose tolerance test 120-min glucose, insulin, HbA1c, triglycerides and HDL-cholesterol were measured. A composite metabolic syndrome (MetS) score was calculated. Self-administered Beck's Depression Inventory, State-Trait Anxiety Inventory and Perceived Stress Scale questionnaires were used to assess mental well-being. Hand grip strength (HGS) was measured using a dynamometer at year 11 study visits. Multivariable regression analyses were used to study the associations between plasma vitamins and metabolic, musculoskeletal and mental health outcomes. Thiamine monophosphate, pyridoxal-5′-phosphate, and cholecalciferol showed a positive association with favourable metabolic health outcomes such as reduced fasting insulin, increased HDL-cholesterol and reduced MetS scores. Plasma all-trans retinol, α-tocopherol, γ-tocopherol, and phylloquinone showed a positive association with increased MetS scores, however this was attenuated by taking into account triglyceride concentrations. Folate showed a positive association with decreased perceived stress. The significant inverse associations of the B-vitamers and cholecalciferol with MetS scores were only present in women with BMI ≥ 23 kg/m^2. Our analysis demonstrated significant associations of plasma vitamins with metabolic and mental health outcomes in the Asian women.

Keywords Healthy ageing, Midlife women, Perimenopause, BMI, Vitamins, Metabolites

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Vitamins play an essential role in a variety of metabolic pathways involved in energy metabolism and neuronal function[1–3]. At certain life stages vitamins are more important for women than for men. During menstruation, pregnancy and menopause there is an increase in nutritional needs among women[4,5]. Women tend to be more susceptible to vitamin deficiencies especially when they transition into midlife as they undergo significant hormonal changes that demand higher levels of certain vitamins. This is potentially contributing to physical and psychological changes[4]. Furthermore, many Asian women, particularly those from South and East Asian backgrounds, are at risk of vitamin deficiencies due to genetic variations, cultural and lifestyle influences, and traditional dietary patterns[6–8]. Vitamin D, for instance, plays a key role in glucose metabolism and insulin sensitivity; its deficiency, which is highly prevalent among Asian women due to limited sun exposure and low dairy intake, has been linked to increased risk of metabolic syndrome and type 2 diabetes[9,10]. B vitamins, particularly B12 and folate are essential in methylation processes and homocysteine metabolism which can impair energy production and increase cardiovascular risk[11–13]. Vitamin B6, folate and B12 are also critical in the synthesis of neurotransmitters such as serotonin and dopamine, which regulate the mood[14]. The deficiencies of these B vitamins are common in vegetarian diets prevalent in many Asian cultures and can negatively influence metabolic health as well as mental well-being. Vitamin A influences adipocyte differentiation and lipid metabolism, and inadequate levels may exacerbate fat accumulation and metabolic disturbances[15]. Moreover, vitamin E, an antioxidant combats oxidative stress and contributes to inflammation and insulin resistance, key features of metabolic dysfunction[16]. Vitamin insufficiency can also amplify the effects of high-carbohydrate diets, which are typical in many Asian diets, by further impairing metabolic regulation[17,18].

Asians are more prone to central obesity, insulin resistance and metabolic syndrome even at similar or lower body mass index compared to Western populations[19,20]. Metabolic syndrome is defined as a cluster of cardiometabolic risk factors including hypertension, hyperglycaemia, abdominal obesity, and dyslipidaemia[21]. The clustering of these risk factors over the lifecourse increases the odds of developing type 2 diabetes, coronary heart disease and stroke[22–24]. The odds are known to be increased when women approach midlife, the transition from perimenopause leading up to menopause[25]. Obesity and metabolic syndrome can also increase the risk of vitamin insufficiency due to a combination of factors including unhealthy diets, insulin resistance, and obesity related chronic inflammation[26,27].

Mental well-being of women is also significantly affected during midlife with hormonal changes contributing to increased risk of anxiety, and depression[28,29]. In addition, vitamin deficiencies such as vitamin B9, B12 and vitamin D deficiencies have been shown to be important contributors to metabolic comorbidities and mental wellbeing[27]. The decline in musculoskeletal health such as muscle strength and muscle mass through various late menopausal stages for women, is also well recognized[30]. Vitamins play an important role in muscle homeostasis contributing to energy production, nerve function, and protection against oxidative stress, thereby maintaining optimal muscle function[31–34]. Deficiency of vitamins such as B1, B6, B12 and folate, and vitamin D in mid-life women was linked to decline in muscle strength and increased risk of sarcopenia independent of age and lifestyle factors[31–34].

As the prevalence of chronic metabolic diseases are escalating across Asia and among Asian women globally, understanding associations between vitamin deficiencies and health outcomes to devise tailored nutrition guidelines, education, and appropriate vitamin supplementation becomes critical. We hypothesize that lower vitamin B and D levels are associated with poorer metabolic health, and further explore whether these and other vitamins have any relationship with mental wellbeing and musculoskeletal health. The aims of this study were to investigate the relationships between plasma vitamin levels and health outcomes and to examine whether these associations differ by BMI in Asian women from the prospective the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study.

Methods

Women were from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, a prospective longitudinal birth cohort study in Singapore (ClinicalTrials.gov: NCT01174875)[35]. A detailed description of the study has been previously published[35,36]. In brief, pregnant women who were 18 years or older, of Chinese, Malay, or Indian ethnic background, were recruited during their first trimester (< 14 weeks) between June 2009 and September 2010 from two major maternity hospitals (National University Hospital (NUH) and KK Women's and Children's Hospital (KKH)) in Singapore and who had the intention to reside in Singapore in the next 5 years, and to deliver their child at NUH or KKH[35]. Pregnant women who were on chemotherapy, psychotropic drugs, or had type 1 diabetes mellitus were excluded[35].

The study was approved by the Institutional Review Board of the National Healthcare Group, Singapore (D/2009/00021, date of approval 26 February 2009) and the Centralized Institutional Review Board of SingHealth, Singapore (2018/2767/D, date of approval 02 March 2009). Written informed consent was obtained from all participants.

A total of 1247 pregnant women were recruited[35]. The present analysis included women who attended the post-pregnancy study visits 8–8.5 years after delivery and had both vitamin concentrations and comprehensive metabolic markers measured. Sociodemographic characteristics such as age, income and ethnicity, and dietary supplement intake, were ascertained through interviewer administered questionnaires. A validated food frequency questionnaire (FFQ) was performed at post-pregnancy study visit 6 years after delivery and the total daily energy intake in kcal was estimated from the FFQ. A healthy eating index (HEI) score to assess diet quality was derived from the FFQ as previously described[37].

Measurements of plasma vitamin levels

Blood samples were collected after 8 h overnight fasting. Fasted blood samples were processed within 4 h and stored at −80 °C and subsequently analyzed to measure plasma concentrations of vitamins and metabolic markers.

Vitamin B1 (thiamine), thiamine monophosphate (TMP), vitamin B2 (riboflavin, flavin mononucleotide (FMN)), vitamin B3 (nicotinamide, N1-methylnicotinamide (N1-MNAM)), vitamin B6 (pyridoxal-5'-phosphate (PLP) and pyridoxal (PL)), vitamin A (all-trans retinol), vitamin D (25-hydroxyvitamin D3), vitamin E (γ-tocopherol, α-tocopherol) and vitamin K1 (phylloquinone), were measured using a targeted liquid chromatography-tandem mass spectrometry platform (BEVITAL AS Ltd., Bergen, Norway, www.bevital.no). Vitamin B9 (folate) and vitamin B12 (cobalamin) were measured using microbiological assays based on a chloramphenicol-resistant strain of *Lactobacillus casei*, and a colistin sulfate-resistant strain of *Lactobacillus leichmannii*, respectively (BEVITAL AS Ltd., Bergen, Norway, www.bevital.no). The microbiological assay for folate is considered as the gold standard and method of choice[38] and the microbiological assay cobalamin has been shown to have excellent assay performance over a wide range of concentrations[39]. Quality control data showed coefficients of variation < 10%[40,41].

Vitamin D status was defined based on the Endocrine Society Clinical Practice Guideline[42]. Vitamin D < 50 nmol/L was considered deficiency and < 30 nmol/L was defined as severe deficiency[42,43]. Vitamin B12 level of < 150 pmol/L was considered as deficiency while 150–220 pmol/L was considered B12 insufficiency[44,45]. Folate level < 10 nmol/L was considered deficiency based on the World Health Organization (WHO) recommendation[46,47].

Metabolic markers

Height (cm) and weight (kg) were measured in duplicates and the average of the 2 measurements was used for the analysis. BMI was calculated as weight/ height^2 (kg/m^2). BMI was also examined by dichotomizing into higher BMI (BMI ≥ 23 kg/m^2) and lower BMI (BMI < 23 kg/m^2) using BMI threshold of 23 kg/m^2, cut-off for overweight and obesity according to World Health Organization BMI classification for Asians[48].

Peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in duplicates from the right upper arm in a sitting position (Dinamap CARESCAPE V100, GE Healthcare, Milwaukee, WI) and the average of the 2 measurements was used for the analysis.

A 75 g oral glucose tolerance test (OGTT) was performed. Fasting plasma glucose (FPG) and plasma glucose 2 h after the glucose load, were analyzed using the hexokinase method on an automated analyzer (Abbott Architect c8000) in the clinical laboratory. Haemoglobin A1c (HbA1c) was measured in fasted whole blood using an automated direct enzymatic method (Abbott Architect c8000) in the clinical laboratory. Fasting serum insulin using a sandwich chemiluminescent immunoassay on an automated analyzer (Beckman DxI 800), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol) and total cholesterol using automated enzymatic methods (Beckman AU5800) in the clinical laboratory.

The marker of insulin resistance, the homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) was calculated by multiplying fasting insulin in mU/L by FPG in mmol/mL and dividing by 22.5[49]. A composite score of metabolic health, MetS severity score was calculated using the sum of the z-scores of FPG, BMI, (SBP + DBP)/2, TG minus the z-score of HDL-cholesterol[50].

Mental well-being

An internationally validated 21-item self-administered inventory, the Beck's Depression Inventory-II (BDI-II) was used to measure the severity of depression in adults[51]. Women were asked to rate the depressive symptoms over the past two weeks in a 4-point Likert scale, and the scores were summed to derive a total score. Higher scores indicate greater severity of depressive symptoms.

The State Trait Anxiety Inventory (STAI), a 40-item, self-administered inventory was used to measure symptoms of anxiety in adults[52]. Using Likert scale, women rated how anxious they felt at the current moment (state anxiety; STAI-S) and also their dispositional anxiety (trait anxiety; STAI-t). Scores were summed to compute a total STAI (STAI-S + STAI-T) score, with higher scores indicating higher levels of anxiety. The Perceived Stress Scale (PSS), a 10-item questionnaire to measure levels of perceived stress scored on a 5-point scale: the higher the total score the higher level of perceived stress[53].

Maximum hand grip strength

Maximum hand grip strength (HGS) was measured using the microFET® HandGRIP hand dynamometer at year 11 postnatal visit. Women were asked to sit straight upright with the elbow extended at the side, with a neutral grip. Research coordinators demonstrated the use of the dynamometer first and women were subsequently instructed to squeeze the dynamometer as hard as possible for 3 s and then let go. The HGS measurement was conducted two times for dominant hand. Measurements were recorded to the nearest 0.5 Newton, and the maximum HGS value of the two tests were used for analysis in this study.

Statistical analyses

Vitamin levels were log-transformed (log10) to reduce skewness. Univariate and multivariable regression models were performed to examine the associations between vitamin levels as the exposures and health outcomes as the outcomes of interest. All models were adjusted for ethnicity, age and educational attainment which are known to influence the associations between vitamins and health outcomes. Each model included a vitamin level as an exposure of interest, and a health outcome adjusting for covariates.

In this analysis, we focused on the associations between circulating levels of multiple vitamins as objective biomarkers and health outcomes. Diet and physical activity were not included as covariates for several reasons.

Adjusting for overall diet, e.g., dietary scores or total energy intake may introduce overadjustment bias and may remove meaningful variation in vitamin levels that is itself driven by dietary intake, potentially underestimating their associations with health outcomes. For physical activity, its role as a potential confounder is not consistent across all vitamins; while it may influence vitamin D levels via sun exposure, it may not be relevant for B vitamins such as B12, folate, or fat-soluble vitamins obtained primarily through diet. In addition, adjusting for physical activity in this context could introduce collider bias, particularly if both vitamin status and health outcomes influence activity levels. Exclusion of nutrition and physical activity may minimize model complexity and reduce the risk of overfitting,

Among lipid-soluble vitamins, vitamin D has its specific carrier[54] and is not transported by lipoprotein particles. Vitamin A is known to be transported in a multifaceted nature including through lipoproteins[55] while vitamin E and vitamin K are circulated in the blood stream by triglyceride-rich lipoproteins particles[54]. Therefore, in multivariable regression models for vitamins A, E and K we further adjusted for triglyceride concentration.

Overweight and obesity could alter metabolism of vitamins and influence nutritional status which may contribute to development of adverse health outcomes especially metabolic health[56,57]. We therefore investigated whether associations between vitamins and the composite metabolic marker, MetS score were modified by BMI status, higher vs. lower BMI. The statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. False discovery rate (FDR)-corrected p-value obtained using the Benjamini–Hochberg method for adjusting for multiple comparisons.

Results

Table 1 shows the characteristics of the study participants. A total of 662 women from the three major ethnic groups in Singapore were included: 388 (58.7%) Chinese, 161 (24.4%) Malay and 112 (16.9%) Indian women. The mean (SD) of age of the women was 39.8 (5.1) years the age range being 27–55 years. 125 (18.9%) women were < 35 years, 214 (32.3%) were 35–40 years and 323 (48.8%) were > 40 years. The range of BMI varied from 17.0 to 47.6 kg/m^2 with a mean (SD) of 25.4 (5.2) kg/m^2. 60.6% of the women had a BMI ≥ 23 kg/m^2 and had a less favourable metabolic profile but similar mental wellbeing scores (BDI, STAI and PSS) compared to women with BMI < 23 kg/m^2 (Table 1). There was no significant difference in HEI score and total energy intake between women with BMI ≥ 23 kg/m^2 compared to women with BMI < 23 kg/m^2, however more women with BMI < 23 kg/m^2 reported dietary supplement intake.

Over 30% of the women had folate deficiency, 15.3% of the women had vitamin B12 deficiency or insufficiency, and 48.7% of the women had either vitamin D deficiency or severe deficiency. Women with higher BMI more often had insufficiency and/or deficiency of vitamin B12, folate or vitamin D (Supplemental Table 1). Women who reported dietary supplement intake were more likely Chinese and of higher education. These women had lower BMI and HOMA-IR and MetS scores. They also had higher levels of thiamine, thiamine monophosphate, pyridoxal-5'-phosphate, folate, vitamin B12, and 25-hydroxyvitamin D3 levels in their blood (Supplemental Table 2).

Vitamin B1 (thiamine) and vitamin B2 (riboflavin) plasma concentrations were similar in women with higher BMI vs. lower BMI while their metabolites (B1 (TMP) and B2 (FMN)) were lower in women with higher BMI. Vitamin B6 (both PLP and PL), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D and vitamin K were significantly lower in women with higher BMI than those with lower BMI. Vitamin B3 metabolite (nicotinamide) and vitamin E (α tocopherol and γ tocopherol) were higher in these women with higher BMI. Vitamin A (retinol) and vitamin B3 metabolite (N1-MNAM) were similar in women in the two BMI groups (Table 1).

Vitamins and favorable health outcomes

Associations between vitamin levels/concentrations and favorable health outcomes adjusting for age, ethnicity, and education attainment are described in Table 2.

Metabolic outcomes

Higher TMP (B1 vitamer) was associated with lower FPG, 2-h post-OGTT glucose, HbA1c, fasting insulin, HOMA-IR and higher HDL-cholesterol. Higher PLP (vitamin B6) was associated with lower FPG. Higher PLP (B6) and vitamin D were associated with lower fasting insulin and lower HOMA-IR. Higher vitamin B6 (PLP and PL) and vitamin D were associated with higher HDL-cholesterol (Table 2). TMP (B1 vitamer), vitamin B6 (PLP and PL), vitamin B12 and vitamin D were associated with lower metabolic composite scores i.e. MetS scores. In the stratified analyses by BMI groups, the favourable associations with higher vitamin levels were only observed in women with higher BMI (Table 3).

Mental wellbeing

Higher vitamin B9 Folate was associated with lower depressive symptoms and lower perceived stress (Table 2).

Maximum hand grip strength

Higher vitamin B1 (TMP) was associated with higher HGS. However, associations were not statistically significant after taking age, ethnicity, and educational attainment into account (Table 2).

Vitamins and unfavourable health outcomes

In the adjusted multivariable regression models (Table 2), higher nicotinamide (B3 vitamer) and vitamin E (α tocopherol) were associated with higher SBP and DBP. Higher nicotinamide (B3 vitamer), vitamin A, vitamin E (α and γ tocopherol) and vitamin K1 were associated with TG. Higher vitamin A and vitamin E (α and γ tocopherol) were associated with markers of worse glucose metabolism such as higher FPG, 2-h post-OGTT

Characteristics of participants	N	All	Women with BMI ≥ 23 kg/m² 402 (60.8%)	Women with BMI < 23 kg/m² 259 (39.2%)	*P*
Age (years)	662	39.8 (5.1)	39.6 (5.3)	40.1 (4.8)	0.175
Ethnicity	661				< 0.001
Chinese		388 (58.7)	183 (47.2)	205 (52.8)	
Malay		161 (24.4)	132 (82.0)	29 (18.0)	
Indian		112 (16.9)	87 (77.7)	25 (22.3)	
Education	570				0.001
Secondary and below		155 (27.2)	105 (67.7)	50 (32.3)	
ITE, GTC and Diploma		194 (34.0)	127 (65.5)	67 (34.5)	
University and higher		221 (38.8)	116 (52.5)	105 (47.5)	
BMI (kg/m²)	661	25.42 (5.24)	28.44 (4.54)	20.73 (1.50)	< 0.001
Healthy eating index (HEI) score	546	55.95 (7.38)	55.69 (7.33)	56.38 (7.42)	0.287
Total energy intake (from FFQ)	546	2417.62 (919.66)	2435.84 (952.46)	2388.96 (872.44)	0.560
Supplement use	650				
Yes		209 (32.3)	110 (28.1)	99 (38.4)	0.003
No		441 (67.8)	282 (71.9)	159 (61.6)	
Metabolic markers					
Systolic blood pressure (mmHg)	631	112 (13)	115 (14)	106 (10)	< 0.001
Diastolic blood pressure (mmHg)	631	67 (10)	69 (10)	64 (8)	< 0.001
Fasting glucose (mmol/L)	633	5.00 (1.03)	5.13 (1.11)	4.79 (0.86)	< 0.001
2-h post-OGTT glucose (mmol/L)	624	6.34 (2.17)	6.82 (2.47)	5.62 (1.34)	< 0.001
Glycated haemoglobin (HbA1c) (%)	661	5.27 (0.61)	5.35 (0.66)	5.16 (0.51)	< 0.001
Fasting insulin (mIU/L) †	655	6.00 (5.70)	7.90 (6.90)	4.40 (2.63)	< 0.001
HOMA-IR†	628	1.29 (1.34)	1.76 (1.77)	0.91 (0.67)	< 0.001
Fasting triglycerides (mmol/L) †	560	0.89 (0.53)	0.91 (0.58)	0.78 (0.40)	< 0.001
Fasting HDL-cholesterol (mmol/L)	560	1.37 (0.29)	1.31 (0.27)	1.47 (0.30)	< 0.001
Metabolic syndrome severity score (MetS)	514	0.04 (3.24)	1.47 (3.08)	− 2.24 (1.90)	< 0.001
Mental wellbeing					
Beck Depression Inventory (BDI) score†	306	4.0 (9.3)	4.0 (9.0)	3.5 (10.0)	0.926
State Trait Anxiety Inventory (STAI) total score†	347	65.0 (27.0)	65.0 (27)	65.0 (27)	0.485
Perceived Stress Scale (PSS) score†	465	15.0 (8.0)	15.0 (8.0)	15.0 (6.0)	0.665
Hand grip strength (Newton)	460	183 (64)	183 (65)	184 (63)	0.396
B-vitamin biomarker levels†					
Vitamin B1 Thiamine (nmol/L)	662	1.89 (1.05)	1.87 (1.00)	1.91 (1.21)	0.584
Vitamin B1 Thiamine monophosphate (nmol/L)	662	6.37 (2.91)	6.03 (2.80)	6.84 (2.95)	< 0.001
Vitamin B2 Riboflavin (nmol/L)	662	13.55 (15.70)	12.80 (15.16)	13.90 (15.51)	0.256
Vitamin B2 Flavin mononucleotide (nmol/L)	662	16.20 (7.00)	15.60 (6.50)	16.80 (7.20)	0.002
Vitamin B3 Nicotinamide (nmol/L)	654	779 (341)	800 (360)	739 (285)	< 0.001
Vitamin B3 N1-methylnicotinamide (nmol/L)	654	125 (66)	122 (65)	133 (67)	0.317
Vitamin B6 Pyridoxal-5'-phosphate (nmol/L)	662	48.55 (31.25)	45.20 (27.60)	55.40 (36.20)	< 0.001
Vitamin B6 Pyridoxal (nmol/L)	662	7.58 (4.36)	7.26 (4.10)	8.29 (4.81)	< 0.001
Vitamin B9 Folate (nmol/L)	661	12.76 (9.41)	11.76 (7.37)	15.30 (11.45)	< 0.001
Vitamin B12 Cobalamin (pmol/L)	662	326 (155)	313 (140)	347 (165)	< 0.001
Lipid soluble vitamins†					
Vitamin A Retinol (μmol/L)	662	1.48 (0.37)	1.48 (0.38)	1.49 (0.36)	0.978
Vitamin D 25-hydroxyvitamin D3 (nmol/L)	662	50.75 (30.4)	44.25 (30.03)	58.80 (24.90)	< 0.001
Vitamin E Gamma tocopherol (μmol/L)	662	1.86 (0.88)	1.89 (0.95)	1.78 (0.81)	0.005
Vitamin E Alpha tocopherol (μmol/L)	662	33.85 (9.60)	35.20 (10.20)	32.50 (8.80)	< 0.001
Vitamin K Phylloquinone (nmol/L)	533	1.06 (1.02)	0.95 (1.04)	1.20 (0.94)	0.017

Table 1. Characteristics of participants Data shown are N (%) for categorical variables, mean (SD) for continuous variables, and median (interquartile range) as indicated by.† *P*-values were derived from two sample *t*-tests for continuous variables with normal distribution, Wilcoxon rank sum tests for continuous variables with non-normal distribution and Fisher exact tests for categorical variables. p values < 0.05 was considered significant.

Log10 transformed vitamin	SBP (mmHg)		DBP (mmHg)		Fasting glucose		2-h OGTT glucose		HbA1c	
	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p
Vitamin B1 (Thiamine)										
Model 1	− 0.04 (− 4.80, 4.72)	9.90E−01	− 0.93 (− 4.43, 2.57)	7.85E−01	− 0.21 (− 0.59, 0.16)	4.87E−01	0.25 (− 0.55, 1.05)	7.24E−01	− 0.00 (− 0.22, 0.22)	9.94E−01
Model 2	3.07 (− 1.95, 8.08)	4.38E−01	1.16 (− 2.69, 5.02)	7.45E−01	− 0.21 (− 0.64, 0.22)	5.69E−01	0.42 (− 0.47, 1.31)	5.71E−01	0.03 (− 0.22, 0.28)	9.10E−01
Vitamin B1 (TMP)										
Model 1	− 10.95 (− 17.43, − 4.47)	**6.29E−03**	− 7.25 (− 12.02, − 2.48)	**1.56E−02**	− 1.14 (− 1.65, − 0.64)	**1.27E−04**	− 2.00 (− 3.09, − 0.92)	**2.61E−03**	− 0.44 (− 0.74, − 0.15)	**1.56E−02**
Model 2	− 6.18 (− 13.38, 1.02)	2.47E−01	− 4.78 (− 10.31, 0.76)	2.46E−01	− 1.32 (− 1.93, − 0.71)	**3.29E−04**	− 1.76 (− 3.05, − 0.47)	**3.17E−02**	− 0.50 (− 0.84, − 0.16)	**2.00E−02**
Vitamin B2 (Riboflavin)										
Model 1	− 3.46 (− 6.37, − 0.56)	7.29E−02	− 0.94 (− 3.09, 1.21)	6.05E−01	− 0.16 (− 0.39, 0.07)	3.64E−01	0.12 (− 0.36, 0.61)	7.95E−01	0.01 (− 0.12, 0.14)	9.56E−01
Model 2	− 1.96 (− 5.05, 1.12)	4.22E−01	− 0.06 (− 2.44, 2.31)	9.76E−01	− 0.13 (− 0.40, 0.13)	5.43E−01	0.33 (− 0.21, 0.87)	4.49E−01	0.03 (− 0.12, 0.18)	8.56E−01
Vitamin B2 (FMN)										
Model 1	− 4.33 (− 10.44, 1.79)	3.64E−01	− 1.13 (− 5.63, 3.37)	7.95E−01	− 0.42 (− 0.90, 0.06)	2.36E−01	− 0.50 (− 1.52, 0.52)	5.61E−01	− 0.11 (− 0.39, 0.16)	6.32E−01
Model 2	− 2.94 (− 9.50, 3.61)	5.90E−01	− 0.18 (− 5.2, 4.87)	9.73E−01	− 0.46 (− 1.01, 0.09)	2.65E−01	− 0.18 (− 1.32, 0.96)	8.64E−01	− 0.07 (− 0.38, 0.25)	8.38E−01
Vitamin B3 (Nicotinamide)										
Model 1	15.01 (7.42, 22.61)	**1.11E−03**	9.97 (4.40, 15.55)	**3.66E−03**	0.75 (0.15, 1.36)	5.91E−02	1.50 (0.20, 2.80)	8.59E−02	0.60 (0.26, 0.94)	**6.29E−03**
Model 2	13.60 (5.68, 21.52)	**6.29E−03**	8.63 (2.56, 14.69)	**2.35E−02**	0.64 (− 0.05, 1.34)	1.95E−01	1.34 (− 0.10, 2.82)	1.95E−01	0.60 (0.22, 0.98)	**1.11E−02**
Vitamin B3 (N-methyl nicotinamide)										
Model 1	1.88 (− 3.52, 7.27)	6.92E−01	2.25 (− 1.70, 6.20)	4.83E−01	− 0.27 (− 0.69, 0.15)	4.14E−01	− 0.44 (− 1.34, 0.45)	5.61E−01	− 0.00 (− 0.25, 0.24)	9.90E−01
Model 2	1.25 (− 4.32, 6.82)	8.24E−01	1.49 (− 2.77, 5.74)	6.92E−01	− 0.38 (− 0.85, 0.09)	2.84E−01	− 0.27 (− 1.26, 0.72)	7.73E−01	− 0.04 (− 0.31, 0.23)	8.80E−01
Vitamin B6 (Pyridoxal phosphate)										
Model 1	− 5.05 (− 9.27, − 0.82)	6.99E−02	− 3.59 (− 6.69, − 0.48)	8.59E−02	− 0.55 (− 0.88, − 0.22)	**6.29E−03**	− 0.75 (− 1.45, − 0.06)	1.12E−01	− 0.24 (− 0.43, − 0.05)	5.69E−02
Model 2	− 3.32 (− 7.84, 1.21)	3.51E−01	− 2.44 (− 5.92, 1.04)	3.68E−01	− 0.55 (− 0.93, − 0.17)	**2.00E−02**	− 0.56 (− 1.35, 0.23)	3.66E−01	− 0.20 (− 0.42, 0.02)	2.02E−01
Vitamin B6 (Pyridoxal)										
Model 1	− 1.32 (− 5.40, 2.76)	7.21E−01	− 0.77 (− 3.77, 2.23)	7.95E−01	− 0.26 (− 0.57, 0.06)	2.84E−01	− 0.32 (− 0.99, 0.35)	5.69E−01	− 0.12 (− 0.30, 0.06)	3.96E−01
Model 2	− 0.77 (− 4.97, 3.44)	8.56E−01	0.08 (− 3.15, 3.31)	9.76E−01	− 0.29 (− 0.65, 0.06)	2.73E−01	− 0.24 (− 0.97, 0.50)	7.23E−01	− 0.13 (− 0.33, 0.08)	4.31E−01
Vitamin B9 (Folate)										
Model 1	− 4.68 (− 8.86, − 0.50)	9.50E−02	− 2.10 (− 5.18, 0.98)	3.90E−01	− 0.15 (− 0.48, 0.17)	5.71E−01	0.34 (− 0.35, 1.03)	5.66E−01	− 0.04 (− 0.23, 0.15)	8.24E−01
Model 2	− 3.39 (− 8.05, 1.27)	3.53E−01	− 0.53 (− 4.19, 3.13)	8.79E−01	− 0.20 (− 0.60, 0.20)	5.55E−01	0.55 (− 0.28, 1.38)	4.00E−01	− 0.05 (− 0.28, 0.18)	8.38E−01
Vitamin B12 (Cobalamin)										
Model 1	− 3.71 (− 10.32, 2.89)	4.90E−01	− 3.03 (− 7.89, 1.83)	4.31E−01	0.05 (− 0.46, 0.56)	9.26E−01	0.05 (− 1.02, 1.12)	9.61E−01	− 0.14 (− 0.43, 0.16)	5.71E−01
Model 2	− 1.62 (− 8.85, 5.61)	8.24E−01	− 1.14 (− 6.70, 4.42)	8.38E−01	0.28 (− 0.33, 0.88)	5.83E−01	0.60 (− 0.66, 1.85)	5.71E−01	0.03 (− 0.32, 0.38)	9.30E−01
Vitamin A (Retinol)										
Model 1	15.43 (3.43, 27.43)	5.09E−02	9.39 (0.55, 18.22)	1.20E−01	0.89 (− 0.06, 1.84)	1.91E−01	2.75 (0.74, 4.75)	**3.17E−02**	0.47 (− 0.07, 1.01)	2.43E−01
Model 2	15.50 (3.15, 27.85)	5.69E−02	10.03 (0.54, 19.52)	1.22E−01	0.73 (− 0.35, 1.80)	3.90E−01	3.30 (1.09, 5.50)	**1.56E−02**	0.47 (− 0.15, 1.08)	3.32E−01
Vitamin D (Cholecalciferol)										
Model 1	− 8.41 (− 13.65, − 3.16)	**1.11E−02**	− 3.92 (− 7.79, − 0.04)	1.46E−01	− 0.30 (− 0.71, 0.12)	3.60E−01	− 0.94 (− 1.80, − 0.07)	1.12E−01	− 0.17 (− 0.41, 0.06)	3.51E−01
Model 2	− 3.87 (− 10.96, 3.22)	5.03E−01	− 0.49 (− 5.95, 4.97)	9.28E−01	− 0.33 (− 0.93, 0.26)	4.92E−01	− 0.25 (− 1.48, 0.98)	8.38E−01	− 0.13 (− 0.47, 0.22)	6.78E−01
Vitamin E (Alpha tocopherol)										
Model 1	28.47 (17.47, 39.19)	**4.50E−06**	17.56 (9.63, 25.50)	**1.81E−04**	2.69 (1.84, 3.54)	**4.63E−08**	5.37 (3.54, 7.21)	**4.25E−07**	1.63 (1.15, 2.11)	**2.72E−09**
Model 2	20.99 (9.56, 32.43)	**2.15E−03**	14.55 (5.73, 23.36)	**6.29E−03**	2.60 (1.64, 3.56)	**3.68E−06**	5.24 (3.22, 7.26)	**1.07E−05**	1.68 (1.13, 2.23)	**1.84E−07**
Vitamin E (Gamma tocopherol)										
Model 1	7.44 (0.88, 14.00)	8.89E−02	3.54 (− 1.30, 8.37)	3.51E−01	1.35 (0.84, 1.86)	**4.77E−06**	2.92 (1.83, 4.01)	**3.68E−06**	0.83 (0.54, 1.12)	**1.07E−06**

Continued

Log10 transformed vitamin	SBP (mmHg)		DBP (mmHg)		Fasting glucose		2-h OGTT glucose		HbA1c	
	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p
Model 2	11.84 (5.10, 18.57)	**6.29E−03**	4.84 (− 0.50, 10.17)	2.15E−01	1.46 (0.88, 2.04)	**1.40E−05**	3.16 (1.94, 4.38)	**5.74E−06**	0.81 (0.47, 1.14)	**4.03E−06**
Vitamin K1 (Phylloquinone)										
Model 1	0.22 (− 4.15, 4.60)	9.61E−01	− 1.79 (− 5.01, 1.42)	4.91E−01	0.15 (− 0.23, 0.52)	6.49E−01	0.51 (− 0.26, 1.27)	4.00E−01	0.10 (− 0.11, 0.31)	5.71E−01
Model 2	0.41 (− 4.30, 5.11)	9.29E−01	− 0.74 (− 4.38, 2.89)	8.38E−01	0.11 (− 0.32, 0.54)	7.92E−01	0.58 (− 0.28, 1.44)	3.90E−01	0.11 (− 0.14, 0.35)	6.05E−01

Log10 transformed vitamin	Fasting insulin		HOMA-IR		Triglycerides		HDL-cholesterol	
	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p
Vitamin B1 (Thiamine)								
Model 1	− 1.10 (− 3.22, 1.02)	5.38E−01	− 0.39 (− 0.95, 0.22)	4.27E−01	0.04 (− 0.17, 0.24)	8.56E−01	0.18 (0.06, 0.29)	**1.11E−02**
Model 2	0.07 (− 2.29, 2.43)	9.74E−01	− 0.11 (− 0.75, 0.53)	8.56E−01	0.075 (− 0.16, 0.31)	7.21E−01	0.11 (− 0.01, 0.23)	2.23E−01
Vitamin B1 (TMP)								
Model 1	− 9.79 (− 12.62, − 6.96)	**1.31E−09**	− 2.98 (− 3.75, − 2.21)	**7.89E−12**	− 0.19 (− 0.46, 0.10)	4.00E−01	0.42 (0.27, 0.57)	**1.75E−06**
Model 2	− 9.27 (− 12.56, − 5.99)	**3.26E−06**	− 2.90 (− 3.78, − 2.02)	**8.39E−08**	− 0.09 (− 0.41, 0.24)	7.76E−01	0.29 (0.12, 0.46)	**6.29E−03**
Vitamin B2 (Riboflavin)								
Model 1	− 1.14 (− 2.44, 0.16)	2.35E−01	− 0.29 (− 0.65, 0.07)	2.84E−01	− 0.03 (− 0.15, 0.10)	8.38E−01	0.10 (0.03, 0.17)	**2.00E−02**
Model 2	− 0.62 (− 2.04, 0.81)	6.05E−01	− 0.14 (− 0.53, 0.25)	6.79E−01	0.04 (− 0.11, 0.18)	7.95E−01	0.07 (0.00, 0.15)	1.39E−01
Vitamin B2 (FMN)								
Model 1	− 4.17 (− 6.87, − 1.47)	**1.56E−02**	− 1.15 (− 1.89, − 0.40)	**1.56E−02**	0.03 (− 0.24, 0.30)	9.10E−01	0.30 (0.16, 0.45)	**4.23E−04**
Model 2	− 3.62 (− 6.46, − 0.77)	5.45E−02	− 0.99 (− 1.78, − 0.19)	5.91E−02	0.14 (− 0.15, 0.44)	5.69E−01	0.19 (0.04, 0.34)	5.69E−02
Vitamin B3 (Nicotinamide)								
Model 1	4.38 (0.96, 7.80)	5.09E−02	1.22 (0.27, 2.17)	5.09E−02	0.53 (0.20, 0.86)	**1.11E−02**	− 0.18 (− 0.36, 0.01)	1.65E−01
Model 2	2.39 (− 1.47, 6.25)	4.32E−01	0.67 (− 0.36, 1.71)	4.08E−01	0.60 (0.21, 0.98)	**1.11E−02**	− 0.11 (− 0.32, 0.09)	4.91E−01
Vitamin B3 (N-methyl nicotinamide)								
Model 1	− 1.34 (− 3.76, 1.09)	4.97E−01	− 0.47 (− 1.13, 0.19)	3.61E−01	0.18 (− 0.06, 0.42)	3.24E−01	0.05 (− 0.08, 0.18)	6.74E−01
Model 2	0.47 (− 2.15, 3.09)	8.56E−01	− 0.12 (− 0.83, 0.58)	8.56E−01	0.19 (− 0.07, 0.45)	3.61E−01	− 0.06 (− 0.20, 0.08)	6.28E−01
Vitamin B6 (Pyridoxal phosphate)								
Model 1	− 4.17 (− 6.00, − 2.34)	**1.15E−04**	− 1.23 (− 1.73, − 0.72)	**3.19E−05**	0.12 (− 0.07, 0.30)	4.27E−01	0.23 (0.13, 0.33)	**5.84E−05**
Model 2	− 3.37 (− 5.34, − 1.40)	**6.29E−03**	− 1.00 (− 1.56, − 0.46)	**2.73E−03**	0.08 (− 0.13, 0.29)	6.78E−01	0.17 (0.07, 0.28)	**1.11E−02**
Vitamin B6 (Pyridoxal)								
Model 1	− 1.80 (− 3.57, − 0.01)	1.46E−01	− 0.51 (− 1.00, − 0.01)	1.37E−01	0.10 (− 0.07, 0.28)	4.60E−01	0.18 (0.08, 0.27)	**2.17E−03**
Model 2	− 1.84 (− 3.69, 0.01)	1.54E−01	− 0.51 (− 1.03, 0.00)	1.56E−01	− 0.00 (− 0.20, 0.19)	9.81E−01	0.18 (0.08, 0.29)	**4.33E−03**
Vitamin B9 (Folate)								
Model 1	− 3.90 (− 5.73, − 2.07)	**3.45E−04**	− 0.98 (− 1.48, − 0.48)	**1.33E−03**	0.05 (− 0.13, 0.22)	7.92E−01	0.18 (0.08, 0.27)	**3.19E−03**
Model 2	− 2.54 (− 4.63, − 0.44)	6.82E−02	− 0.66 (− 1.24, − 0.08)	8.71E−02	0.09 (− 0.12, 0.31)	6.05E−01	0.08 (− 0.03, 0.19)	3.64E−01
Vitamin B12 (Cobalamin)								
Model 1	− 5.04 (− 7.91, − 2.17)	**4.43E−03**	− 1.11 (− 1.89, − 0.32)	**2.66E−02**	− 0.05 (− 0.33, 0.24)	8.56E−01	0.34 (0.19, 0.49)	**1.77E−04**
Model 2	− 3.00 (− 6.19, 0.20)	1.92E−01	− 0.50 (− 1.38, 0.38)	4.83E−01	− 0.09 (− 0.42, 0.24)	7.73E−01	0.21 (0.05, 0.38)	6.99E−02
Vitamin A (Retinol)								
Model 1	5.69 (0.38, 11.01)	1.18E−01	1.79 (0.32, 3.25)	6.56E−02	2.00 (1.51, 2.49)	**9.14E−13**	0.05 (− 0.24, 0.33)	8.56E−01
Model 2	6.96 (1.36, 12.56)	5.91E−02	1.92 (0.36, 3.47)	6.24E−02	2.18 (1.63, 2.73)	**9.14E−13**	− 0.20 (− 0.50, 0.13)	3.96E−01
Vitamin D (Cholecalciferol)								
Model 1	− 6.97 (− 9.27, − 4.68)	**1.43E−07**	− 1.73 (− 2.37, − 1.10)	**2.63E−06**	0.11 (− 0.12, 0.33)	5.71E−01	0.43 (0.31, 0.55)	**1.54E−10**
Model 2	− 5.01 (− 8.16, − 1.85)	**1.11E−02**	− 1.35 (− 2.22, − 0.48)	**1.11E−02**	0.33 (0.01, 0.64)	1.35E−01	0.29 (0.12, 0.45)	**6.29E−03**
Vitamin E (Alpha tocopherol)								
Model 1	9.13 (4.25, 14.00)	**2.17E−03**	3.24 (1.89, 4.60)	**4.35E−05**	2.52 (2.10, 2.95)	**1.42E−25**	0.37 (0.11, 0.63)	**2.35E−02**
Model 2	10.42 (5.07, 15.76)	**9.92E−04**	3.44 (2.01, 4.87)	**4.27E−05**	2.62 (2.15, 3.09)	**4.46E−25**	0.27 (− 0.00, 0.55)	1.58E−01
Vitamin E (Gamma tocopherol)								
Model 1	2.50 (− 0.43, 5.44)	2.51E−01	1.16 (0.36, 1.96)	**2.35E−02**	0.64 (0.36, 0.91)	**8.00E−05**	− 0.03 (− 0.18, 0.13)	8.56E−01
Model 2	3.72 (0.48, 6.97)	8.71E−02	1.53 (0.66, 2.39)	**3.49E−03**	0.80 (0.49, 1.10)	**2.63E−06**	− 0.12 (− 0.29, 0.05)	3.61E−01
Vitamin K1 (Phylloquinone)								
Model 1	− 0.44 (− 2.39, 1.51)	8.24E−01	0.03 (− 0.52, 0.58)	9.56E−01	0.29 (0.09, 0.48)	**2.35E−02**	0.05 (− 0.05, 0.16)	5.42E−01
Model 2	1.59 (− 0.57, 3.76)	3.51E−01	0.45 (− 0.15, 1.04)	3.39E−01	0.44 (0.21, 0.66)	**2.15E−03**	− 0.09 (− 0.20, 0.03)	3.32E−01

	Mental wellbeing							
	Beck depression inventory (BDI)		State-trait anxiety inventory		Perceived stress scale		Hand grip strength (Newton)	
log10 transformed vitamin	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p	B (95% CI)	FDR-p
Vitamin B1 (Thiamine)								
Model 1	2.08 (− 1.89, 6.05)	5.34E−01	6.07 (− 3.25, 15.39)	4.08E−01	0.67 (− 1.74, 3.08)	7.73E−01	30.46 (3.89, 57.04)	8.71E−02
Model 2	3.63 (− 0.78, 8.05)	2.76E−01	2.60 (− 7.84, 13.04)	7.95E−01	0.95 (− 1.74, 3.63)	6.90E−01	22.76 (− 6.65, 52.18)	3.18E−01
Vitamin B1 (TMP)								
Model 1	0.33 (− 4.96, 5.62)	9.52E−01	8.45 (− 4.16, 21.06)	3.96E−01	0.47 (− 2.83, 3.76)	8.80E−01	71.14 (33.80, 108.47)	**1.89E−03**
Model 2	0.82 (− 5.49, 7.13)	8.93E−01	1.38 (− 13.39, 16.15)	9.26E−01	− 0.69 (− 4.52, 3.13)	8.56E−01	50.84 (8.85, 92.83)	6.82E−02
Vitamin B2 (Riboflavin)								
Model 1	1.01 (− 1.33, 3.34)	6.05E−01	2.37 (− 3.18, 7.93)	6.05E−01	− 1.63 (− 3.19, − 0.20)	8.89E−02	− 1.04 (− 17.48, 15.40)	9.52E−01
Model 2	1.51 (− 1.07, 4.09)	4.68E−01	3.55 (− 2.58, 9.69)	4.74E−01	− 0.85 (− 2.49, 0.79)	5.38E−01	− 8.34 (− 26.21, 9.54)	5.73E−01
Vitamin B2 (FMN)								
Model 1	1.61 (− 3.38, 6.60)	7.21E−01	6.22 (− 5.33, 17.76)	5.14E−01	− 2.30 (− 5.49, 0.90)	3.60E−01	− 7.09 (− 41.48, 27.65)	8.38E−01
Model 2	2.61 (− 3.13, 8.34)	5.84E−01	5.88 (− 7.06, 18.83)	5.84E−01	− 2.33 (− 5.88, 1.21)	4.00E−01	− 28.27 (− 66.26, 9.72)	3.42E−01
Vitamin B3 (Nicotinamide)								
Model 1	0.22 (− 6.17, 6.61)	9.73E−01	1.58 (− 13.12, 16.27)	9.10E−01	0.67 (− 3.38, 4.71)	8.56E−01	− 28.18 (− 73.29, 16.93)	4.31E−01
Model 2	1.57 (− 5.43, 8.57)	8.24E−01	2.61 (− 13.57, 18.79)	8.56E−01	0.75 (− 3.80, 5.30)	8.56E−01	− 24.03 (− 72.65, 24.59)	5.61E−01
Vitamin B3 (N-methyl nicotinamide)								
Model 1	0.54 (− 4.03, 5.12)	9.08E−01	5.05 (− 5.40, 15.50)	5.69E−01	1.19 (− 1.52, 3.89)	6.04E−01	3.46 (− 27.60, 34.52)	9.10E−01
Model 2	1.33 (− 3.47, 6.13)	7.73E−01	4.12 (− 6.86, 15.10)	6.71E−01	1.77 (− 1.10, 4.64)	4.32E−01	− 10.66 (− 44.18, 22.85)	7.23E−01
Vitamin B6 (Pyridoxal phosphate)								
Model 1	0.26 (− 3.54, 4.07)	9.49E−01	3.62 (− 5.62, 12.86)	6.49E−01	− 1.13 (− 3.37, 1.12)	5.55E−01	25.61 (0.90, 50.32)	1.33E−01
Model 2	0.34 (− 3.96, 4.64)	9.36E−01	− 0.46 (− 10.92, 10.00)	9.65E−01	− 1.41 (− 3.89, 1.07)	4.83E−01	10.22 (− 17.63, 38.06)	6.78E−01
Vitamin B6 (Pyridoxal)								
Model 1	2.61 (− 1.19, 6.42)	3.84E−01	4.48 (− 4.92, 13.89)	5.71E−01	− 0.28 (− 2.40, 1.84)	8.92E−01	9.78 (− 13.33, 32.89)	6.09E−01
Model 2	3.38 (− 0.88, 7.64)	3.00E−01	1.88 (− 8.46, 12.22)	8.56E−01	− 0.03 (− 2.27, 2.21)	9.88E−01	− 1.22 (− 26.26, 23.82)	9.61E−01
Vitamin B9 (Folate)								
Model 1	− 4.70 (− 8.15, − 1.24)	**3.55E−02**	− 0.45 (− 8.63, 7.72)	9.57E−01	− 3.01 (− 5.13, − 0.89)	**2.35E−02**	26.51 (2.56, 50.46)	1.01E−01
Model 2	− 5.12 (− 9.40, − 0.85)	6.99E−02	− 1.68 (− 11.35, 7.99)	8.56E−01	− 3.26 (− 5.71, − 0.81)	**3.94E−02**	8.59 (− 18.09, 35.26)	7.21E−01
Vitamin B12 (Cobalamin)								
Model 1	− 4.68 (− 10.29, 0.93)	2.69E−01	3.77 (− 9.51, 17.04)	7.71E−01	− 1.00 (− 4.51, 2.52)	7.71E−01	9.62 (− 30.28, 49.53)	8.08E−01
Model 2	− 4.98 (− 11.33, 1.37)	3.08E−01	1.62 (− 13.09, 16.32)	9.10E−01	0.05 (− 3.98, 4.07)	9.90E−01	− 7.83 (− 51.95, 36.29)	8.56E−01
Vitamin A (Retinol)								
Model 1	− 2.42 (− 12.65, 7.81)	8.13E−01	2.55 (− 20.90, 25.99)	9.10E−01	− 3.66 (− 9.93, 2.60)	4.68E−01	18.26 (− 49.89, 86. 42)	7.84E−01
Model 2	− 1.84 (− 13.04, 9.37)	8.56E−01	4.33 (− 21.70, 30.35)	8.56E−01	− 4.23 (− 11.13, 2.66)	4.36E−01	− 5.11 (− 78.85, 68.64)	9.49E−01
Vitamin D (Cholecalciferol)								
Model 1	0.45 (− 3.97, 4.87)	9.16E−01	3.93 (− 6.54, 14.41)	6.71E−01	− 0.94 (− 3.60, 1.73)	6.90E−01	40.43 (10.45, 70.41)	**3.55E−02**
Model 2	0.16 (− 6.24, 6.56)	9.76E−01	− 9.35 (− 24.23, 5.53)	4.27E−01	− 2.00 (− 5.89, 1.89)	5.41E−01	− 4.29 (− 47.45, 38.87)	9.18E−01
Vitamin E (Alpha tocopherol)								
Model 1	− 1.76 (− 11.11, 7.58)	8.56E−01	− 3.34 (− 23.73, 17.06)	8.56E−01	− 1.23 (− 6.86, 4.39)	8.27E−01	− 28.01 (− 93,15, 37.14)	6.05E−01
Model 2	− 1.08 (− 11.18, 9.02)	9.10E−01	− 8.78 (− 32.03, 14.48)	6.71E−01	− 1.89 (− 7.92, 4.14)	7.27E−01	− 11.36 (− 80.97, 58.25)	8.56E−01
Vitamin E (Gamma tocopherol)								
Model 1	1.80 (− 3.68, 7.28)	7.19E−01	− 5.78 (− 18.53, 6.96)	5.84E−01	0.11 (− 3.25, 3.47)	9.73E−01	− 1.60 (− 38.96, 35.77)	9.65E−01
Model 2	0.82 (− 5.25, 6.88)	8.89E−01	− 9.75 (− 23.68, 4.19)	3.68E−01	− 1.51 (− 5.21, 2.20)	6.32E−01	− 14.96 (− 56.15, 26.24)	6.79E−01
Vitamin K1 (Phylloquinone)								
Model 1	− 2.59 (− 6.05, 0.88)	3.42E−01	− 2.95 (− 11.26, 5.36)	6.88E−01	− 0.90 (− 3.01, 1.21)	6.05E−01	25.42 (0.92, 49.93)	1.33E−01
Model 2	− 3.55 (− 7.49, 0.40)	2.19E−01	− 7.93 (− 17.47, 1.60)	2.70E−01	− 0.84 (− 3.27, 1.59)	6.92E−01	21.80 (− 5.55, 49.14)	2.97E−01

Table 2. Associations between vitamins and health outcomes. The table presents the changes in health outcomes with 1 $\log_{10}$ unit change in vitamin concentrations. The change is presented as β, the estimated regression coefficient with 95% confidence intervals (CI). Each row represents a multivariable regression model. Model 1 was the unadjusted model and Model 2 was adjusted for age, ethnicity, and highest education attainment. Bold texts indicate the significant associations i.e. FDR-corrected $p < 0.05$. SBP: TMP: Thiamine monophosphate, FMN: Flavin mononucleotide, Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, OGTT: oral glucose tolerance test, HbA1c: Haemoglobin A1c, HDL: high density lipoprotein

log10 transformed vitamin	All		BMI > = 23 kg/m^2		BMI < 23 kg/m^2	
	B (95%CI)	FDR-p	B (95%CI)	FDR-p	B (95%CI)	FDR-p
Vitamin B1 (Thiamine)						
Model 1	−0.86 (−2.13, 0.41)	2.97E−01	−0.29 (−1.89, 1.31)	8.10E−01	−1.25 (−2.40, −0.10)	8.49E−02
Model 2	0.09 (−1.24, 1.41)	9.19E−01	0.79 (−0.93, 2.50)	5.16E−01	−1.27 (−2.52, −0.02)	9.61E−02
Vitamin B1 (TMP)						
Model 1	−6.09 (−7.76, −4.42)	**2.39E−10**	−5.15 (−7.16, −3.13)	**1.28E−05**	−1.36 (−3.72, 0.46)	2.31E−01
Model 2	−4.48 (−6.33, −2.63)	**3.14E−05**	−4.12 (−6.39, −1.85)	**3.41E−03**	−1.30 (−3.34, 0.75)	3.25E−01
Vitamin B2 (Riboflavin)						
Model 1	−1.00 (−1.80, −0.21)	**3.90E−02**	−1.00 (−1.97, −0.03)	9.44E−02	−0.40 (−1.16, 0.36)	4.43E−01
Model 2	−0.41 (−1.24, 0.42)	4.71E−01	−0.68 (−1.72, 0.36)	3.09E−01	−0.01 (−0.85, 0.83)	9.84E−01
Vitamin B2 (FMN)						
Model 1	−2.80 (−4.47, −1.13)	**4.87E−03**	−2.86 (−4.83, −0.89)	**1.80E−02**	0.12 (−1.59, 1.83)	9.19E−01
Model 2	−1.60 (−3.34, 0.14)	1.23E−01	−2.29 (−4.40, −0.18)	8.50E−02	0.65 (−1.19, 2.49)	6.42E−01
Vitamin B3 (Nicotinamide)						
Model 1	3.96 (1.84, 6.07)	**1.82E−03**	2.02 (−0.53, 4.56)	2.02E−01	2.23 (0.10, 4.35)	9.23E−02
Model 2	2.48 (0.24, 4.72)	7.94E−02	0.87 (−1.92, 3.67)	6.63E−01	2.47 (0.15, 4.78)	9.00E−02
Vitamin B3 (N-methyl nicotinamide)						
Model 1	−0.48 (−1.96, 0.99)	6.59E−01	−0.32 (−2.12, 1.49)	8.13E−01	0.45 (−0.93, 1.83)	6.59E−01
Model 2	0.56 (−0.96, 2.09)	6.27E−01	−0.13 (−2.04, 1.78)	9.19E−01	1.42 (−0.08, 2.92)	1.15E−01
Vitamin B6 (Pyridoxal phosphate)						
Model 1	−2.77 (−3.91, −1.63)	**2.90E−05**	−2.37 (−3.88, −0.86)	**7.83E−03**	0.29 (−0.77, 1.35)	6.87E−01
Model 2	−1.92 (−3.15, −0.69)	**7.83E−03**	−1.79 (−3.49, −0.09)	9.23E−02	−0.15 (−1.28, 0.98)	8.58E−01
Vitamin B6 (Pyridoxal)						
Model 1	−1.30 (−2.30, −0.04)	9.44E−02	−1.00 (−2.56, 0.56)	3.24E−01	0.27 (−0.63, 1.17)	6.64E−01
Model 2	−1.17 (−2.29, −0.01)	9.61E−02	−0.73 (−2.39, 0.94)	5.41E−01	−0.38 (−1.34, 0.58)	6.00E−01
Vitamin B9 (Folate)						
Model 1	−2.36 (−3.48, −1.25)	**2.65E−04**	−1.48 (−2.96, 0.00)	1.00E−01	−0.01 (−1.03, 1.01)	9.84E−01
Model 2	−1.18 (−2.43, 0.07)	1.15E−01	−0.52 (−2.22, 1.17)	6.63E−01	−0.08 (−1.26, 1.10)	9.19E−01
Vitamin B12 (Cobalamin)						
Model 1	−3.28 (−5.06, −1.49)	**2.19E−03**	−3.24 (−5.49, −0.98)	**1.80E−02**	0.31 (−1.36, 1.98)	8.10E−01
Model 2	−1.99 (−3.95, −0.03)	9.61E−02	−2.46 (−5.00, 0.07)	1.05E−01	0.43 (−1.45, 2.31)	7.52E−01
Vitamin A (Retinol)						
Model 1	5.69 (2.41, 8.98)	**3.78E−03**	4.86 (0.72, 9.01)	6.19E−02	4.20 (1.24, 7.16)	**2.00E−02**
Model 2	8.12 (4.77, 11.47)	**2.90E−05**	6.39 (1.89, 10.89)	**2.00E−02**	4.93 (1.78, 8.07)	**7.83E−03**
Vitamin D (Cholecalciferol)						
Model 1	−4.80 (−6.19, −3.40)	**1.98E−09**	−2.72 (−4.40, −1.03)	**7.83E−03**	−0.55 (−2.29, 1.19)	6.63E−01
Model 2	−2.53 (−4.47, −0.60)	**3.21E−02**	−2.24 (−4.66, 0.18)	1.22E−01	0.70 (−1.38, 2.78)	6.59E−01
Vitamin E (Alpha tocopherol)						
Model 1	8.65 (5.76, 11.54)	**1.64E−07**	7.81 (4.27, 11.35)	**1.57E−04**	2.73 (−0.15, 5.62)	1.15E−01
Model 2	9.08 (6.13, 12.03)	**7.58E−08**	8.24 (4.46, 12.02)	**1.48E−04**	3.37 (0.27, 6.46)	6.27E−02
Vitamin E (Gamma tocopherol)						
Model 1	2.93 (1.19, 4.68)	**4.87E−03**	2.08 (−0.05, 4.21)	1.05E−01	1.04 (−0.66, 2.75)	3.44E−01
Model 2	4.73 (2.96, 6.51)	**2.05E−06**	4.13 (1.77, 6.49)	**3.77E−03**	1.47 (−0.39, 3.33)	2.02E−01
Vitamin K1 (Phylloquinone)						
Model 1	0.12 (−1.09, 1.33)	9.05E−01	0.81 (−0.65, 2.26)	4.06E−01	0.17 (−1.01, 1.35)	8.55E−01
Model 2	1.62 (0.34, 2.89)	**3.90E−02**	1.99 (0.39, 3.55)	**4.35E−02**	0.37 (−0.98, 1.64)	6.64E−01

Table 3. Associations between vitamins and health outcomes. The table presents the changes in health outcomes with 1 $\log_{10}$ unit change in vitamin concentrations. The change is presented as β, the estimated regression coefficient with 95% confidence intervals (CI). Each row represents a multivariable regression model. Model 1 was the unadjusted model and Model 2 was adjusted for age, ethnicity, and highest education attainment. Bold texts indicate the significant associations i.e. FDR-corrected $p < 0.05$. SBP: TMP: Thiamine monophosphate, FMN: Flavin mononucleotide, Systolic blood pressure, DBP: Diastolic blood pressure, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, OGTT: oral glucose tolerance test, HbA1c: Haemoglobin A1c, HDL: high density lipoprotein.

glucose, fasting insulin, and HOMA-IR. Vitamin A, vitamin E (both α and γ tocopherol) and vitamin K had a positive relationship with MetS scores (Table 3). The significant associations between vitamin A, vitamin E (α tocopherol) and vitamin K were observed only in women in the higher BMI group (Table 3).

Fat soluble vitamins and unfavorable health outcomes adjusted for TG

Lipid-soluble vitamins are circulated in the blood stream by TG-rich lipoproteins particles. Therefore, TG was additionally adjusted for, in the multivariable regression models in the associations between lipid-soluble vitamins and metabolic health outcomes (Supplemental Table 3). The inverse associations between vitamins A, E and K, and metabolic outcomes were attenuated.

Discussion

This study provides a comprehensive profile of plasma vitamin concentrations and their associations with metabolic, mental and musculoskeletal health outcomes in Asian women. These health outcomes are important for women and become more relevant especially when they approach menopausal transition and start to experience hormonal changes. Higher concentrations of B vitamins (vitamin B1, B2, B6, B9, B12) and vitamin D were associated with fewer metabolic risk markers. On the other hand, higher concentrations of fat-soluble vitamins (A, E, K) were associated with an unfavorable metabolic profile in these Asian women. The observed associations were more pronounced in women with a BMI ≥ 23 kg/m$^{2.}$ They also appeared to have lower levels of vitamins and a greater prevalence of vitamin deficiencies compared to women with a BMI < 23 kg/m^2. These findings imply that adiposity may influence the relationship between the studied vitamins, B-vitamins and lipid soluble vitamins, and health outcomes. Higher vitamin B1 (TMP) was associated with higher HGS while higher folate was associated with lower depressive symptoms and less perceived stress.

The Asian women who participated in this study had lower vitamin B1 (thiamine) concentrations than previously reported in Western populations[58,59], but had comparable to those (mean 1.6 nmol/L) from other of parts of Southeast Asia, a region known for being at risk of thiamine deficiency[60]. Vitamin B1 is an important coenzyme for key biological processes involved in glucose, insulin and energy metabolism and contributes to lipid oxidation through its antioxidative property[34,61–63]. When circulating thiamine levels decrease, stored thiamine pyrophosphate in erythrocytes is hydrolyzed to TMP, to be converted to the active form, thiamine diphosphate and released into circulation to promote glucose and insulin metabolism[64]. Higher plasma TMP levels may therefore be a reflection of an increased phosphorylation due to thiamine deficiency. Therefore, the observation of lower thiamine in Asian women in this study and the associations between higher thiamine metabolite TMP and better metabolic profile scores were in line with propositions from previous studies. Additionally, TMP also showed a positive association with maximum HGS. This association can be attributed to an increased availability of TPP hydrolysis derived ATP which is crucial for muscle contraction, hence promoting muscle strength[65].

Our results showed that higher PLP, the active form of vitamin B6 was associated with lower MetS in Asian women. These associations are aligned with existing evidence from other observational studies, where plasma PLP concentrations were inversely associated with MetS, obesity, and diabetes[66–68]. Vitamin B6 has anti-inflammatory properties and can mitigate chronic inflammation which are hallmarks of insulin resistance and metabolic syndrome, this improving metabolic health[69,70].

Water soluble B vitamins; vitamin B6, B9 and B12 are essential for DNA methylation and maintains metabolism of amino acid and lipid balance through one-carbon metabolism[71]. This complex pathway, driven by folate and methionine, and other B vitamins as cofactors produce methyl donors crucial for cellular functions. Deficiencies in B vitamins involved in this pathway disrupt DNA synthesis, provoke inflammation, and increase lipid and homocysteine levels. Homocysteine can cause endothelial damage leading to insulin resistance, metabolic syndrome, cardiovascular and cerebrovascular diseases[72,73]. Supplements like folic acid, vitamin B12, and other B-complex vitamins have been shown to effectively lower plasma homocysteine levels, reducing the risk of chronic cardiometabolic diseases related to their deficiencies[71–74]. We observed an inverse relationship between plasma folate levels, and perceived stress scores. Low levels of folate and vitamin B12 have been found in studies on depression suggesting beneficial effects of folate and B12 for mental wellbeing[75]. Most of the women in this study generally had positive mental health i.e., having low scores for BDI, STAI and PSS. This may explain the lack of associations between vitamins and mental wellbeing measures.

Vitamin D deficiency was prevalent in the study cohort, with half of the women having 25-OHD3 levels below 50 nmol/L and 20% having levels below 30 nmol/L. The inverse relationship of vitamin D to poorer metabolic outcomes is similar to that observed in other studies[76–78]. Many studies have addressed the association between vitamin D deficiency and metabolic markers including MetS[79]. One potential underlying mechanism is through the vitamin D receptor which is expressed in pancreatic β cells and in musculoskeletal and adipose tissues. Vitamin D deficiency can compromise the capacity of β cells to convert pro-insulin into insulin and consequently have a negative influence on glucose-insulin metabolism[80].

On the other hand, higher vitamin B3, vitamin A and vitamin E were associated with an unfavourable metabolic profile in this study. These findings were consistent with findings from many previous studies. These observations could be attributed to elevated levels of circulatory vitamin B3, or triglyceride-dependent lipid soluble vitamin A and E, highlighting the need to consider circulatory levels of vitamins or lipids in interpreting these associations.

Vitamin B3 is a precursor for nicotinamide adenine dinucleotide (NAD+) which is a coenzyme essential for many cellular functions involving energy production, glycolysis and mitochondrial function. Therefore, NAD^+ may support insulin sensitivity and metabolic function[81]. However, chronic overload of nicotinamide, a consequence from B vitamins fortification to prevent deficiency[82], is recognized to induce adverse metabolic health[83]. Grains such as flour and cereals are primary sources of niacin-fortification[84] and widely consumed as an integral part of dietary intake. An excessive intake of nicotinamide has been proposed to trigger oxidative stress

which could disrupt glucose metabolism[85,86] and also impair endothelial function[87] which is an important risk factor for hypertension[88]. Vitamin B3 concentrations in the women in this study appeared to be higher (median of 777 nmol/L) than reported concentrations of 261–449 nmol/L in women in previous studies[89,90]. The elevated nicotinamide levels may be attributable to grain fortification in Singapore, as white rice is a common staple food. Higher vitamin B3 nicotinamide in these women was associated with higher SBP, DBP, HbA1c and metabolic syndrome scores. These findings are consistent with findings from many studies which reported the adverse health impacts from chronic overload of vitamin B3[83–85,91,92]. In an ongoing longitudinal cohort study, the China Health and Nutrition Survey, the risk of new-onset hypertension significantly increased with the incremental increase in dietary niacin intake[87]. Women with lower BMI seemed to be more sensitive to elevated levels of vitamin B3 and further investigation is needed to determine the underlying reason for this observation.

Higher TG and higher metabolic markers were also observed with higher levels of lipid-soluble vitamins i.e., vitamin A retinol and vitamin E, both α- and γ-tocopherol, in this study. These vitamins have antioxidant property and are known to reduce oxidative stress[93] However, these lipid soluble vitamins levels might be dynamic in a chronic inflammatory state and in oxidative stress and can act as ether pro- or antioxidants[94,95]. Many studies including those in Asian populations have shown the positive associations between vitamin A, and impaired glucose tolerance, insulin resistance and in development of type 2 diabetes[96–98]. These relationships were proposed to be mediated through TG[97]. Retinoids increase TG levels by increasing Apo C-III expression[99], an antagonist of serum TG catabolism and involved in glucose metabolism, inflammation, and endothelial function[99]. These findings suggested a possible role of serum TG in mediating the effect between serum retinol and an unfavourable metabolic profile. Vitamin E as a fat soluble vitamin is transported in lipoprotein particles in circulation and therefore, highly correlates with triglyceride and cholesterol levels[100]. When lipid levels are elevated, vitamin E tends to remain in circulation longer, reducing its distribution to tissues where it exerts its antioxidant effects[101]. Thus, levels of circulating vitamin E, the antioxidant and anti-inflammatory marker increases, which in turn lead to compensatory increase in these markers in insulin resistant states[102]. These propositions may explain our findings of positive associations with metabolic risk markers such as high blood pressure, HOMA-IR and metabolic syndrome. The positive associations between vitamin A, α- and γ-tocopherols and metabolic markers were attenuated when TG level was adjusted for in the models further supporting the role of TG in the unfavorable associations between vitamin E and metabolic outcomes.

The strengths of the study include a relatively large cohort of Asian women where multiple vitamin concentrations were measured in plasma by accurate methods, and assessment of important metabolic risk markers and measures of mental health, as well as HGS. While clinical vitamin deficiencies have been well studied, research on the spectrum of vitamin levels and their associations with health outcomes is limited, particularly in Asians. Comprehensive assessment of varying levels of vitamins and health outcomes provide a holistic understanding of those relationships in Asian women. The findings from this study provide population specific insights focusing and guiding in development or personalized nutrition and targeted supplementation recommendations in Asian women.

This study also has some limitations. The study is a cross-sectional observational study thus limiting its ability to establish causality. Observed associations do not confirm that vitamin levels directly influence metabolic or mental health outcomes. The study only includes early midlife and midlife Asian women, thus may potentially limit generalizability to other age groups or to other populations. While vitamin levels are indicative of nutrition and dietary habits, the observed associations with health outcomes may, in part, reflect the influence of overall diet and nutrition rather than a direct effect of the vitamins themselves. Therefore, caution is warranted when interpreting these findings. Adjusting for diet attenuated the inverse associations of the B vitamins and vitamin D with metabolic risk markers (Supplementary Table 4), suggesting that higher plasma B vitamins and vitamin D levels may reflect a healthy dietary pattern. On the other hand, the inverse associations of the B vitamins and vitamin D with MetS scores were more apparent in women who did not report supplement use (Supplementary Table 5), suggesting supplement intake may have a beneficial effect in reducing metabolic risk. In addition, although we have tried to adjust for multiple confounders, there may be residual confounders as with observational studies. The diet and supplement intake data and mental wellbeing scores were self-reported, which might have introduced subjectivity and recall bias. However, the observations in this study in Asian women on vitamins and health outcomes were in line with previous studies conducted on single vitamins or using a combination of a few vitamins.

Taken together, findings from this study suggest that plasma vitamins may play a role in metabolic and mental health in Asian women. Higher circulating vitamin concentrations, indicative of adequate nutrient intake through balanced diets and/or supplementation, are likely to exert beneficial effects on metabolic regulation and mental wellbeing. These findings provide evidence to devise interventions for personalized balanced nutrition and appropriate supplementation in Asian women. Such intervention is important for women to reduce the risk of mobidity and related risk of chronic diseases due to insufficiency or deficiency in these vitamins especially when they approach to midlife and menopause transition. Given the multitude of health benefits of these vitamins, future randomized controlled trials (RCTs) on vitamin supplementation are warranted to confirm their influence on metabolic outcomes in Asian women.

Data availability

Data from the GUSTO study are not publicly available due to multi-institutional cohort data governance and ethical restrictions. Access procedures can be used to obtain the data. After a request is submitted, it is reviewed and approved by the GUSTO Executive Committee. Applicants are required to comply with all applicable laws and partner with GUSTO investigators to access the data. Full collaboration guidelines can be found at: https://gustodatavault.sg/about/request-for-data.

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Author contributions

MTT, VG, SSLT, and JGE designed research; MTT, KMLT, and MZLK conducted research; MDI and RMC analyzed data; and MTT, MDI, RL and KMLT wrote the paper. MTT, KMLT and JGE had primary responsibility for final content. All authors read and approved the final manuscript.

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Declarations

Competing interests

RL, VG and SSLT are employees of Haleon, GlaxoSmithKline Consumer Healthcare Pte Ltd, Singapore. All other authors declare that they have no conflicts of interest.

Ethics approval

The conduct of the GUSTO study was based on the guidelines in the Declaration of Helsinki and all procedures were approved by the Institutional Review Board of the National Healthcare Group, Singapore (D/2009/00021, date of approval 26 Feb 2009) and the Centralized Institutional Review Board of SingHealth, Singapore (2018/2767/D, date of approval 02 March 2009). Written informed consent was obtained from all participants.

Consent for publication

All authors read and approved the final manuscript. Consent for publication has been obtained from the executive committee of the GUSTO study, from Haleon, GlaxoSmithKline, and from the Agency for Science Technology and Research (A*STAR).

Additional information

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