國立臺灣大學公共衛生學院環境與職業健康科學研究所
碩士論文
Graduate Institute of Environmental and Occupational Health Sciences
College of Public Health
National Taiwan University
Master Thesis

NHANES調查2017-2018中，成年人血液中多種維生素與原維生素與共暴露血壓的相關性研究

Associations of multiple serum vitamins and provitamins co-exposure with blood pressure among adults in NHANES, 2017–2018

程心喆
Xin-Zhe, Cheng

指導教授: 郭育良 教授
Advisor: Yue-Liang Guo, M.D., MPH, Ph.D.

中華民國 113 年 1 月
January 2024

doi:10.6342/NTU202400005

國立臺灣大學（碩）博士學位論文
口試委員會審定書

使用美國 2017-2018 年 NHANES 調查探討成年人血液中多種維生素及維生素原共暴露與血壓的相關性研究

Associations between combined multiple serum vitamins/ provitamins and blood pressure among adults in 2017–2018

本論文係程心喆君（學號 R09449015）在國立臺灣大學環境衛生研究所完成之碩士學位論文，於民國 112 年 7 月 20 日承下列考試委員審查通過及口試及格，特此證明

口試委員：郭育良（簽名）

（指導教授）

致謝

三年的時間就如白駒過隙，慕然回首，自己已經度過了碩士的旅程。經過這幾年的不懈努力，學生終於完成了自己的碩士研究，現在想要用此文對於自己研究過程中無私幫助的各位提供謝意。首先非常感謝郭老師，在我站在人生的十字路口，對於未來十分迷茫時，願意幫助我轉學到環職所，能夠繼續我感興趣的研究。另外，在研究過程中，老師總是在鼓勵我前進的同時，對於我的研究提供非常關鍵而且寶貴的建議，啓發我的思考；在不斷與老師討論的過程中我也學到了很多嚴謹至學態度。另外也非常感謝我的口試委員蘇大成老師，杜裕康老師，楊孝友老師以及盧冠宏老師對於我的口試提出的非常有建設性的意見以及對我研究的肯定。通過老師們的建議能夠讓我有機會更加完善自己的研究，以及對於我的研究未來可能應用的方面以及發展有一個更好的認識。同時也要感謝實驗室的學長姐以及學弟妹在每一次實驗室 meeting 中對於我的研究提出的寶貴意見。我的同鄉好友樂樂，圓圓以及宜臻的相互陪伴讓我們在外努力的日子都充滿了歡樂。感謝盧藝以及其他我的高中好友們，不管在什麼時候都愿意抽空聽我報告，不管是對於內容的建議還是對於 ppt 排版的建議都讓我收穫良多。我也想感謝我的家人在我對於不確定的人生選擇的時候給予我完全的信任，讓我有機會能夠一直繼續我的夢想。最後我想要感謝秉宸，在我進入自己完全不熟悉的領域的時候是你一直鼓勵并幫助我，讓我度過了最黑暗無助的時間，另外當我面臨人生的選擇的時候，也是你一直支持我的選擇。

這三年在臺大的時光度過的非常快，但是卻讓我收穫滿滿。這段時間雖然有黑暗，但更多的是快樂，在這裏向每一個陪伴我經歷過這段時光的人表示感謝。

doi:10.6342/NTU202400005

中文摘要

近年來，系統性動脈高血壓被認為是世界範圍內致病和死亡的最主要風險因子之一。以前的研究發現單一的血清原維生素或是維生素和血壓之間有一定相關性。然而，單個維生素往往不能解釋高血壓病情的發生和發展，同時可能忽略潛在的交互作用，因此本研究透過使用三種不同混合暴露模型針對維生素的共同暴露狀態及其對血壓的整體影響進行探討，並觀察各維生素於此共同影響下扮演的角色。因此，我們使用了來自 2017-2018 年美國國家健康與營養檢查調查的數據（NHANES），從 1370 名美國成年人中估計了 13 種維生素與血壓狀況之間的關係。我們使用單一暴露模型、加權分位數總和（WQS）回歸和分位數半參數 G 模型建立線性模型，模擬了維生素混合物的整體效應和混合物中相對重要的成分。此外, 我們還利用貝葉斯核機器回歸（BKMR）建立了非線性回歸模型，估計多種維生素共同暴露與血壓之間的相關性。單一暴露模型顯示，胡蘿蔔素和維生素 D 對收縮壓有負作用，而沒有維生素對舒張壓起具統計學意義之效應。在混合物總體效果估計方面，在三個不同的模型中，維生素混合物通過增加百分位數顯示出對收縮壓的明顯降低作用，而對舒張壓沒有明顯影響。 WQS 模型還表明，順式和反式β胡蘿蔔素和維生素 D 對收縮壓的降低起著相對較爲重要作用。此外，多種維生素和血壓之間的劑量反應關係被 BKMR 模型所證實。與 WQS 模型的結果相同，13 種維生素對血壓有綜合影響；風險隨著混合物水平從第 10 百分位到第 90 百分位遞減。我們的研究結果表明，13 種加入的維生素以及收縮壓的降低之間存在一定關係，其中 β 胡蘿蔔素和維生素 D 相對重要。同時，順式和反式β胡蘿蔔素之間存在一定的交互作用。

關鍵詞：食品與營養；心血管疾病; 加權分位數; 貝葉斯核機器回歸; 混合模型

doi:10.6342/NTU202400005

Abstract

In recent years, systemic arterial hypertension has been regarded as one of the most substantial risk factors for all causes of mobility and mortality worldwide. Previous research has found some correlations between single serum vitamins and blood pressure. Because individual vitamins cannot explain the beginning and course of the disorder, it is necessary to investigate the co-exposure status of vitamins and their precursors (provitamins) as well as their overall impact on blood pressure. Therefore, we estimated the relationship between 13 vitamins and blood pressure status from 1370 American adults based on the National Health and Nutrition Examination Survey (NHANES), 2017–2018. We used a single exposure model, weighted quintile sum (WQS) regression, and g-computation to build linear models, finding the overall effect of the vitamin mixture and the relatively important components of the mixture. Furthermore, we also built nonlinear regression models using Bayesian kernel machine regression (BKMR) to estimate the functional correlation between multiple vitamin exposure and blood pressure. Single exposure model showed that carotene and vitamin D had a negative effect on systolic blood pressure, while no vitamins show a statistically significant effect on diastolic blood pressure. For overall effect estimation, among three different models, the vitamin mixture showed a significant reducing effect on systolic blood pressure by increasing percentile, while it had no significant effect on diastolic blood pressure. The WQS model also demonstrated that cis and trans beta carotene and vitamin D played a significant role in the systolic blood pressure reduction impact. Furthermore, the dose-response relationship between multiple vitamins and blood pressure was confirmed by the BKMR model. Same results as the WQS models， a combined impact of the 13 vitamins was seen on blood

doi:10.6342/NTU202400005

pressure; the risk decreased with mixture levels from the 10th to the 90th percentil. Our findings demonstrated a non-linear relationship between the 13 joined vitamins as well as the reduction in systolic blood pressure, beta-carotene and vitamin D were relatively important in this effect. Meanwhile, cis and trans beta carotene might have non-additive effects.

Keywords: Food and nutrition; Cardiovascular diseases; WQS regression; BKMR; Mix-model

doi:10.6342/NTU202400005

Contents

doi:10.6342/NTU202400005

doi:10.6342/NTU202400005

doi:10.6342/NTU202400005

Table Contents

doi:10.6342/NTU202400005

Figure Contents

doi:10.6342/NTU202400005

Chapter1. Introduction

1.1 The introduction of high blood pressure.

The force of blood against the artery walls is known as blood pressure (BP)[1]. It travels from your heart to different regions of your body via arteries. Blood pressure typically fluctuates and decreases the entire day. Consequently, staying high for longtime it may hurt your heart and lead to health issues[2]. Two factors influence blood pressure: Systolic pressure, the first force, is generated as blood pumps from the heart into the arteries that make up the circulatory system. Diastolic pressure, the second force, is produced while the heart is at rest in between heartbeats. In a blood pressure reading, these two forces are each represented by a number. Nonetheless, the control of blood pressure is extremely complicated. The neurological and endocrine systems play major roles in controlling blood pressure in two different ways[3]. According to one type of autonomic activity, the carotid artery's pressure receptors can detect variations in blood pressure and control it through autonomic reflexes. The downstream mechanisms drive the heart to beat more quickly and simultaneously enhance the heart contraction force, increasing peripheral vascular resistance. On the contrary, parasympathetic nerve activities have the opposite effect on the cardiovascular system, which lowers blood pressure. On the other hand, the Renin-Angiotensin-Aldosterone System (RAAS) also adjusts blood pressure. The declination of renal blood flow activates the RAAS system together with the secretion of Renin. Renin participates in the maturation of angiotensin and aldosterone, which raises blood pressure due to the narrowing of peripheral blood arteries brought on by angiotensin and the

doi:10.6342/NTU202400005

increased sodium reabsorption in the renal tubules brought on by aldosterone. Even though there isn't any proof of a danger threshold across the typical BP range in clinical practice, Prospective observational studies have consistently shown a significant, ongoing, and positive association between BP and cardiovascular disease (CVD)[4]. Along with heart failure, peripheral artery disease, coronary artery disease, ischemic and hemorrhagic stroke, as well as end-stage renal disease, all major symptoms of CVD observed in both sexes, at whole ages throughout adulthood, have a link with blood pressure[567]. Moreover, both systolic and diastolic blood pressure are affected by this relationship, though the adult systolic BP relationship is a little more substantial. High blood pressure, also known as hypertension, involves abnormally elevated blood pressure. The American College of Cardiology and the American Heart Association attributed enhanced guidelines for the treatment of hypertensive disorders in 2017, which defined high hypertension as a blood pressure of 130/80 mmHg or higher. In recent years, systemic arterial hypertension has been regarded as one of the most substantial risk factors for all causes of worldwide morbidity and mortality, affecting more than 25% of adults[8]. Less than fifty percent of individuals with hypertension are conscious of their condition, and many more are aware but are not treated or are treated insufficiently.

1.2 Factors associated with high blood pressure.

Numerous studies have discovered that environmental factors, as well as gene disposition, contribute to the progression of the disease.[9] There is no exception when it comes to the emergence of hypertension-related disorders. Environmental factors can be simply divided

doi:10.6342/NTU202400005

into external and internal factors[10]. A few fundamental biochemical markers, such as c-reactive protein, hematocrit, blood urea, or metabolic markers, for instance, triglycerides, low-density lipoprotein, high-density lipoprotein, are included in the first category of internal factors that take part in the progression of hypertension. Meanwhile, external variables also have a significant impact on our blood pressure. First and foremost, there is a strong correlation between blood pressure and conventional variables including age, gender, race, and body mass index. Additionally, various daily exposed chemicals, for example, air pollutants, heavy metals, household pesticides, phthalates, and so on, affect our blood pressure through inhalation, ingestion, or direct contact. Among them, diet is a crucial exposure pathway. Chemical substances described above may significantly impact blood pressure after entering the body through the digestive tract[111213].

1.3 Dietary nutrients and their healthy effect

Survival, development, and reproduction of creatures rely on nutrients, which are significant environmental components imbibed by lives through diet. Nutrients provided by diet are later digested, absorbed, and transformed into small units that create body tissues or into energy-carrying molecules that support the energy consumption of vital life processes.[14] Moderate and balanced diets can prevent the occurrence of acute and long-term illnesses. According to previous research, hypertension[15] may arise from both undernutrition[16] and overnutrition[17], which are typical phenomena resulting in the uneven distribution of food resources in modern society.

1.3.1 Macronutrients

doi:10.6342/NTU202400005

Compared to micronutrients, which people need in smaller amounts, macronutrients are nutrients that human bodies need in vast amounts. [18]. Examples of macronutrients include lipids, fiber, protein, and water. Human bodies receive around 4 kcal of energy per gram of protein or carbohydrate, compared to approximately 9 kcal per gram of fat[19]. The majority of macronutrients are linked to overnutrition[20], a condition that is especially pronounced in developed nations[21]. Owing to the preference for high-calorie diets[22] and the decreasing level of physical activity[23] of modern people, individuals nowadays regularly uptake energy that exceeds the Total Daily Energy Expenditure (TDEE). Surplus energy is converted into subcutaneous, internal organs accumulating fat, leading to obesity[24]. On the other hand, the number of lipid-carrying lipoproteins also rises in the blood under overnutrition conditions[25]. During this period, lipoproteins tend to lodge in the internal arterial vessel wall, triggering local inflammatory responses which recruit monocytes to enter and aggregate in the vessel wall. Activated monocytes eventually transform into gradual plaques forming foam cells after differentiating into macrophages that engulf accumulated lipoproteins[26]. While chemokines secreted by macrophages recruit more immune cells, cytokines released by macrophages induce the proliferation of vascular smooth muscle cells in the affected area, resulting in plaque fibrosis and accelerating the progression of arteriosclerosis[27]. The buildup of gradual plaque decreases the lumen size of blood vessels by narrowing the cross-section area, which restricts blood flow and increases blood pressure. Not all macronutrients, though, participates in the raising of blood pressure. Short-chain fatty acids and polyunsaturated fatty acids, like Omega-3, one kind of anti-oxidation macronutrient might assist with maintaining the heart and blood vessels healthy[28]. According to previous studies, Omega-3, for instance, is not only a crucial fatty acid for the

doi:10.6342/NTU202400005

organism but also a precursor and intermediate product of eicosanoid synthesis[29]. The term "eicosanoids" refers to a group of polyunsaturated fatty acids containing 20 carbons, of which prostaglandins, thromboxane, and leukotrienes are the most well-known. These fatty acids have actions similar to those of hormones and are present in all tissues and organs[30]. In addition to being present in seafood, the bulk of polyunsaturated fatty acids also exist in vegetable oils like olive oil[31].

1.3.2 Micronutrients

Micronutrients include vitamins and minerals[32]. Previous research has shown that minerals, like calcium, magnesium, and potassium, can assist the maintenance of osmotic pressure equilibrium in the human body, relax blood vessel walls, enable the muscles in blood vessel walls to contract and relax appropriately, and regulate the release of hormones and enzymes in the body, all of which are important for blood pressure control[33]. However, excessive intake of minerals can also break the balance of blood pressure. Overexpose of sodium is a critical contributor to hypertension[34]. Furthermore, the additional volume of blood will place more strain on the kidney and heart's blood arteries, boosting the risk of cardiovascular disease and kidney diseases over time. The likelihood of edema and the risk of heart disease occurrence both rise with an increase in body fluids, as maintained by clinical statistics[35].

1.3.3 Vitamins and provitamins

Another group of micronutrients is vitamins, which are further classified into two primary categories - fat-soluble vitamins and water-soluble vitamins. Despite being unable to

doi:10.6342/NTU202400005

provide energy, they are essential to physiological processes in life[36]. Most of these vitamins have antioxidant capacity to help maintain health.

Vitamins A, D, E, and K are well-investigated (mentioned) fat-soluble vitamins in healthcare. Vitamin A is vital for growth and development, maintenance of the immune system, and good vision. [3738] In addition to playing a leading role in the absorption of calcium, magnesium, and phosphate, vitamin D is also involved in neuromuscular function and inflammation control. Moreover, vitamin D also affects the expression and translation of multiple genes that regulate cell proliferation, differentiation, and apoptosis. [39] Vitamin E is one of the significant antioxidants protecting cell membranes from reactive oxygen species[40], while vitamin K functions as a post-synthetic modifier for proteins that facilitate blood clotting and calcium management[41].

On the other hand, water-soluble vitamins also participate in a wide range of physiological functions throughout the human body. Along with vitamins B1, B2, B6, and B12, water-soluble vitamins include niacin, folic acid, and vitamin C. These water-soluble vitamins described above mainly take part in crucial metabolic pathways as cofactors in the form of coenzymes or precursors to vitamin B[4243].

Furthermore, vitamin precursors, or provitamins, substances that may be converted within the body to a vitamin, have similar physiological functions as vitamins.

1.4 Vitamins and other provitamins for the high blood pressure

Due to the vital roles of vitamins in the human body, it is reasonable to assume that correlations between vitamin exposure levels and blood pressure may exist. According to prior studies, after adjusting for covariates such as age, gender, race, chronic diseases, total

doi:10.6342/NTU202400005

dietary energy, and fat intake, vitamins A and E are discovered to lead an increased effect in both systolic and diastolic blood pressure. Furthermore, researchers also identify that vitamin D lowers diastolic blood pressure while vitamin C decreases systolic blood pressure under the same condition.[4445].

As research progressed, researchers further identify that rather than being a single distinct compound, vitamins typically exist as a class of structurally related substances. In particular, vitamin A contains numerous precursors and analogs, including the best-known alpha and beta carotenoids; cryptoxanthin, which is present in fruits like grapefruit and papaya; lycopene, which is also abundant in tomatoes; lutein, and zeaxanthin, that could potentially function as a photosynthetic pigment. Additionally, because they resemble vitamin A in composition, they also have multiple unsaturated bonds and act as antioxidants in the blood to support the health of the cardiovascular system[46].

Previous study has shown that high correlation between serum vitamins and their precursors. It is unknown how total vitamins generally affect blood pressure[4748]. Furthermore, since individuals uptake multiple vitamins simultaneously instead of consuming only a specific vitamin in their daily diet, considering total vitamins with diverse types of them can better represent the realistic vitamin exposure situation. Additionally, as different vitamins may have varying degrees of effects on blood pressure, several specific vitamins may have relative vital impacts on blood pressure compared to others in the total-vitamin exposure condition. It remains unknown how total vitamins generally affect blood pressure and whether specific vitamins have distinct effects on blood pressure under total-vitamin exposure conditions.

doi:10.6342/NTU202400005

1.5

1.5 Research question and specific aim

Previous studies have shown a correlation between blood provitamins and vitamin levels and blood pressure. However, those studies mostly used univariate linear regression after correction for confounders. Thus, this poses several problems, starting with the strong relationship between multi nutrients exposed through diet, making it difficult to interpret whether the significance of the study results is representative of the true effect of vitamins on blood pressure. In addition, as research progresses, scientists are now finding that other vitamin analogs in food have similar functions compared to vitamins, but their relationship to blood pressure is not clear; furthermore, the possible additive, multiplicative or antagonistic effects of different vitamins make it difficult for researchers to simply calculate the total effect of vitamins on blood pressure using coefficients from linear models; last but not least, since most studies have used linear models to explain the association between blood vitamin concentrations and blood pressure, we are not sure whether nonlinear models have better explanatory power in interpreting the relationship.

Furthermore, because of the high correlation between serum provitamins and vitamins, we can define them as chemical mixtures. As we know, in real-world settings, exposure to individual environmental contaminants does not happen in isolation. Many chemical components exist as a mixture, like provitamins and vitamins. They enter the body through food, while we are eating and drinking. They have similar half-lives, and similar absorption, distribution, metabolism, and excretion profiles in the body, and they both have antioxidant

doi:10.6342/NTU202400005

chemical structures that can help prevent many inflammatory diseases. We can estimate the mixture effect of the provitamins and vitamins and find the key component of the mixture.

Therefore, the purpose of this study was to evaluate the total effect of exposure to various provitamin and vitamin concentrations on blood pressure and which component plays a more essential role in this effect. We assumed that the effect of all vitamins on blood pressure was significant and used linear regression, weighted quintile sum (WQS) regression, and Quantile g-computation (Q-gcomp) to build linear models to find the total effect of the mixture and the relatively important components. In contrast to past studies, we would also build nonlinear regression models using g-computation as well as Bayesian kernel machine regression (BKMR) to determine the functional relationship between the independent and dependent variables. Finally, we would use the g-computation as well as the BKMR model to further determine whether there would be interactions between different nutrients.

doi:10.6342/NTU202400005

Chapter2. Material and method

2.1Study population

Study data used in this study come from the National Health and Nutrition Examination Survey (NHANES). The NHANES is a nationwide health and nutrition study that is simultaneously run by the Centers for Disease Control and the U.S. Center for Health Statistics[49]. Its goal is to track changes in the well-being and nutritional situation of both adults and kids in the US over time. Approximately 5,000 people from a nationally representative sample are chosen each year, which is carried out every two years. The survey's reach is fairly extensive., and it typically asks about the subjects' age, gender, race, social standing, and economic situation in addition to more in-depth questions about their physical and mental health. Simultaneously, particular biological samples are examined for exposure variables during specific cycles. A tremendous quantity of sample data has been gathered and made available to all researchers worldwide since the organization's founding in 1960. The majority of the participants in this research are obtained from the NHANES 2017–2018 survey cycle because this cycle's participants had access to more comprehensive data on serum vitamin concentrations. We chose participants who are older than 20 and have to provide information on their hypertension and serum provitamin and vitamin levels. Additionally, our exclusion criteria were as follows: (1) taking hypertension medicines; (2) lack of blood pressure readings; (3) without the ratio of family income to poverty (PIR), body mass index (BMI), or serum triglyceride levels. In conclusion, 1370 subjects' data were included in our research.

doi:10.6342/NTU202400005

2.2 Blood pressure status

The mobile examination (MEC) facility takes the participant's blood pressure. Rashes, gauze dressings, casts, edema, paralysis, tubes, exposed sores or wounds, withered limbs, a-shunts, and radical skin changes are all grounds for exclusion from the study. Only after the eligible participant has sat still for five minutes and achieved the highest inflation level (MIL) is blood pressure taken. If there are no extenuating conditions, the participant's right hand is used to take their blood pressure. Three blood pressure readings are taken frequently, and if any of the results are inaccurate or unreasonable, a fourth reading is taken[50].

Therefore, 1-4 blood pressure readings are taken for each individual. When a subject only has one bit of information, that information serves as the final record. If there are multiple instances, the first set of data will not be used. After the first set of data is eliminated, the ultimate blood pressure is the average.

2.3Serum provitamins and vitamins measurement

Vitamin A, alpha-carotene, cis and trans-beta-carotene, alpha and beta-cryptoxanthin, cis-lycopene (total- subtract trans-), trans-lycopene, lutein and zeaxanthin, vitamin C, vitamin D, vitamin E, and gamma-tocopherol, for a total of 13 species, are included in this trial. Everything was gleaned from the 2017–2018 period. At the Mobile Medical Center, participants gave fasting blood samples, which were then stored at -20 degrees Celsius and sent to National Hospital Care Survey (NHCS) for analysis. Vitamins A, alpha-carotene, cis-and trans-carotene, alpha- and beta-cryptophanes, total lycopene, trans-lycopene, lutein and zeaxanthin, vitamin E, and gemma-tocopherol were measured using a modified high-

doi:10.6342/NTU202400005

performance liquid chromatography method with photodiode array detection[51]; vitamin C was measured using isocratic ultra-high performance liquid chromatography (UPLC)[52]. Vitamin D was measured using high-speed liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)[53]. Values below the limit of detection (LOD) were replaced with LOD divided by the square root of 2 by the NHANES guideline.

2.4 Covariates

Age for over 20, sex (male or female), race including Mexican American, Other Hispanic, non-Hispanic white, non-Hispanic black, and Other race, the ratio of family income to poverty (PIR), body mass index (BMI), taking medication for hypertension, hematocrit, high-sensitivity c-reactive protein, blood cadmium, and urine creatinine total cholesterol were considered as covariates. Serum samples were taken while physical exams were conducted in a mobile medical facility. Serum samples from the NHCS were also used to measure hematocrit, and urinary creatinine total cholesterol. All the details can be obtained at www.cdc.gov/nchs/nhanes/.

2.5 Statistics

2.5.1 Descriptive Statistics and Single Linear Regression

We used software R4.2.1 to analyze the post-sampling data from the NHANES database. We utilized ANOVA and Chi-square tests to assess the participants' initial characteristics based on their blood pressure state. N (%) was used to represent categories variables and

doi:10.6342/NTU202400005

mean variation was used to represent continuous variables. The linear regression also used to ascertain the relationship between specific provitamins and vitamins and blood pressure is shown along with the estimated 95% confidence interval (CI) (beta, (95%CI)) and estimated coefficient (beta). The correlations between Ln-transformed provitamins and vitamins in blood were also identified utilizing Pearson Correlation Analysis.

2.5.2 WQS regression

One strategy that is spreading more widely over time is the weighted quantile sum (WQS), which was created especially for environmental mixtures analysis. Producing overall evaluations of composites in a supervised manner facilitates the examination of mixture exposure and health outcome connections[5455]. WQS, or weighted quantile sum regression, is a statistical model that operates in a trained structure for multiple factors in datasets with high dimensions. In order to determine the total impact of the combined substance on the outcome of interest, it offers just one rating (the weighted quantile sum), which considers the exposure to the outcome as a mixture. The score is generated as a weighted total (so that exposures with weaker effects on the result have lower weight in the index), and all exposures are divided into quartiles, or further sections so that the highest and lowest values possess minimal influence on the weight estimation.

A WQS regression model corresponds to this:

$$g(\mu) = \beta_0 + \beta_1 \left(\sum_{i=1}^{c} w_i q_i \right) + z\varphi$$

doi:10.6342/NTU202400005

g(μ) represents the dependent variable, which can follow the Gaussian distribution or binomial distribution. β_0 is intercept and $z\varphi$ mean covariates. We regard the mixture-exposure data that can be combined into an Index and has c connected components. The $\sum_{i=1}^{c} w_i\, q_i$term is an index that weighs and adds the mixture's constituent parts. β_1 will therefore serve as the coefficient that summarizes the total impact of the (weighted) combination. A forecast of the individual weights w_i will also supply the corresponding weights for every exposure in the context of the mixture-outcome relationship. We will score the c element values into quantiles, which we'll refer to as qi (for quartiles, in the 1st, 2nd, 3rd, or 4th quartile, for values in qi = 0, 1, 2, or 3, respectively). This will be done with the assumption that i = 1 to c.

A training dataset and a validation dataset can be created from the data, one being used to estimate the weights and the other being utilized for figuring out the significance of the ultimate WQS index. The weighted index for the selected class of c compounds, as well as the bootstrap method, is used to estimate the weights, with the condition that they must sum to one and have a range of zero to one. The weights are bound to sum to one:$\sum_{i=1}^{c} w_i$=1 and $0 \leq w_i \leq 1$. With every bootstrap sample (often B=100 total samples), a dataset is created using selection with substitution from the training dataset, and an optimization method is used to estimate the model's parameters.

Once the weights have been collected, the model is fitted to produce the regression coefficients associated with every aggregate phase. After the bootstrap ensemble is complete, the projected weights are added across all bootstrap samples to get the WQS index:

doi:10.6342/NTU202400005

$$WQS = \sum_{i=1}^{C} \overline{w_i}\, q_i$$

Weights are typically calculated within a set of training variables for a generalized linear model before being employed to create a WQS index in a set used for validation. Following are some examples of how to use this index to determine whether the combination and the outcome on health are related:

$$g(\mu) = \beta_0 + \beta_1 WQS + Z'\varphi$$

Testing the importance of the Beta1 to determine whether the WQS index and the result are related can be done after the final model is finished. The weights are able to be interpreted if the coefficient is significantly different from 0; the greatest values indicate the connected components as the important contributors to the association. To determine whether compounds have a substantial weight in the index, selection criteria can be chosen in advance.

For our purpose of determining the overall effect of vitamins and their relative contributions, we used weighted quantile regression (WQS regression). Using the R package ("gWQS"), we were able to estimate the WQS index, which is based on weighted averages of individual vitamin concentration[56]. It reflected the overall weight of the 13 serum vitamin components and their relative importance, ranging from 0 to 1. WQS regression were used to investigate the relationships between the vitamin mixture and blood pressure. We estimate the mixture effect on systolic and diastolic blood pressure in both directions. we would separate our participants into two parts, the training set (40%) and the

doi:10.6342/NTU202400005

validation set (60%), and bootstrapping 1000 times from training data to increase sensitivity in detecting important predictors through perturbing the data.

2.5.3 Quantile g-computation (Q-gcomp) regression

The WQS regression assumes that the direction of action of all the constituents is the same, but usually, the direction of action of the constituents in a mixture is not necessarily the same; therefore, we use fractional g-computation to confirm whether the action of the mixture is significant without restricting the direction of action of the constituents.

An estimate of the impact of all exposures simultaneously increasing by one quantile is produced by quantile g-computation. In order to analyze exposure mixtures (such as air pollution, nutrition, and aquatic pollution), its estimated "mixture effect" is beneficial. Quantile g calculations estimate the variable parameters of a marginal structural model that explains the modification in the predicted probable result given the combined intervention regardless of exposures, maybe depending on confounding factors, applying terminology established for causal impact estimates. This model produces the causal impact of the modification on every component if the presumptions of exchangeability, causal coherence, positivity, absence of interference, and proper model specification are met. Although these hypotheses are not always true, they offer a helpful framework for analyzing the Q-gcomp fit outcomes and indicate the amount of work that needs to be done to guarantee reliable model specification and the choice of exposures necessary to control for common contaminant confounding[57].

doi:10.6342/NTU202400005

Imagine that we have a consequence Y, some exposure X, and perhaps some other factors (such potential confounders) designated by Z. A combined marginal structure model described by:

$$E(YXq|Z,\psi,\eta)=g(\psi 0+\psi 1Sq+\eta Z)$$

Where ψ0 act as the model intercept, η represents the model coefficient for a set of covariates, Sq serves as an "index" representing the joint value of exposures, as well as g(·) is the relationship function within a generalized linear model. By default, quantile g-computation converts all exposures X into Xq, a "score" that represents the categorized "bin" of exposures and has variables such as 0, 1, 2, etc. Xq=0 indicates that X is below the 25th percentile of observations for that exposure because each exposure has four divisions by definition with a uniform distribution of quartile cut points. All exposures are assigned to the same value (again, by default, discrete values 0,1,2,3), as indicated by the exponent Sq. Thus, provided that all exposures rise by one quartile at once, the parameter ψ1 quantifies the anticipated shift in the findings and can be adjusted for Z.

For our purpose of determining the overall effect of vitamins in both directions, using the R package ("qgcomp"), we were able to estimate the G index, which is based on weighted averages of individual vitamin concentration[58]. We both estimated the conventional coefficient without bootstrapping and the marginal coefficient by bootstrapping 1000 times. It needs to be clarified that Q-gcomp only provides the non-bootstrapping weight with many biases, so the values of weights are not as reliable compared to WQS regression.

doi:10.6342/NTU202400005

2.5.4 Bayesian kernel machine regression (BKMR)

Furthermore, the relationship between vitamin mixtures and blood pressure might be a non-linear relationship. To calculate the nonlinear relationship between mixed exposures and health outcomes, the BKMR model was employed to evaluate the combined impact of all micronutrients on blood pressure. The strategy combines Bayesian and statistical learning techniques to predict nonlinearities and/or interactions in exposure-outcome associations. Modeling flexibility for exposure-response functions is provided by BKMR, which makes it simple to visualize the effects of either a single exposure or a sequence of exposures. To calculate the total impact of vitamin co-exposure on blood pressure, we used the R package BKMR. Also, we were able to obtain exposure-response as well as dose-effect relationship functions for single vitamins on blood pressure; in addition to this, we were able to estimate interactions not only among vitamins but also interferers between vitamins and confounders.

In an adaptable non-parametric manner, Bayesian Kernel Machine Regression (BKMR) is aimed at tackling a number of objectives, including identifying and estimating the magnitude of an effect of the general mixture, the determination of the pollutant or group of pollutants responsible for the observed mixture effects, the visualization of the exposure-response function, and the detection of interactions between individual pollutants.

BKMR's central notion is to use a kernel function to model exposure. The machine learning field commonly employs an approach known as kernel machine regression (KMR), also known as Gaussian process regression[59]. The basic goal of KMR is to effectively model the correlation between a substantial number of independent variables and a certain outcome (dependent variable). This article's basic modeling methodology is

doi:10.6342/NTU202400005

$$g(\mu_i) = h(z_i1, \ldots, z_iM) + \beta x_i, \quad i = 1, \ldots, n$$

where g is a continuous function, a normally distributed health outcome; a versatile function of the predictor variables is h; $z_i1$through z_iM and $x_i$are a variety of confounders believed to possess the linear connection with the result.

Predictors z will be referred to as exposure variables, and $h(\,.\,)$ will be referred to as the exposure-response function. When there are numerous exposures present or the exposure-response function is a multifaceted, perhaps nonlinear, and non-additive relation, it may be challenging to characterize a set of basis functions to represent h. In these conditions, a kernel machine representation of h offers an alternate method of characterizing it. The kernel function that is utilized under KMR to symbolize h has a variety of options. Here, we concentrate on the Gaussian kernel, which may be stated as and is sufficiently adaptable to represent a variety of underlying functional forms for h.

$$K(z_m, z'_m) = \exp\{-\sum_{m=1}^{M} r_m (z_m - z'_m)^2\}$$

The tuning parameter known as r_m0 controls how smooth h is as a function of exposure use z_m. It makes natural sense that the kernel function minimizes the estimated health effects of two individuals with similar exposure profiles on one another.

To calculate the nonlinear relationship between mixed exposures and health outcomes, the BKMR model was employed to evaluate the combined impact of all micronutrients on blood pressure. Using the R package ("BKMR"), it would be simple to simple to visualize the effects of either a single exposure or a sequence of exposures[60]. We iterated our simple for 20000 times to make a convincible result.

doi:10.6342/NTU202400005

Chapter3. Results

3.1 Fundamental characteristics and provitamins and vitamins concentration detection

We calculated the patients' blood pressure values. The average systolic blood pressure was 118mmHg and the average diastolic blood pressure was 69.8mmHg among the 1370 individuals in the 2017–2018 NHANES. Table 1 displayed the fundamental features of the study population. The subjects were divided into groups based on their systolic quartiles. Overall, about systolic and diastolic blood pressure, age, gender, race, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index were statistically significant differences between different systolic blood pressure quartiles groups, while family PIR did not have significant differences.

Initially, we determined the participants' serum provitamin and vitamin concentrations. Table 2 displays the distribution of provitamin and vitamin concentrations in blood (umol/L) and standardized concentrations (Z score) in terms of detection rate, median, and interquartile range. All other vitamins were discovered at a rate higher than 75%, however, cis-β-carotene was only detected at a rate of 49.21%.

3.2. Analysis of the relationships between individual vitamins and changes in blood pressure using linear regression.

doi:10.6342/NTU202400005

We subsequently estimated the effect of a single vitamin's blood concentration on systolic and diastolic blood pressure. Participants were divided into four groups based on their serum vitamin quartiles. We used a combination of continuous data and grouped categorical factors to assess the link between individual blood vitamins and systolic and diastolic blood pressure. The systolic blood pressure consistently decreased with each unit rise in Ln-alpha carotene, Ln-cis-beta carotene, Ln-trans-beta carotene, and Ln-vitamin D respectively (all $p \leq 0.05$). Systolic blood pressure among them significantly dropped with the steady increase of the alpha-carotene, cis-beta-carotene, trans-beta-carotene, and vitamin D quartiles groups.

The correlation among the Ln-transformed serum provitamin and vitamin concentrations was depicted by Pearson's coefficient (Figure 1), demonstrating a high relationship among serum provitamins and vitamins concentration. So we would define provitamins and vitamins as a chemical mixture and utilize three co-exposure models.

3.3 To evaluate the relationships between vitamin co-exposure and blood pressure using WQS models.

The first method we used was WQS regression. Due to the high correlation between the components in chemical mixtures, their co-existence in the model often leads to collinearity. Therefore, the WQS model would set the influence of all components in the same direction when establishing assumptions. For example, if the mixture effect is protective, all coefficients of components will be negative. By establishing assumptions in two different directions, coefficient errors caused by collinearity can be avoided.

doi:10.6342/NTU202400005

The impact of the blood's overall vitamin composition on blood pressure would be estimated. To start with, we utilized the WQS regression. Larger weights indicated a bigger contribution of those vitamins to the total correlation, while WQS regression coefficients showed the strength of the link between the mixture and outcomes. The findings of each coefficient were listed in Figure 2. Vitamin A, alpha-carotene, cis and trans-beta-carotene, alpha and beta-cryptoxanthin, cis-lycopene, trans-lycopene, lutein and zeaxanthin, vitamin C, vitamin D, vitamin E, and gamma-tocopherol were all taken into account when adjusting the models for age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index. Since the WQS coefficient contributes only partially to the total coefficient of zero and fails to offer useful information when the WQS coefficient was zero or not statistically distinguished from zero, we neglected to highlight the weight of the WQS coefficient for the entire sample's 95% CI crossing with zero.

3.3.1 Overall effect of provitamins and vitamins by WQS regression

The WQS index of blood metals was negatively correlated with systolic blood pressure in all participants, as shown in Figure 2 (-1.18 (-2.09,-0.18)), which suggested that a one decile increase in the weighted quantile total of the provitamins and vitamins mixture was linked with a 1.18 mmHg decrease in systolic blood pressure with full-sample 95% CIs not overlapping zero (full-sample 95% CI: This link was proven to be significant by the p-value of the confirmatory permutation test (confirmatory p = 0.011). We also noticed that there didn't seem to be much of a connection between the provitamins and vitamins mixture's concentration and diastolic blood pressure.

doi:10.6342/NTU202400005

We also looked at the model's performance. In addition, we showed the direction and shape of the association between the WQS index and systolic blood pressure (2B), as well as a diagnostic graph of residuals vs. fitted values (2C). It was discovered that exposure and outcome have a declining trend, and the residuals display a random distribution. Additionally, we determined the model's performance: R-squared to be 0.3419 and its root-mean-square deviation (RMSE) to be 11.84 (mmHg).

Table 5 showed three sequential WQS regression and three multivariate linear regression models with increasing levels of adjustment for Covariates employed to explore the associations of each of the mixtures with SBP. Model 1 adjusted all covariates except serum total cholesterol and serum triglyceride; model 2 adjusted all covariates except serum triglyceride model 3 was the full model. All models showed statistical significance between serum provitamin and vitamin mixture and blood pressure.

3.3.2 Relative important weight of provitamin and vitamin

The sum of the 13 provitamins and vitamins' weight was equal to one, which indicated that the average weight of individual provitamins and vitamins in the total mixture is 0.076 (1 to 13). If any weight of nutrients in the mixture is over the average weight, it would be considered a relatively important one.

Figure 3 depicted a bar plot showing the weights of the various provitamin and vitamin and the table demonstrating the weights. The redline indicated the average weight of single nutrients in the mixture. Those with weights above the red line were thought to be relatively important, including alpha-carotene, cis-beta-carotene, trans-beta-carotene, and vitamin D.

doi:10.6342/NTU202400005

3.4. Models using G-computation to evaluate the relationships between co-exposure to vitamins and blood pressure.

WQS uses a model constraint to make sure that all of the weights are moving in the same direction, however, these restrictions inevitably result in inaccurate effect estimates. The g-computation employs a different methodology and permits "weights" to move either way. Serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and serum body mass index were all taken into account when adjusting the models for age, gender, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

3.4.1 Overall effect of provitamins and vitamins by Q-gcomp regression

Figure.4 displayed the findings for each coefficient. As seen in Figure 4, the G-calculated index of blood provitamins and vitamins was negatively correlated with systolic blood pressure for all participants. The highest weights were for cis-beta-carotene and vitamin D. A one-decile increased in the sum of the weighted quartiles of provitamin and vitamin mixtures was associated with a 1.26 mmHg decrease in systolic blood pressure. Additionally, we calculated conventional beta values (-1.46 (-2.49, -0.42)) and marginal beta values (-1.46 (-2.54,-0.38)). This connection was proven to be significant by the p-value of the confirmatory envelope test (confirmatory p conventional=0.0013, p marginal=0.022). Additionally, we noticed that there didn't seem to be a connection between diastolic blood pressure and the concentration of the provitamins and vitamins mixture. We further assessed the entire exposure effect's linearity. Systolic blood pressure declined as the concentration of the vitamin mixture rose, using the first (4B) and second

doi:10.6342/NTU202400005

(4C) quartiles as references. Additionally, we determined the model's performance: R-squared to be 0.34, its RMSE to be 13.64 (mmHg), and the mean absolute error (MAE) to be 10.13 (mmHg). The G-computation method, however, also has a disadvantage in that it cannot divide and bootstrap at the same time, making the weight values less trustworthy than with WQS regression.

Table 6 showed three sequential Q-gcomp regression and three multivariate linear regression models with increasing levels of adjustment for covariates employed to explore the associations of each of the mixtures with SBP. Model 1 adjusted all covariates except serum total cholesterol and serum triglyceride; model 2 adjusted all covariates except serum triglyceride model 3 was the full model. All models showed statistical significance between serum provitamin and vitamin mixture and blood pressure.

3.4.2 Relative important weight of provitamin and vitamin

Furthermore, 5A displayed the bar chart of the weights of the various vitamins, with the exception of vitamin A, trans-lycopene, alpha-cryptoxanthin, and vitamin E, all of which have negative effects. It was not appropriate to compare the left and right sides of the plot because the length of the bars only depicts the effect magnitude with respect to other effects in the same direction. Due to the overall positive "mixture" impact, the bars on the right (positive) side of the plot in this situation were darker. The extent of the influence was shown by how dark the bars are. The shading allowed for an informal comparison of the left and right sides. In comparison to a large, light-hued bar, a large, deeply colored bar indicated a larger independent impact.

doi:10.6342/NTU202400005

3.5. The co-exposure of vitamins and changes in blood pressure are examined using the BKMR model.

Last but not least, we aimed to calculate the correlation between blood pressure and the dose impact of the vitamin mixture in the blood. The BKMR model demonstrated the overall correlation between the vitamin combination and the change in both systolic and diastolic blood pressure (mmHg). We adjusted the models for age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

3.5.1 Overall effect of provitamins and vitamins using the BKMR method

Fig. 6 indicated systolic and diastolic blood pressure changes in blood mixed with provitamins and vitamins (Fig. 6A). X-axis represented the exposure quantile of the total provitamin and vitamin mixture level and Y-axis represented the blood pressure changes. We estimated the overall mixture effect by 5 percentiles of total concentration in a group from the 10^{th} percentile to 90^{th} percentile concentration, using the median concentration group as a reference. Figure 6A revealed a decreasing trend in all subjects with statistically significant, except 50% to 80%. This graph displayed the estimated blood pressure change and 95% confidence interval (CI) when the median provitamin and vitamin concentrations for each group were maintained at certain percentiles, which indicated systolic blood pressure increased substantially below exposure to the median concentration of provitamins and vitamins but remained marginally significant above it. However, there was no statistically significant relationship between the diastolic blood pressure and the vitamin combination content in the blood (Figure 6B).

doi:10.6342/NTU202400005

3.5.2 Univariate relationship between each provitamin and vitamin and the outcome

We usually want to see the predictor-response function, or h() by the BKMR method. Instead of viewing a high-dimensional surface, we examine different cross-sections of it. We accomplished this by concentrating on the connections between 1 or 2 exposures and the result and assigning specific values to the other exposures. The univariate association between each compound and the result, where all other exposures are fixed to a specific percentile, is one cross-section of interest.

3.5.3 Interaction of an individual factor with all other compounds in the total mixture

Figure 8 showed that when the concentrations of the other compounds in the total mixture were held constant at the 25th (red), 50th (green), or 75th (blue) percentiles, a special individual factor and its effect on systolic and diastolic blood pressure.

This figure showed no significant and detrimental effect on the change in systolic and diastolic blood pressure, while the 25th (red), 50th (green), or 75th (blue) percentiles' concentrations of the other elements were kept constant.

3.5.4 Interaction of an individual factor with all other covariates in the total mixture

Figure 9 showed that when the concentrations of the other covariates we adjusted were held constant at the 25th (red), 50th (green), or 75th (blue) percentiles, a special individual factor and its effect on systolic and diastolic blood pressure.

This figure showed no significant and detrimental effect on the change in systolic and diastolic blood pressure, while the 25th (red), 50th (green), or 75th (blue) percentiles' concentrations of the other elements were kept constant (Fig. 9).

doi:10.6342/NTU202400005

As a result, there showed no interactions not only of an individual factor with all other compounds in the total mixture but also of an individual factor with all other covariates in the total mixture.

3.5.5 Interaction of one individual factor with another factor

Furthermore, we would like to figure out whether there is an interaction between pairs of antioxidant nutrients. We investigate the predictor-response function of a single predictor in provitamins and vitamins for the second predictor in provitamins and vitamins held at their corresponding 25^{th} (red), 50^{th} (green), or 75^{th} (blue) percentile on systolic and diastolic blood pressure when the rest of 11 compounds held at 50^{th} percentile. If the three predictor-response lines overlapped, there was no interaction between the two factors; if the three lines are parallel, the two factors have an additive interaction; if the three lines intersect, then there was a non-additive interaction between the two factors. We de-emphasized the interactions among mixture on diastolic blood pressure because its overall effect showed no statistically significant.

For the effect on systolic blood pressure, we found when cis-beta-carotene, trans-beta-carotene, and vitamin D were fixed, predictor-response function showed a parallel line, which indicated these provitamins and vitamins may have some addictive effect on systolic blood pressure.

Moreover, we found when cis-beta-carotene is fixed, three lines intersect for trans-beta-carotene and systolic blood pressure function, indicating cis-beta-carotene and trans-beta-carotene might have non-additive interactions on systolic blood pressure.

doi:10.6342/NTU202400005

Chapter 4. Discussion

4.1 Our findings from three different co-exposure approaches

Our study examined the association between systolic and diastolic serum pressure in the general American population and serum provitamin and vitamin concentrations. The linear regression results revealed that serum concentrations of provitamin and vitamins were inversely associated with systolic serum pressure, among which cis-beta-carotene, trans-beta-carotene, and vitamin D were relatively important. Only vitamin C showed a statistically significant correlation between provitamin and vitamin mixture and diastolic serum pressure. Unlike previous studies, we used multiple approaches to analyze the relationship between provitamin and vitamin co-exposure and systolic and diastolic serum pressure. In addition, we emphasized the weight of a single provitamin and vitamins as a component in the overall effect of nutrients. The results of WQS, Quantile-g-computation, and BKMR method all indicated that the concentration of multi provitamin and vitamins in serum was correlated with systolic serum pressure negatively, but there was no statistical correlation with diastolic blood pressure serum pressure. Among them, cis-beta-carotene, trans-beta-carotene, and vitamin D played a relatively important role.

4.2 Beta-carotene

4.2.1 Basic information on beta-carotene

The orientation of the ninth carbon in the molecule differs between the beta-carotene isomers-cis-beta-carotene and trans-beta-carotene. Its primary sources are fruits and fungi, however, there are differences in the amounts of cis and trans-carotene in these foods[61].In

doi:10.6342/NTU202400005

our study, serum provitamin and vitamins are from both food sources and supplementary carotenoids. Food-derived carotenoids must be dissociated from plant cells and incorporated into lipid-containing micelles in order to be bioavailable to intestinal enterocytes during digestion. In comparison to that from foods, there is a higher bioavailability if the substance is previously extracted (or manufactured) and then provided in an oil-filled dietary supplement capsule[62].

4.2.2 Protentional function of beta-carotene

Circulating beta-carotene concentrations have been linked to vascular dysfunction, elevated lipid peroxidation, and inflammatory markers, all of which have been linked to CVD. Furthermore, minerals and pigments influence endothelial dysfunction and irritation similar to that of phytonutrients, which lowers the risk of atherosclerosis. Numerous in vitro investigations, particularly those that utilized subsystems, have contributed to the discovery of a connection between carotene, peroxidation, and inflammation. The influence of beta-carotene on intracellular signaling cascades, which affects gene expression and protein translation, has recently been related to many of these functions. Beta-carotene can interact with the nuclear factor-B pathway and prevent the generation of inflammatory cytokines like interleukin-8 or prostaglandin E2 by preventing nuclear factor-B from moving to the nucleus. By interacting with the nuclear factor erythroid 2-related factor 2 pathway, facilitating its translocation into the nucleus, and activating phase II enzymes and antioxidants such glutathione-S-transferases, beta-carotene can also prevent oxidative stress. Using these protentional pathways, beta-carotene may prevent many kinds of CVDs[63].

4.2.3 Consistent results from other epidemiological studies

doi:10.6342/NTU202400005

Additionally, epidemiological studies have demonstrated a negative correlation between beta-carotene and hypertension risk (OR, 0.89; 95% CI, 0.82 to 0.97) as well as systolic serum pressure (beta=−0.92 (−1.39, −0.45))[64]. Low serum levels of beta-carotene may raise the risk of developing a variety of cardiovascular diseases, including acute myocardial infarction（HR=2.78, 95% CI, 1.23-6.25, p=0.014[65] and congestive heart failure (OR:1.60 95% CI 1.09-2.35; P = 0.017)[66]. Our findings showed that serum beta carotene was negatively correlated with systolic serum pressure, indicating that a low serum beta carotene level is a risk factor for high serum pressure. Furthermore, both cis and trans beta are reasonably significant among numerous provitamin and vitamins exposures to our serum pressure, as shown by the WQS regression and qgcomp analysis. On the other hand, high serum pressure (BP) is one of the risk factors for cardiovascular disease that is associated with the highest evidence for causation and has a high exposure prevalence.

4.3 Vitamin D

4.3.1 Basic information about vitamin D

Another essential provitamin and vitamin that has been connected to a reduction in systolic serum pressure is vitamin D (25-hydroxyvitamin and vitamins D, 25[OH]D). The primary natural source of vitamin D is a chemical process product that results in calcified gallstones in the bottom layers of the skin following exposure to sunlight, particularly UVB radiation. Dietary sources of cholecalciferol and ergocalciferol include fish, milk, legumes, cereals, and other foods as well as supplements. After intestinal absorption, the bioactive form of provitamin and vitamin D, calcitriol (also known as 1,25-dihydroxycholecalciferol), is

doi:10.6342/NTU202400005

created by further hydroxylating vitamin D after intestinal absorption by the kidneys[67]. As a hormone, calcitriol circulates in the serum stream with the main purpose of regulating calcium and phosphate levels and fostering healthy bone growth and remodeling. Additionally, calcitriol affects immunological, neuromuscular, and cell proliferation in addition to reducing inflammation[67].

4.3.2 Protentional function of vitamin D

It is thought that vitamin Interacts with the renin-angiotensin system (RAS) to define the intracellular calcium environment of vascular smooth muscle, hence controlling serum pressure*. Animal studies showed that mice lacking vitamin D receptors have increased plasma renin activity and hypertension, and this unfavorable phenotype could be reversed with vitamin D(25[OH]D)[68].

Since the discovery that intracellular calcium concentrations were positively correlated with blood pressure and that 1,25(OH)2D may facilitate the flux of calcium into vascular smooth muscle cells, the relationship between calcium homeostasis and blood pressure regulation has been well established.

Previous studies demonstrated that dietary salt loading enhanced 1,25(OH)2D concentrations in human hypertension. Additionally, those who had the highest salt-induced increases in 1,25(OH)2D also had the highest salt-induced increases in blood pressure, most likely as a result of rises in intracellular calcium. The precise mechanism for this salt-induced enhancement of 1,25(OH)2D as well as the function of salt and RAS elements in 1,25(OH)2D-mediated calcium entrance into cells are yet unknown[69].

4.3.3 Consistent Results from Other Epidemiological Studies

doi:10.6342/NTU202400005

Previous studies showed consistent results between serum vitamin D concentration and blood pressure. In prospective studies, a 16% decrease in risk of hypertension was observed in participants with high levels of serum vitamin D compared to low levels (RR: 0.84; 95%CI: 0.73, 0.96; 12 effect sizes)[70]. The relationship between plasma 25(OH)D and either serum pressure or prevailing hypertension has been investigated in numerous cross-sectional investigations. Large population-based cohorts in the United States, Germany, and the United Kingdom are among the research that shows that lower circulating 25(OH)D levels are linked to higher serum pressure or a higher prevalence of hypertension. Another study found similar results to ours, showing that serum vitamin D could lower systolic serum pressure (β = – 0.02, 95% CI= − 0.052 to − 0.0001, P-value=0.04) while having no statistically significant effect on diastolic serum pressure (β = – 0.01, 95% CI= − 0.026 to 0.009, P-value=0.3)[71]. For meta-analysis, one research about 22 cross-sectional studies from 21 articles (45,941 participants and 14,890 cases) and 8 prospective studies from 7 articles (49,844 participants and 5,660 cases) were included (Table 1). Compared with the lowest category, the pooled RR of hypertension for the highest category of circulating 25(OH) D levels was 0.69 (0.62–0.77) for prospective studies and 0.80 (0.71–0.90) for cross-sectional studies[72].

4.4 The overall effect of provitamin and vitamins and the interactions

4.4.1 Overall effect of provitamin and vitamins

Though various of the studies found relationships between provitamin and vitamins and blood pressure, seldom of they report the overall effect of provitamin and vitamins. Our

doi:10.6342/NTU202400005

study showed provitamin and vitamins combination was repeatedly shown to be negatively linked with systolic serum pressure in our co-exposure analyses using WQS and Q-gcomp model[73], in which cis-beta-carotene, trans-beta-carotene, and vitamin D play crucial roles in this effect. In actuality, the Q-gcomp model has the potential to produce counteracting effects among exposures, whereas the WQS model is restricted to simultaneously calculating the joint effect in several directions. The two strategies working together appeared to reflect the joint effects of mixed exposure more accurately. Additionally, BKMR was employed to determine the non-additive and non-linear effects of the combined exposure and interactions[74]. Our findings demonstrated that a combination of provitamin and vitamins was linked to a reduction in systolic serum pressure, particularly in all three approaches consistently demonstrated the protective benefits of a provitamin and vitamin combination on systolic serum pressure. WQS and Q-gcomp models, however, only discovered a linear relationship between several provitamin and vitamins and serum pressure. The non-linear analysis between our exposure and outcome is provided by BKMR models. It should be emphasized that trans-beta-carotene exhibits a non-linear association with systolic serum pressure in the dose-response function of BKMR models when all provitamin and vitamins were fixed at the median, first increasing and then decreasing systolic serum pressure.

4.4.2 The mechanism of vitamin and provitamins

Provitamin and vitamins might help control the oxidative environment in our circulation systems. Dietary flavonoids/polyphenols and antioxidant nutrients promote a thiol-rich (high glutathione) pool serving to scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), thus, preventing or reversing protein S-glutathionylation (cysteine

doi:10.6342/NTU202400005

oxidation). This maintains unoxidized the redox-sensitive cofactor tetrahydrobiopterin (BH4) levels and endothelial nitric oxide synthase (eNOS) (eNOS-S-SG2) coupling, producing NO which promotes vasodilation and reduces vascular endothelium-mediated inflammation/injury. This more favorable environment may over time, delay the progression to vascular disease, and other chronic diseases[75].

4.4.3 Interaction among provitamin and vitamin mixture

The bivariate exposure-response function generated by the previous command is the input for the BKMR model, which also investigates the predictor-response function of a single predictor in Z for the second predictor in a mixture fixed at various quantiles (and for the remaining predictors fixed to a specific value). These functions provide evidence that cis-beta-carotene and trans-beta-carotene have some non-additive interactions. Previous research demonstrates that all-trans beta-carotene preferentially accumulates in human chylomicrons and extremely low-density lipoproteins as opposed to the 9-cis geometrical isomer, which might be evidence about the interaction between cis-beta-carotene and trans-beta-carotene, but the mechanism is still unknown.

Additionally, there are substances that act as antioxidants and have addictive effects on one another. We discovered that the relatively significant components discovered by WQS, including cis-beta-carotene, trans-beta-carotene, and vitamin D, exhibit additive interactions. They may interact additively with one another, which may explain their relative importance to other components.

doi:10.6342/NTU202400005

4.5 Strength and limitation

The study we conducted has certain advantages. First, we used a number of models to iteratively validate the outcomes. Second, we discussed the contradictory effects of provitamin and vitamins and how they interact. Of course, there are some restrictions on our study. In the beginning, we were unable to draw conclusions about the cause-and-effect link between provitamin and vitamin exposure and serum pressure due to the cross-sectional study design. Additionally, it might be challenging to determine an individual's genuine exposure status from the exposure data of a single event point. Third, there were still unknown aspects that cannot be addressed and inevitable variances while measuring data, even after we eliminated the interference factors. For instance, dividing the monitoring limit by the square root to calculate the amount of provitamin and vitamins in the serum would introduce some bias from the authentic value. Last but not least, our study was limited to demonstrating the serum pressure state during the exposure range of particular situations. It was unknown whether consuming excessive provitamin and vitamin concentrations would be harmful.

doi:10.6342/NTU202400005

Chapter 5. Conclusion

In conclusion, we found that several provitamin and vitamins, such as serum cis- and trans-carotene, and vitamin D were significantly associated with systolic blood pressure. The mixture-exposed analyses repeatedly demonstrated a negative connection between provitamin and vitamins exposure and a reduction in systolic blood pressure, among which cis-beta-carotene, trans-beta-carotene, and vitamin D were among these nutrients that were somewhat significant. Given the limitations of the current investigation, these findings should be interpreted cautiously, and additional research is required to bolster our conclusions.

doi:10.6342/NTU202400005

Chapter 6. Table

Table 1. Basic characteristics of participants by systolic blood pressure quantiles in the U.S. adults, NHANES 2017–2018.

Table 1

	Q1 (N=413)	Q2 (N=383)	Q3 (N=313)	Q4 (N=197)	Overall (N=1307)	P value
SBP (mmHg)						<0.001
Mean (SD)	102 (4.82)	114 (3.01)	126 (3.94)	147 (13.0)	118 (16.5)	
Median [Min, Max]	103 [87.3, 109]	114 [109, 119]	125 [120, 133]	143 [134, 195]	115 [87.3, 219]	
DBP (mmHg)						<0.001
Mean (SD)	63.7 (7.60)	68.2 (8.71)	74.3 (9.61)	78.5 (12.3)	69.8 (10.7)	
Median [Min, Max]	64.0 [43.3, 79.3]	68.7 [42.7, 91.0]	74.7 [44.7, 103]	78.7 [48.0, 107]	69.3 [42.7, 107]	
AGE (years)						<0.001
Mean (SD)	30.2 (16.0)	35.5 (18.2)	44.7 (17.4)	58.7 (16.4)	39.5 (19.7)	
Median [Min, Max]	26.0 [20.0, 80.0]	31.0 [20.0, 80.0]	44.0 [21.0, 80.0]	62.0 [20.0, 80.0]	37.0 [20.0, 80.0]	
GENDER , n (%)						<0.001
female	272 (20.8%)	189 (14.5%)	129 (9.9%)	87 (6.7%)	677 (51.8%)	
male	141 (10.8%)	194 (14.8%)	184 (14.1%)	110 (8.42%)	630 (48.2%)	
RACE, n (%)						0.158
Mexican American	65 (5.0%)	63 (4.8%)	63 (4.8%)	29 (2.2%)	220 (16.8%)	
Other Hispanic	45 (3.4%)	25 (1.9%)	26 (2.0%)	17 (1.3%)	113 (8.6%)	
Non-Hispanic White	130 (10.0%)	140 (10.7%)	101 (7.7%)	62 (4.7%)	434 (33.2%)	
Non-Hispanic Black	78 (6.0%)	71 (5.4%)	64 (4.9%)	53 (4.1%)	266 (20.4%)	
Other Race	95 (7.2%)	84 (6.4%)	59 (4.5%)	36 (2.8%)	274 (21.0%)	
BMI (kg/m2)						<0.001
Mean (SD)	25.6 (6.09)	27.6 (6.76)	29.8 (6.62)	29.6 (7.76)	27.8 (6.90)	
Median [Min, Max]	24.5 [15.5, 50.6]	26.2 [16.1, 59.1]	29.2 [16.4, 51.3]	27.3 [15.7, 62.0]	26.5 [15.5, 62.0]	
Triglyceride (mg/dL)						<0.001
Mean (SD)	80.4 (50.0)	89.2 (58.8)	115 (68.0)	119 (72.4)	97.2 (62.9)	
Median [Min, Max]	67.0 [10.0, 320]	73.0 [14.0, 386]	100 [21.0, 385]	101 [31.0, 399]	81.0 [10.0, 399]	
Hematocrit (%)						<0.001
Mean (SD)	41.1 (3.75)	42.0 (4.03)	43.0 (3.94)	41.8 (4.57)	41.9 (4.06)	
Median [Min, Max]	41.2 [26.9, 53.6]	42.4 [23.1, 54.8]	43.3 [26.0, 52.7]	42.0 [26.8, 53.1]	42.0 [23.1, 54.8]	
PIR						0.573
Mean (SD)	2.37 (1.54)	2.47 (1.51)	2.46 (1.47)	2.32 (1.41)	2.41 (1.49)	
Median [Min, Max]	2.02 [0, 5.00]	2.02 [0, 5.00]	2.02 [0, 5.00]	2.02 [0, 5.00]	2.02 [0, 5.00]	
Uric acid (umol/L)						<0.001
Mean (SD)	292 (78.8)	309 (76.7)	332 (87.4)	337 (90.4)	313 (84.0)	
Median [Min, Max]	286 [137, 672]	303 [131, 571]	333 [107, 648]	321 [137, 648]	309 [107, 672]	
Total cholesterol (mg/dL)						<0.001
Mean (SD)	172 (37.3)	176 (38.7)	189 (38.6)	196 (43.0)	181 (39.9)	
Median [Min, Max]	168 [91.0, 319]	169 [91.0, 328]	187 [79.0, 313]	192 [102, 315]	175 [79.0, 328]	

doi:10.6342/NTU202400005

Table 2. Distributions of blood vitamins in the study population.

Table 2

Blood	Abbreviation	Detection rate (%)	Concentration (umol/L)		Standardized concentration (Z score)	
			Median	Range	Median	Range
Vitamin A	VIA	100.00%	1.61	(0.13, 4.85)	-0.041	(-7.91, 3.41)
Alpha-carotene	ALC	91.61%	0.05	(0.009, 3.82)	0.046	(-1.95, 4.11)
Cis-beta-carotene	CBC	49.21%	0.009	(0.009, 0.28)	-0.86	(-0.86, 3.86)
Trans-beta-carotene	BEC	99.79%	0.23	(0.01, 4.60)	-0.062	(-3.85, 3.30)
Alpha-cryptoxanthin	ARY	99.83%	0.05	(0.002, 0.62)	0.083	(-6.00, 4.42)
Beta-cryptoxanthin	CRY	99.55%	0.14	(0.01, 2.35)	0.015	(-3.62, 3.49)
Trans-lycopene	LYC	99.86%	0.37	(0.03, 1.50)	-0.10	(-1.85, 5.71)
Cis-lycopene	LCC	99.94%	0.31	(0.037, 1.11)	-0.02	(-0.01, -0.19)
Lutein and zeaxanthin	LUZ	99.88%	0.29	(0.03, 4.78)	-0.025	(-4.57, 4.91)
Vitamin C	VIC	90.30%	50.80	(1.70, 208.00)	0.16	(-4.84, 2.24)
Vitamin D	VID	100.00%	59.40	(9.96, 238.00)	-0.053	(-4.01, 3.02)
Vitamin E	VIE	89.64%	23.92	(7.92, 118.89)	-0.15	(-3.49, 4.69)
Gamma-tocopherol	GTC	100.00%	3.82	(0.61, 19.19)	0.062	(-3.55, 3.23)

doi:10.6342/NTU202400005

Table 3. Associations of single blood vitamins with systolic blood pressure and diastolic blood pressure, NHANES, 2017–2018. Models were adjusted age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

Continuous, Ln-transformed concentration of metal; SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, quartile.

Table 3

	SBP	DBP
	continuous	continuous
Vitamin A	0.16 (-2.86,3.18)	0.32 (-1.83,2.46)
Alpha-carotene	-1.11 (-1.86,-0,35)*	0.31 (-0.22,0.85)
Cis-beta-carotene	-2.16 (-3.26,-1.06)*	-0.13 (-0.92,0.66)
Trans-beta-carotene	-1.90 (-2.88,-0.91)*	-0.12 (-0.82,0.59)
Alpha-cryptoxanthin	-0.40 (-2.01,1.22)	0.16 (-0.98,1.31)
Beta-cryptoxanthin	-0.56 (-1.65,0.54)	-0.53 (-0.24,1.31)
Trans-lycopene	-1.43 (-5.62,2.76)	-0.37 (-3.35,2.61)
Total-lycopene	-1.46 (-3.83,0.92)	-0.24 (-1.93,1.45)
Lutein and zeaxanthin	-1.17 (-2.69,0.36)	0.48 (-6.09,1.56)
Vitamin C	-0.89 (-2.05,0.27)	-0.85(-1.45,-0.25)*
Vitamin D	-2.67 (-4.06,-0.74)*	--0.77 (-2.14,0.61)
Vitamin E	-2.16 (-3.26,-1.06)	-1.96 (-4.89,0.98)
Gamma-tocopherol	-0.81 (-0.87,2.50)	-0.37 (-1.59,0.89)

doi:10.6342/NTU202400005

Table 4 Associations of single blood vitamins with systolic blood pressure and diastolic blood pressure with different models by WQS regression, NHANES, 2017–2018.

Model 1 adjusted for age, gender, race,

Model 2 adjusted for age, gender, race, BMI, family income-to-poverty ratio, serum hematocrit, serum uric acid, and body mass index.

Model 3 is the full model, which was adjusted for age, gender, race/ethnicity, BMI, family income-to-poverty ratio, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

Table 4

Model	Adjusted	beta	P value
1	Age, gender, race	-1.64(-2.39,-0.88)	2.35e-05
2	Age, gender, race, BMI, uranic acid	-1.01(-1.86,-0.19)	0.0155
3	Full model	-1.43 (-2.41,-0.45)	0.00439

doi:10.6342/NTU202400005

Table 5 Associations of single blood vitamins with systolic blood pressure and diastolic blood pressure with different models by Q-gcomp regression, NHANES, 2017–2018.

Model 1 adjusted for age, gender, race /ethnicity,

Model 2 adjusted for age, gender, race /ethnicity, BMI, family income-to-poverty ratio, serum hematocrit, serum uric acid, and body mass index.

Model 3 is the full model, which was adjusted for age, gender, race/ethnicity, BMI, family income-to-poverty ratio, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

Table 5

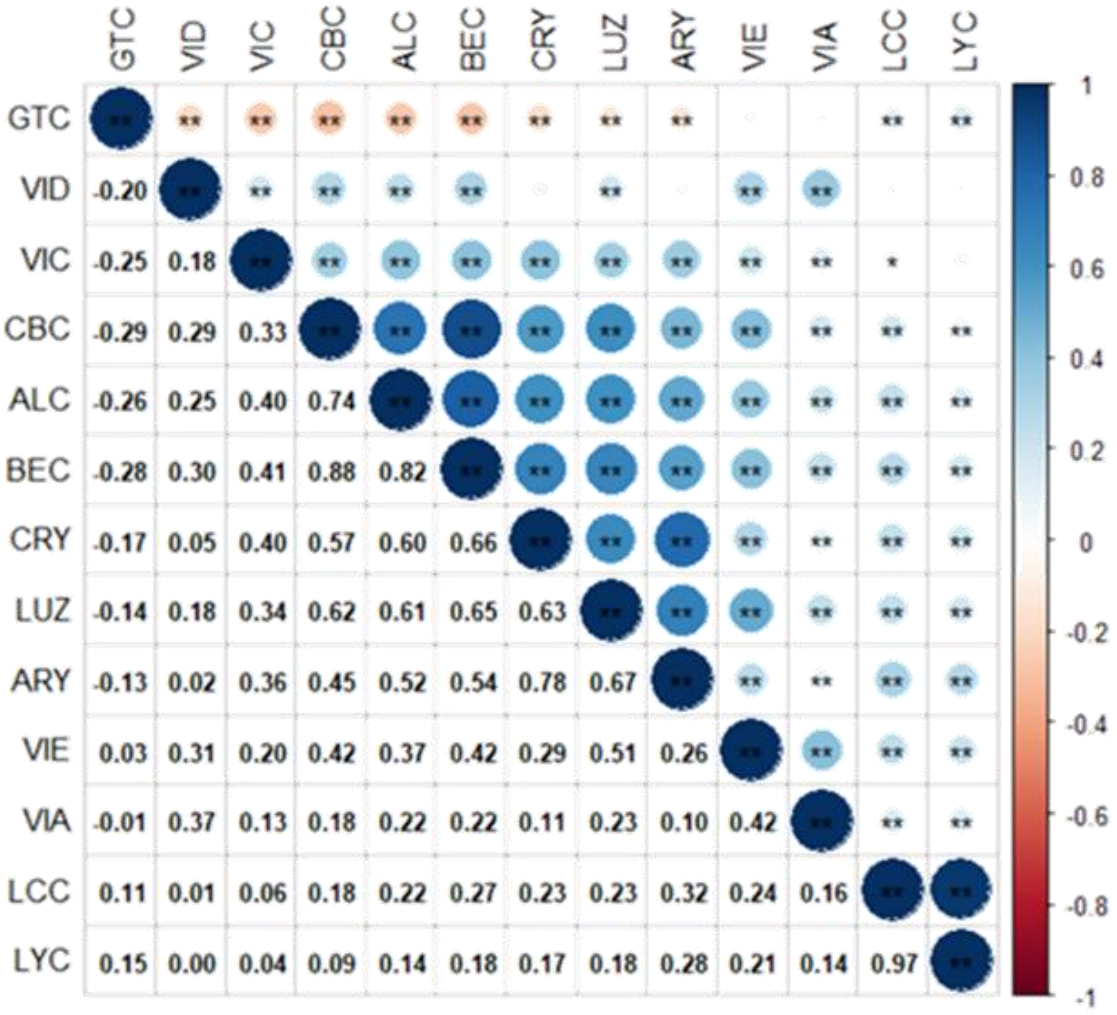
Model	Adjusted	beta	P value
1	Age, sex, race	-1.09(-2.07,-0.11)	0.03*
2	Age, sex, race, BMI, uranic acid	-0.98(-1.95,-0.02)	0.04*
3	Full model	-1.46 (-2.51,-0.38)	0.008**

doi:10.6342/NTU202400005

Chapter7. Figure

Fig. 1. Pearson's correlation matrix among Ln-transformed blood vitamins in the study. Correlation coefficients (r) appear on the bottom triangle, and a graphical display of these values appears on the top triangle.

Figure 1



doi:10.6342/NTU202400005

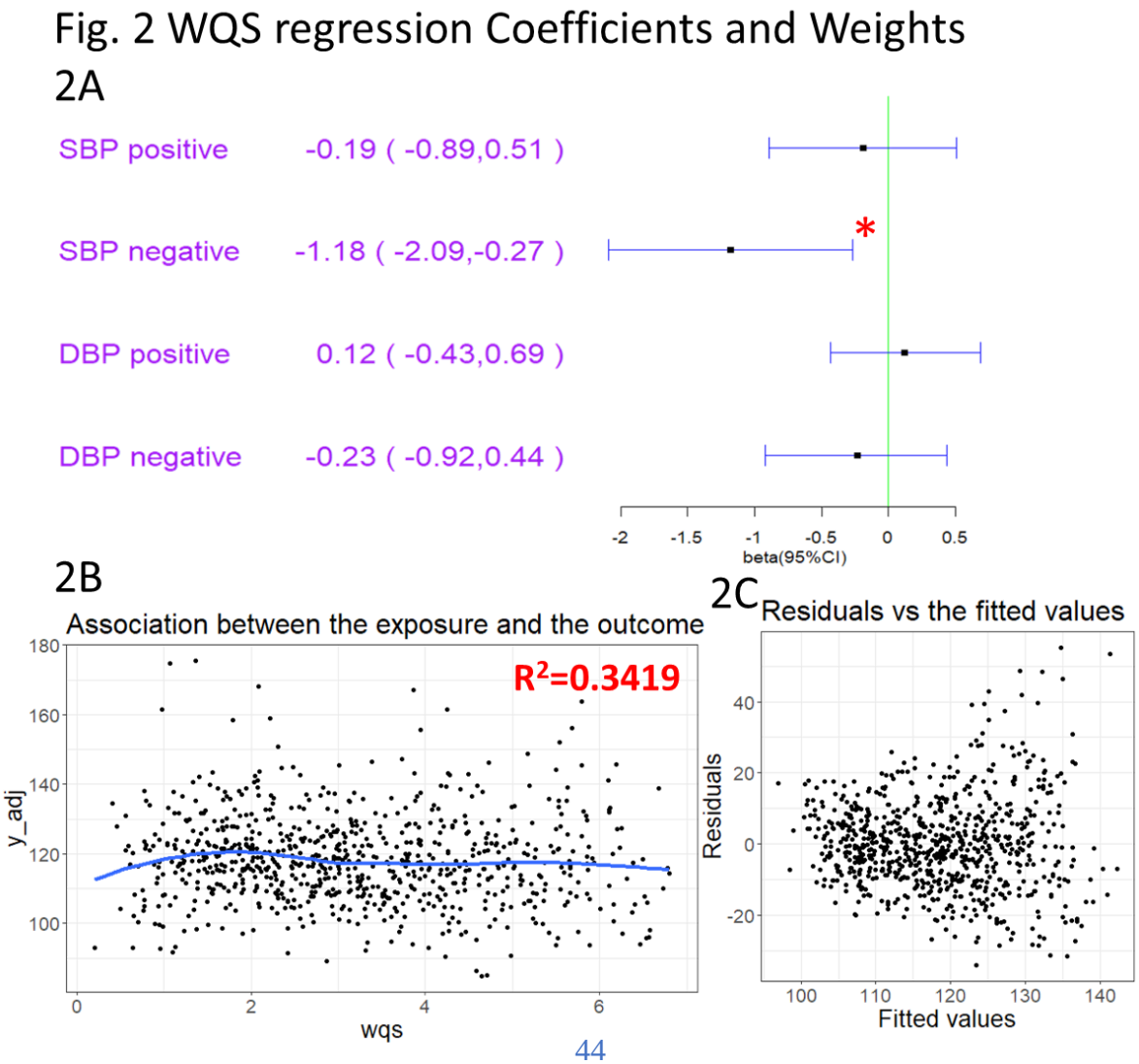
Fig. 2. WQS Regression Coefficients and Weights for Associations between 13 blood vitamin concentrations and systolic and diastolic blood pressure in the study population

A:Weighted quantile sum coefficient means and 95% CIs for the negative and positive directions are presented in the forest plots (labeled “Coefficients”). Models were adjusted for age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index. Coefficients were significant in the WQS regressions denoted with “*”.

B: the direction and the shape of the association between the exposure and the outcome.

C: a diagnostic graph of the residuals vs the fitted values is shown to check if they are randomly spread around zero or if there is a trend.

Figure 2



doi:10.6342/NTU202400005

Fig. 3 The table labeled “Weights” show the weighted quantile sum weights for all vitamins in the mixture, with weights only colored if the full sample 95% CIs for the WQS coefficient do not overlap zero and higher weights display a lighter color.

We de-emphasized the weights for WQS coefficients with full-sample 95% CIs overlapping zero by not color-coding them because when the WQS coefficient is zero or not statistically significantly different from zero, the weights do not convey useful information, as they show a partial contribution to a sum coefficient of zero. WQS coefficients and weights based on fewer than 100 usable bootstraps are omitted from the figure since they are unstable estimates.

Bar plot showing the weights assigned to each variable ordered from the highest weight to the lowest. These results indicate that the variables alpha-carotene, cis-beta-carotene, trans-beta-carotene, and vitamin D are the largest contributors to this mixture effect. The dashed red line represents the cutoff τ (by default equal to the inverse of the number of elements in the mixture as suggested in Carrico et al. 2014) to discriminate which element has a significant weight greater than zero.

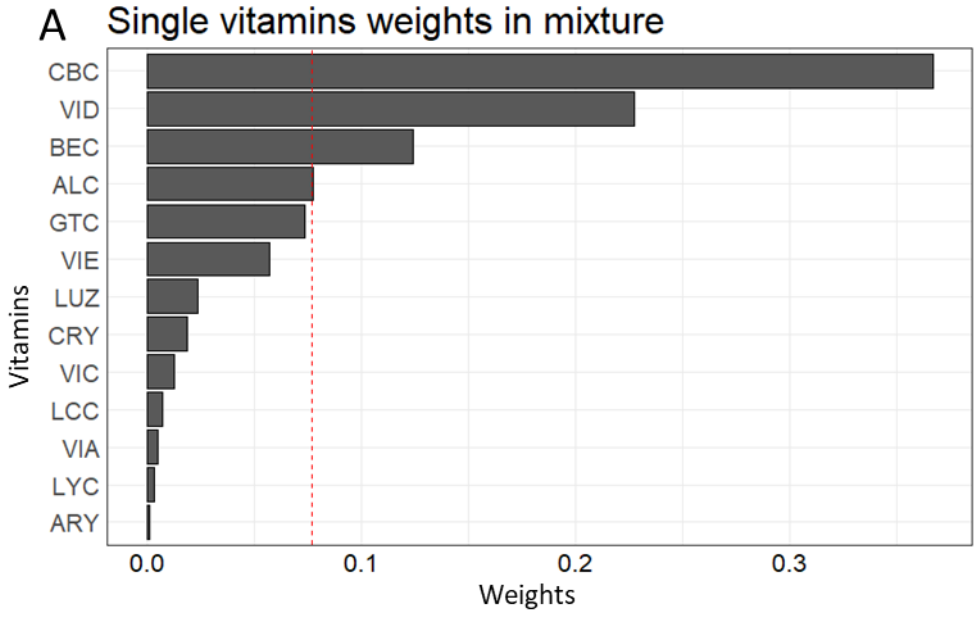
Figure 3

SBP

Weights	VIA	ALC	CBC	BEC	ARY	BEC	LYC	LCC	LUZ	VIC	VID	VIE	GTC
Positive	0.14	0.00	0.00	0.00	0.21	0.07	0.16	0.22	0.00	0.05	0.00	0.04	0.10
Negative	0.00	0.08	0.37	0.12	0.00	0.02	0.01	0.00	0.02	0.01	0.23	0.06	0.07

DBP

Weights	VIA	ALC	CBC	BEC	ARY	BEC	LYC	LCC	LUZ	VIC	VID	VIE	GTC
Positive	0.27	0.03	0.00	0.00	0.15	0.03	0.12	0.02	0.07	0.01	0.02	0.17	0.11
Negative	0.00	0.01	0.41	0.07	0.00	0.02	0.02	0.01	0.00	0.15	0.14	0.02	0.15



doi:10.6342/NTU202400005

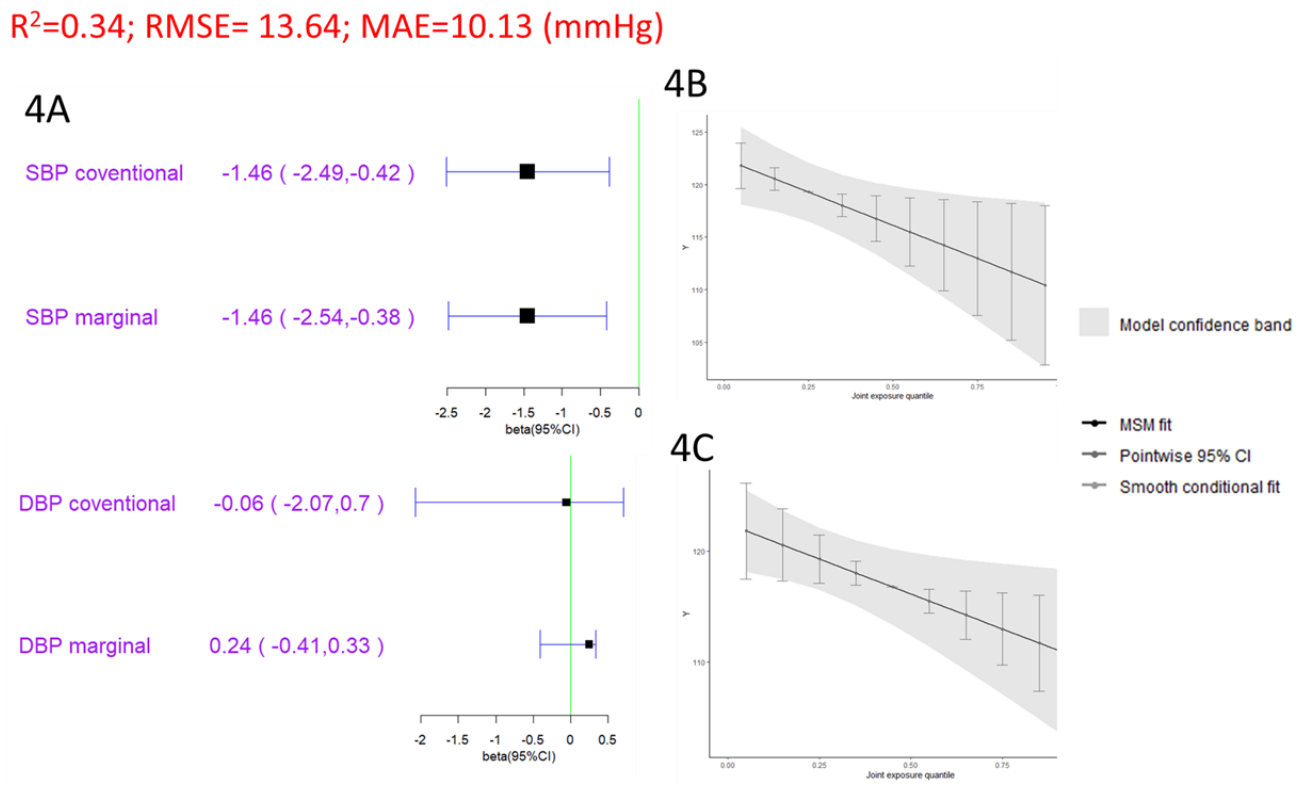
Fig. 4. G-computation Coefficients and Weights for Associations between 13 blood vitamin concentrations and systolic and diastolic blood pressure in the study population.

A: Models were adjusted for age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index. G-computation coefficient means and 95% CIs for both negative and positive directions are presented in the forest plots. Coefficients that were significant in the G-computation are denoted with "*".

B: Linearity of the total exposure effect by g-computation model in 0.25 quantile.

C: Linearity of the total exposure effect by g-computation model in 0.5 quantile.

Figure 4



doi:10.6342/NTU202400005

Fig. 5. The table labeled “Weights” show the G-computation weights for all vitamins in the mixture, with weights only colored if the full sample 95% CIs for the WQS coefficient do not overlap zero and higher weights display a lighter color.

We de-emphasized the weights for G-computation coefficients with full-sample 95% CIs overlapping zero by not color-coding them because when the G-computation coefficient is zero or not statistically significantly different from zero, the weights do not convey useful information, as they show partial contribution to a sum coefficient of zero.

Bar plot showing the weights assigned to each variable ordered from the highest weight to the lowest.

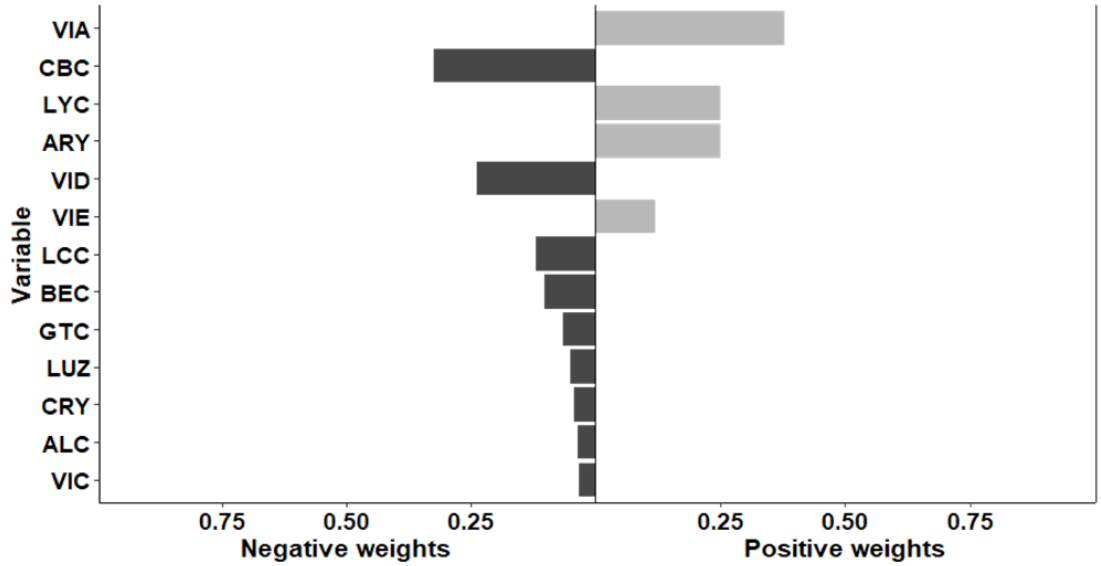
Figure 5

SBP

Weights	VIA	ALC	CBC	BEC	ARY	BEC	LYC	LCC	LUZ	VIC	VID	VIE	GTC
Positive	0.38	0.00	0.00	0.00	0.25	0.00	0.25	0.00	0.00	0.00	0.00	0.12	0.00
Negative	0.00	0.03	0.32	0.10	0.00	0.04	0.00	0.12	0.05	0.03	0.24	0.00	0.07

DBP

Weights	VIA	ALC	CBC	BEC	ARY	BEC	LYC	LCC	LUZ	VIC	VID	VIE	GTC
Positive	0.15	0.23	0.00	0.00	0.00	0.16	0.32	0.00	0.07	0.00	0.00	0.08	0.00
Negative	0.00	0.00	0.10	0.16	0.09	0.00	0.00	0.33	0.00	0.16	0.12	0.00	0.15

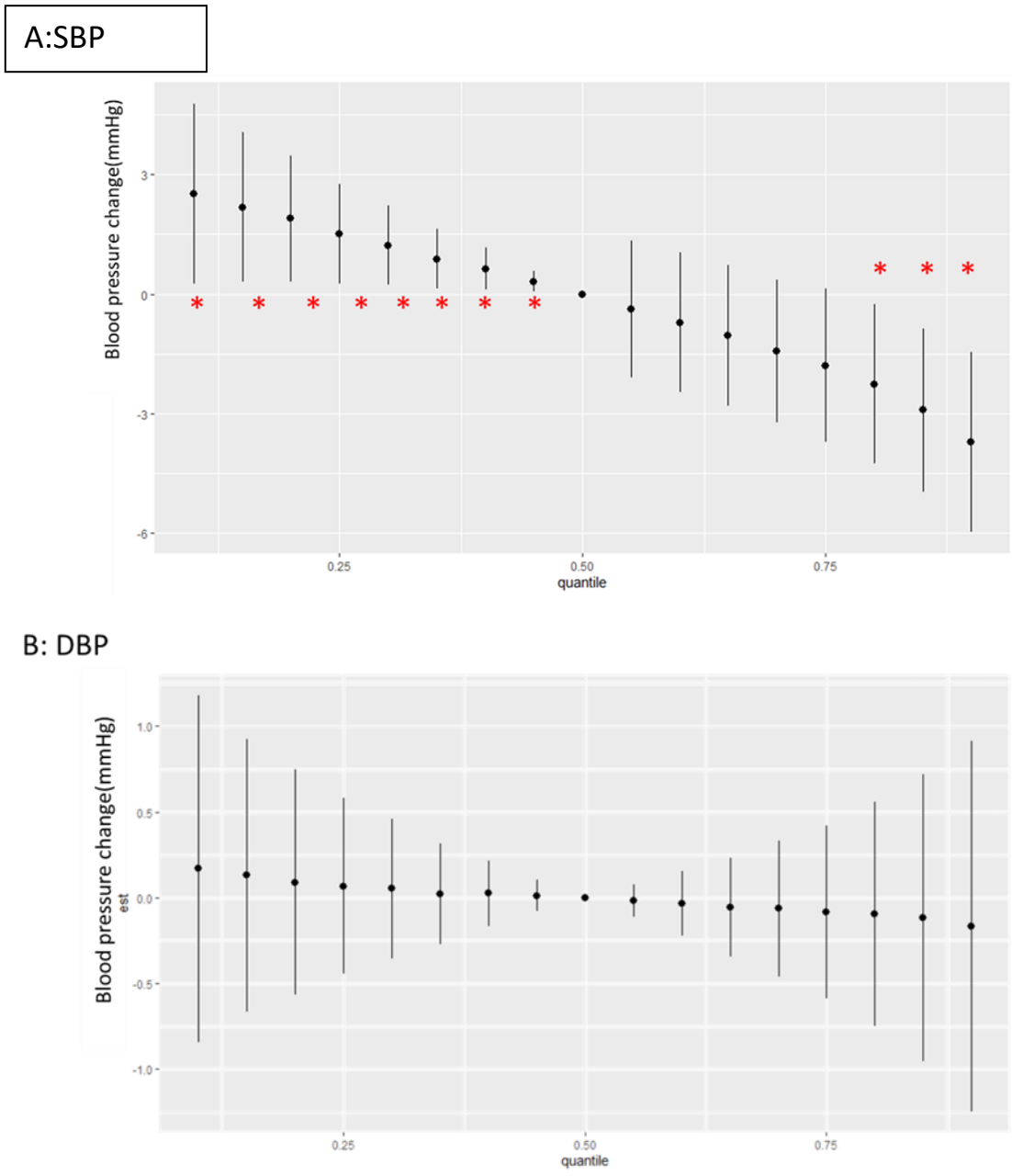


doi:10.6342/NTU202400005

Fig. 6. Combined systolic blood pressure (A) and diastolic blood pressure (B) in total population aby Bayesian Kernel Machine Regression (BKMR) models.

We estimated the overall mixture effect by 5 percentiles of total concentration in a group from the 10th percentile to 90th percentile concentration, using the median concentration group as a reference. Models were adjusted for age, gender, race, family PIR, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index. This plot showed the estimated difference in blood pressure change and 95%CI when all vitamin concentrations were held at particular percentiles compared to their medians.

Figure 6

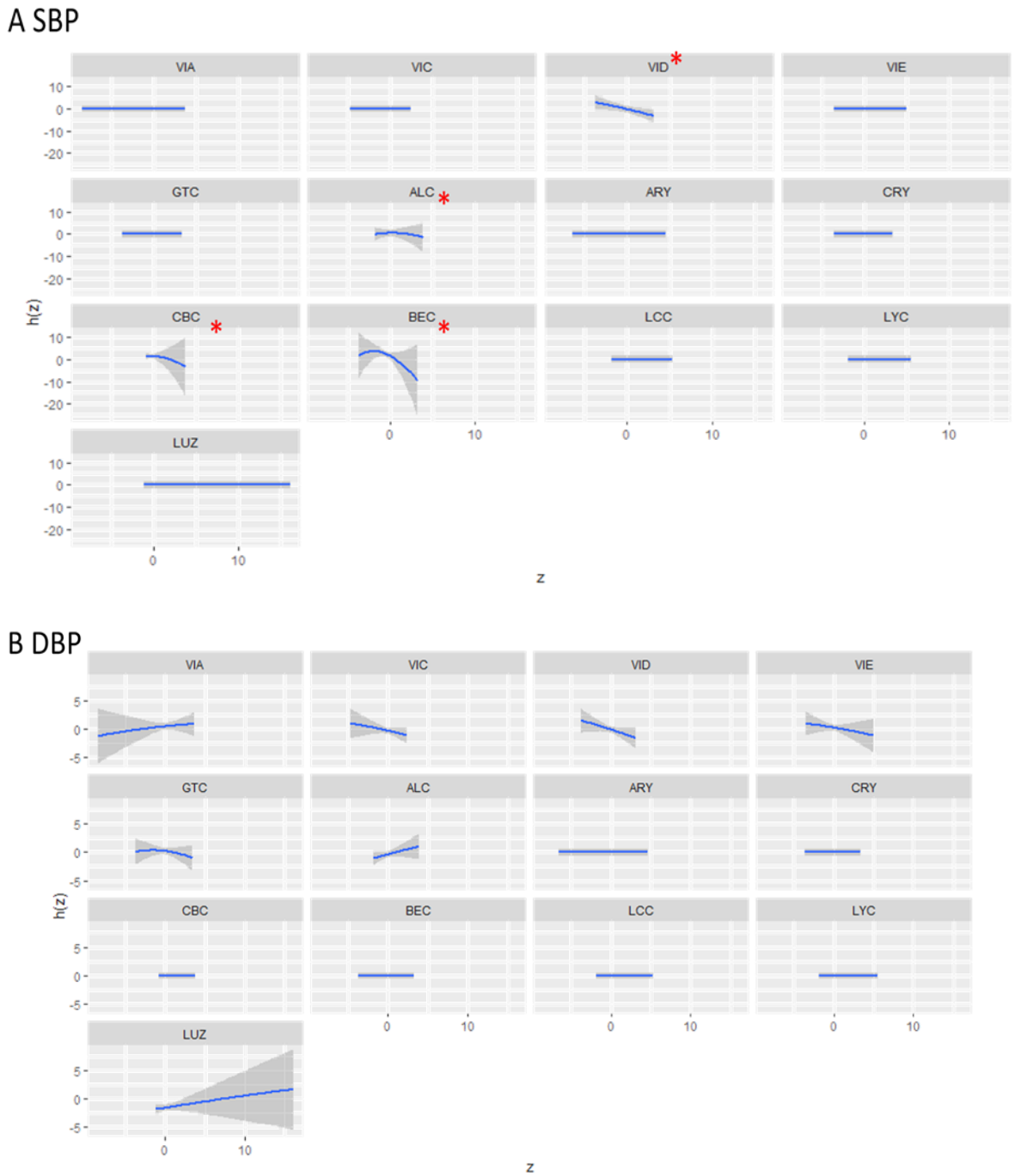


doi:10.6342/NTU202400005

Fig.7. Univariate exposure-response functions for each blood vitamins to systolic blood pressure (A) and diastolic blood pressure (B) .

The results were assessed by the Bayesian Kernel Machine Regression (BKMR) models.

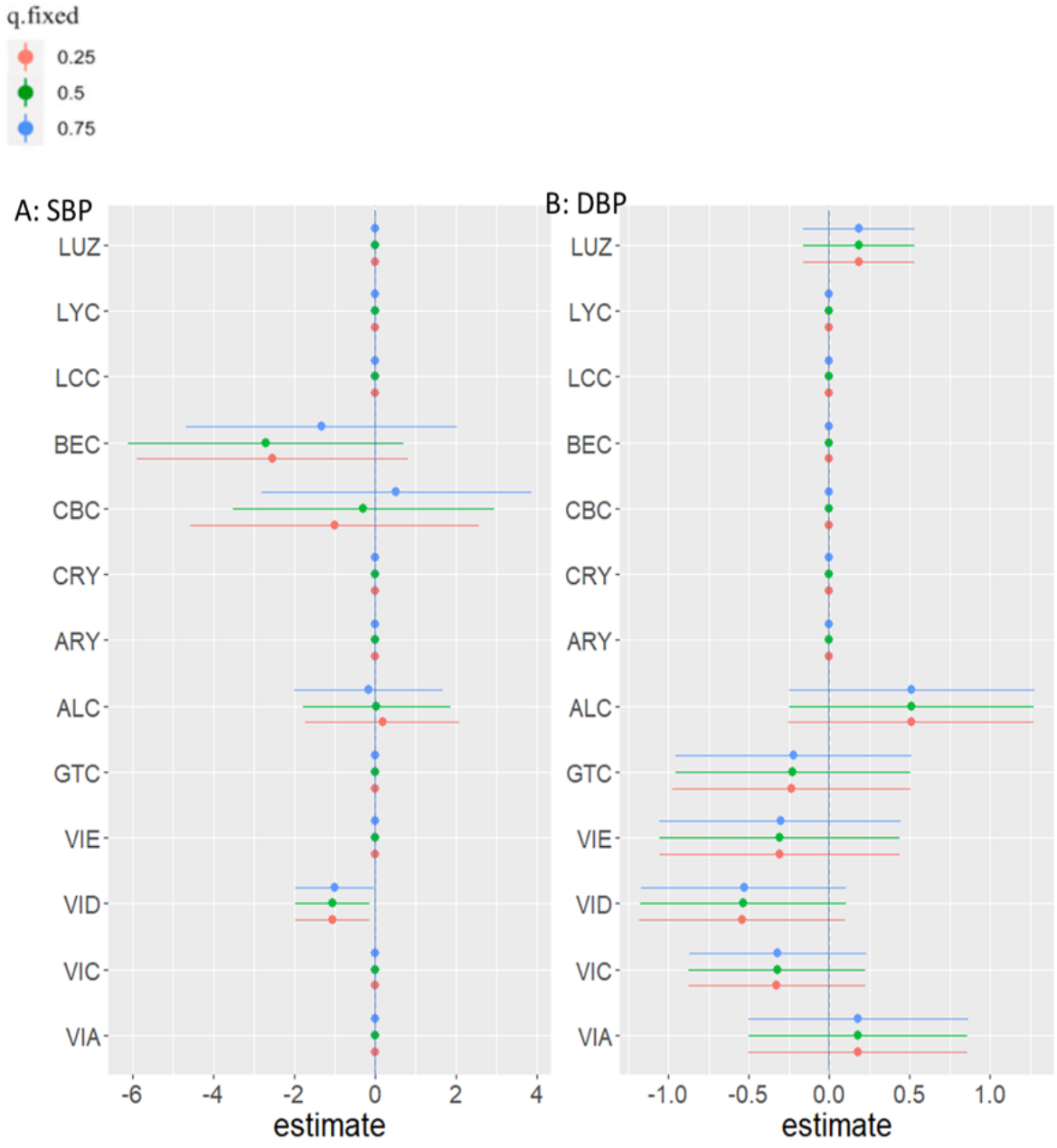
Figure 7



doi:10.6342/NTU202400005

Fig. 8. Associations of single vitamins with systolic blood pressure (A) and diastolic blood pressure change (B) were estimated by Bayesian Kernel Machine Regression (BKMR) in total population , when other all metals were held at their corresponding 25th (red), 50th (green) or 75th (blue) percentile, respectively.

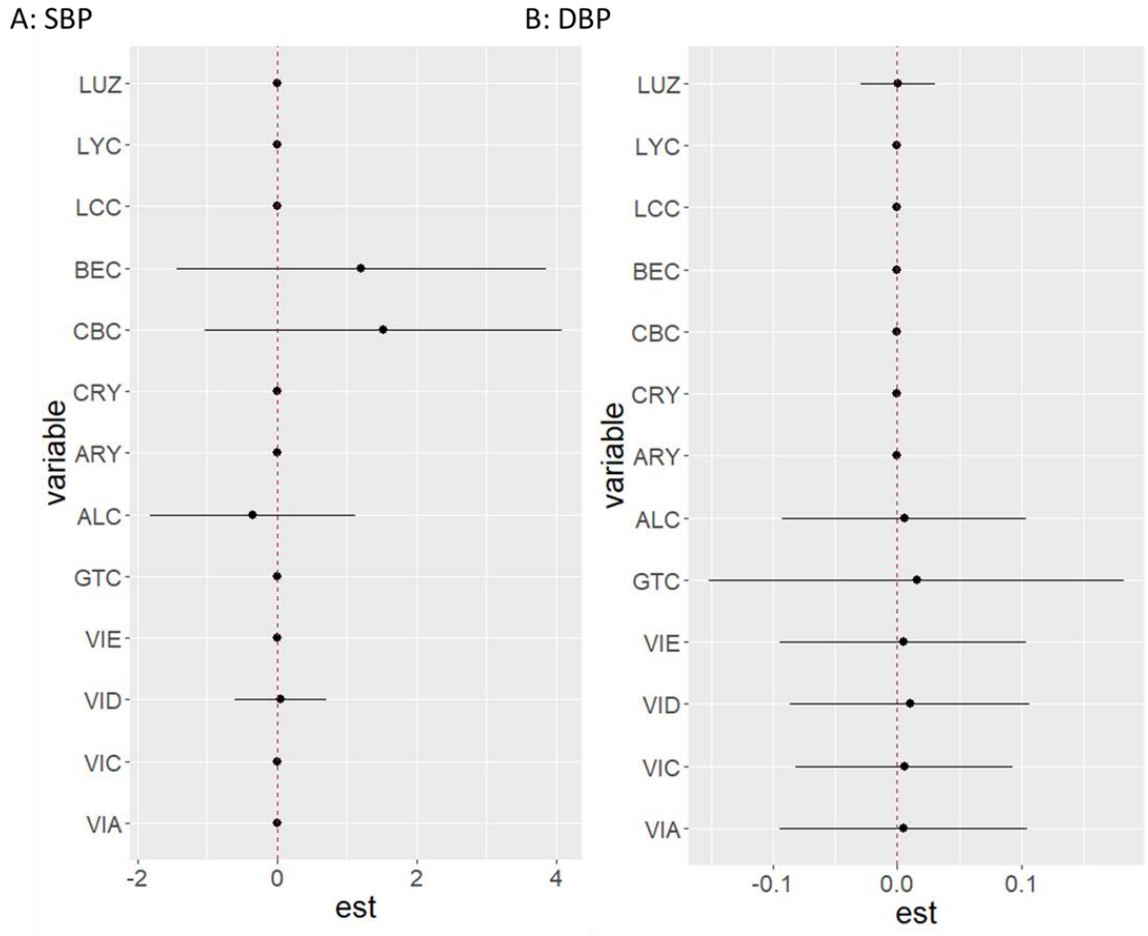
Figure 8



doi:10.6342/NTU202400005

Figure 9: Associations of single provitamins and vitamins with systolic blood pressure (A) and diastolic blood pressure change (B) were estimated by Bayesian Kernel Machine Regression (BKMR) in the total population when other all co-variates were held at their 50th percentile.

Figure 9

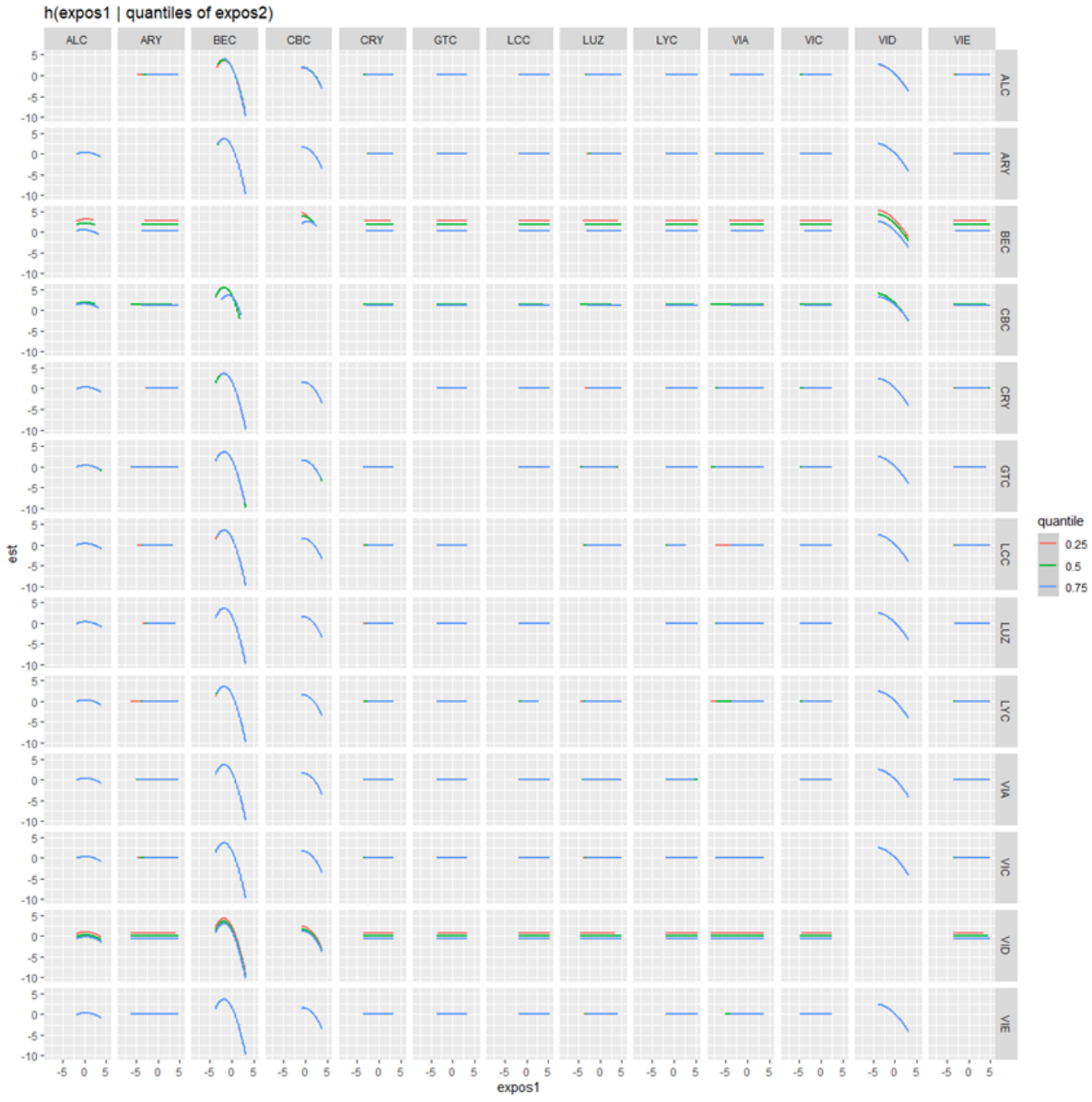


doi:10.6342/NTU202400005

Fig.10 Investigated the predictor-response function of a single predictor in provitamins and vitamins for the second predictor in provitamins and vitamins held at their corresponding 25th (red), 50th (green) or 75th (blue) percentile on systolic blood pressure, respectively.

Models were adjusted for sex, age, race/ethnicity, family income-to-poverty ratio, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid , and body mass index.

Figure 10



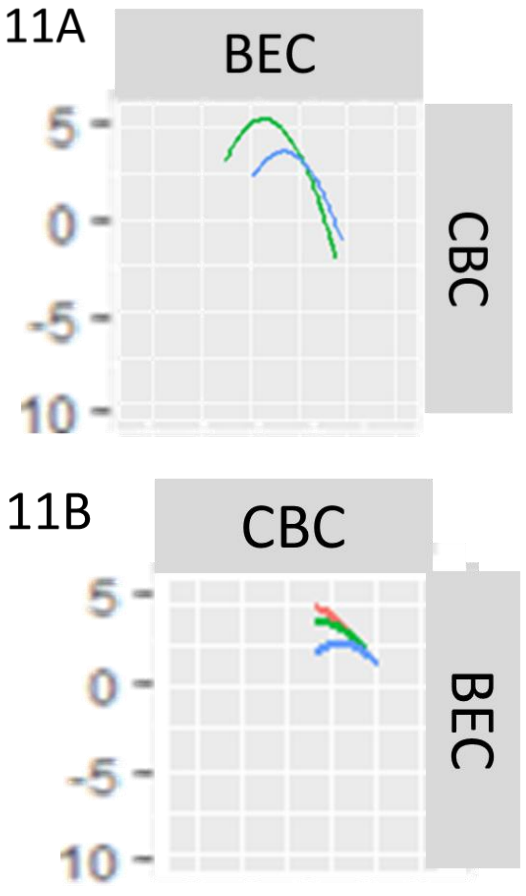
doi:10.6342/NTU202400005

Fig.11

A: Investigated the predictor-response function of trans-beta-carotene in the mixture for systolic blood pressure when cis-beta-carotene held at their corresponding 25th (red), 50th (green), or 75th (blue) percentile.

B: Investigated the predictor-response function of cis-beta-carotene in the mixture for systolic blood pressure when trans-beta-carotene held at their corresponding 25th (red), 50th (green) or 75th (blue) percentile.

Figure 11



doi:10.6342/NTU202400005

Fig.12 Investigated the predictor-response function of a single predictor in provitamins and vitamins for the second predictor in provitamins and vitamins were held at their corresponding 25th (red), 50th (green) or 75th (blue) percentile on diastolic blood pressure, respectively. Models were adjusted for sex, age, race/ethnicity, family income-to-poverty ratio, serum total cholesterol, serum triglyceride, serum hematocrit, serum uric acid, and body mass index.

Figure 12

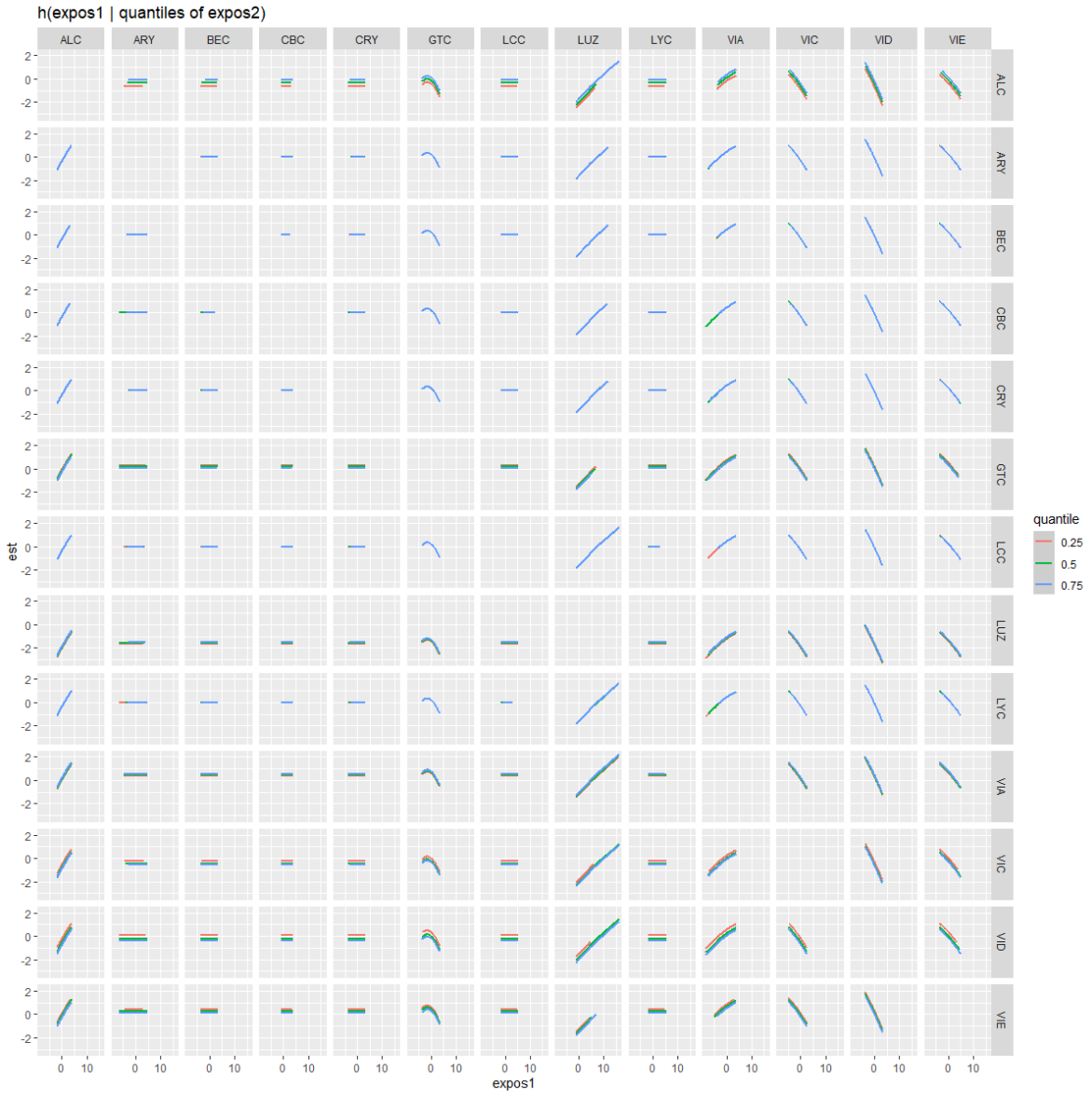


Figure 12

doi:10.6342/NTU202400005

8 Reference

[1] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ , et al. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e563-e595.

[2] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, et al; (2003); Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52.

[3] Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, Grassi G, Jordan J, Poulter NR, Rodgers A, Whelton PK. (2018). Hypertension. Nat Rev Dis Primers. 2018 Mar 22;4:18014.

[4] Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020 Feb;75(2):285-292.

[5] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002 Dec 14;360(9349):1903-13.

[6] Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. (2014). Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 2014 May 31;383(9932):1899-911.

[7] Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. (1996). Blood pressure and end-stage renal disease in men. N Engl J Med. 1996 Jan 4;334(1):13-8.

[8] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):e13-e115.

doi:10.6342/NTU202400005

[9] Poulter NR, Prabhakaran D, Caulfield M. Hypertension. Lancet. 2015 Aug 22;386(9995):801-12.

[10] Pierre CC, Wiencek JR. The impact of environmental factors on external and internal specimen transport. Clin Biochem. 2023 May;115:13-21.

[11] Huang M, Chen J, Yang Y, Yuan H, Huang Z, Lu Y. Effects of Ambient Air Pollution on Blood Pressure Among Children and Adolescents: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2021 May 18;10(10):e017734.

[12] Alengebawy A, Abdelkhalek ST, Qureshi SR, Wang MQ. Heavy Metals and Pesticides Toxicity in Agricultural Soil and Plants: Ecological Risks and Human Health Implications. Toxics. 2021 Feb 25;9(3):42.

[13] Mariana M, Cairrao E. Phthalates Implications in the Cardiovascular System. J Cardiovasc Dev Dis. 2020 Jul 22;7(3):26.
[14] Ensminger AH (1994). Foods & nutrition encyclopedia. CRC Press. pp. 527–.Retrieved 12 October 2010.

[15] Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, Bechthold A, Schlesinger S, Boeing H. Food Groups and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2017 Nov 15;8(6):793-803.

[16] Mphahlele TP, Monyeki KD, Dibakwane WM, Mokgoatšana S. The Relationship between Under-Nutrition and Hypertension among Ellisras Children and Adolescents Aged 9 to 17 Years. Int J Environ Res Public Health. 2020 Dec 1;17(23):8926.

[17] Saha S, Pandya A, Kandre Y, Raval D, Saxena D. Cross-Sectional Analysis of Nutritional Status, Knowledge and Uptake of Nutritional Services Among Adolescent Girls in Western India. Adolesc Health Med Ther. 2021 Dec 14;12:117-125.

[18] Prentice, Andrew M (October 2005). "Macronutrients as sources of food energy". Public Health Nutrition. 8 (7a): 932–939.

[19] "Chapter 3: Calculation Of The Energy Content Of Foods – Energy Conversion Factors". Food and Agriculture Organization of the United Nations. Retrieved 30 March 2017.

[20] Mathur P, Pillai R. Overnutrition: Current scenario & combat strategies. Indian J Med Res. 2019 Jun;149(6):695-705.

[21] Abdullah A. The Double Burden of Undernutrition and Overnutrition in Developing Countries: an Update. Curr Obes Rep. 2015 Sep;4(3):337-49.

doi:10.6342/NTU202400005

[22] de Vries R, de Vet E, de Graaf K, Boesveldt S. Foraging minds in modern environments: High-calorie and savory-taste biases in human food spatial memory. Appetite. 2020 Sep 1;152:104718.

[23] Guthold R, Stevens GA, Riley LM, Bull FC. Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1·6 million participants. Lancet Child Adolesc Health. 2020 Jan;4(1):23-35.

[24] San-Cristobal R, Navas-Carretero S, Martínez-González MÁ, Ordovas JM, Martínez JA. Contribution of macronutrients to obesity: implications for precision nutrition. Nat Rev Endocrinol. 2020 Jun;16(6):305-320.

[25] Kelly RK, Watling CZ, Tong TYN, Piernas C, Carter JL, Papier K, Key TJ, Perez-Cornago A. Associations Between Macronutrients From Different Dietary Sources and Serum Lipids in 24 639 UK Biobank Study Participants. Arterioscler Thromb Vasc Biol. 2021 Jul;41(7):2190-2200.

[26] Lu Y, Cui X, Zhang L, Wang X, Xu Y, Qin Z, Liu G, Wang Q, Tian K, Lim KS, Charles CJ, Zhang J, Tang J. The Functional Role of Lipoproteins in Atherosclerosis: Novel Directions for Diagnosis and Targeting Therapy. Aging Dis. 2022 Apr 1;13(2):491-520.

[27] Barrett TJ. Macrophages in Atherosclerosis Regression. Arterioscler Thromb Vasc Biol. 2020 Jan;40(1):20-33.

[28] Zhang X, Ritonja JA, Zhou N, Chen BE, Li X. Omega-3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2022 Jun 7;11(11):e025071.

[29] Van West, D., & Maes, M. (2003). Polyunsaturated fatty acids in depression. Acta Neuropsychiatrica, 15(1), 15-21.

[30] Lands WE. Biochemistry and physiology of n-3 fatty acids. FASEB J. 1992 May;6(8):2530-6.

[31] Oil, vegetable, corn, industrial and retail, all purpose salad or cooking; USDA Nutrient Data, SR-21. Conde Nast. Retrieved 12 April 2014.

[32] Jane Higdon; Victoria J. Drake (2011). Evidence-Based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations (2nd ed.). Thieme. ISBN 978-3131644725.

[33] Karppanen H. Minerals and blood pressure. Ann Med. 1991 Aug;23(3):299-305.

doi:10.6342/NTU202400005

[34] Grillo A, Salvi L, Coruzzi P, Salvi P, Parati G. Sodium Intake and Hypertension. Nutrients. 2019 Aug 21;11(9):1970.

[35] Bekheirnia MR, Schrier RW. Pathophysiology of water and sodium retention: edematous states with normal kidney function. Curr Opin Pharmacol. 2006 Apr;6(2):202-7.

[36] Capone K, Sentongo T. The ABCs of Nutrient Deficiencies and Toxicities. Pediatr Ann. 2019 Nov 1;48(11):e434-e440.

[37] Wolf G. The discovery of the visual function of vitamin A. J Nutr. 2001 Jun;131(6):1647-50.

[38] Lidén M, Eriksson U. Understanding retinol metabolism: structure and function of retinol dehydrogenases. J Biol Chem. 2006 May 12;281(19):13001-13004.

[39] "Vitamin D". Office of Dietary Supplements, US National Institutes of Health. 12 August 2022. Archived from the original on 9 April 2021. Retrieved 22 February 2022.

[40] Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med. 2007 Jul 1;43(1):4-15.

[41] Shearer MJ, Okano T. Key Pathways and Regulators of Vitamin K Function and Intermediary Metabolism. Annu Rev Nutr. 2018 Aug 21;38:127-151.

[42] Lykstad J, Sharma S. Biochemistry, Water Soluble Vitamins. 2023 Mar 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.

[43] Said HM. Intestinal absorption of water-soluble vitamins in health and disease. Biochem J. 2011 Aug 1;437(3):357-72.

[44] Llopis-González, A., et al., Hypertension and the Fat-Soluble Vitamins A, D and E. International Journal of Environmental Research and Public Health, 2015. 12(3): p. 2793-2809.

[45] Ran L, Zhao W, Tan X, Wang H, Mizuno K, Takagi K, Zhao Y, Bu H. Association between Serum Vitamin C and the Blood Pressure: A Systematic Review and Meta-Analysis of Observational Studies. Cardiovasc Ther. 2020 Apr 29;2020:4940673.

[46] Johra FT, Bepari AK, Bristy AT, Reza HM. A Mechanistic Review of β-Carotene, Lutein, and Zeaxanthin in Eye Health and Disease. Antioxidants (Basel). 2020 Oct 26;9(11):1046.

[47] Alagacone, S., et al., The association between vitamin D deficiency and the risk of resistant
hypertension. Clinical and Experimental Hypertension, 2020. 42(2): p. 177-180.

doi:10.6342/NTU202400005

[48] Schiborn, C., et al., Retinol and Retinol Binding Protein 4 Levels and Cardiometabolic Disease Risk. Circulation Research, 2022. 131(7): p. 637-649.

[49] "About the National Health and Nutrition Examination Survey". CDC/National Center for Health Statistics. U.S. Department of Health & Human Services. Retrieved 18 March 2020.

[50] National Health and Nutrition Examination Survey 2017-2018 Data Documentation Codebook and Frequencies Blood Pressure (BPX_J): Centers for Disease Control and Prevention (CDC) . Available online at: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/BPX_J.htm (accessed February 2020).

[51] National Health and Nutrition Examination Survey 2017-2018 Data Documentation Codebook and Frequencies Vitamin A, Vitamin E & Carotenoids (VITAEC_J): Centers for Disease Control and Prevention (CDC) . Available online at: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VITAEC_J.htm (accessed May 2022).

[52] National Health and Nutrition Examination Survey 2017-2018 Data Documentation Codebook and Frequencies Vitamin C (VIC_J): Centers for Disease Control and Prevention (CDC) . Available online at: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VIC_J.htm (accessed June 2020).

[53] National Health and Nutrition Examination Survey 2017-2018 Data Documentation Codebook and Frequencies Vitamin D (VID_J): Centers for Disease Control and Prevention (CDC) . Available online at: https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VID_J.htm (accessed April 2022).

[54] Carrico, Caroline, Chris Gennings, David C Wheeler, and Pam Factor-Litvak. 2015. “Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting.” Journal of Agricultural, Biological, and Environmental Statistics 20 (1): 100–120.

[55] Colicino, Elena, Nicolo Foppa Pedretti, Stefanie A Busgang, and Chris Gennings. 2020. “Per-and Poly-Fluoroalkyl Substances and Bone Mineral Density: Results from the Bayesian Weighted Quantile Sum Regression.” Environmental Epidemiology (Philadelphia, Pa.) 4 (3).

[56] Stefano Renzetti, Paul Curtin, Allan C Just, Ghalib Bello, Chris Gennings.2021. How to use gWQS package. From URL: https://cran.r-project.org/web/packages/gWQS/vignettes/gwqs-vignette.html

[57] Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ Health Perspect. 2020 Apr;128(4):47004.

doi:10.6342/NTU202400005

[58] Nicole Niehoff, Michiel van den Dries, Emily Werder, Jessie Buckley, and Katie O'Brien. How to use qgcomp package. From URL: https://cran.r-project.org/web/packages/qgcomp/vignettes/qgcomp-vignette.html

[59] Liu, Shelley H, Jennifer F Bobb, Kyu Ha Lee, Chris Gennings, Birgit Claus Henn, David Bellinger, Christine Austin, et al. 2018. "Lagged Kernel Machine Regression for Identifying Time Windows of Susceptibility to Exposures of Complex Mixtures." Biostatistics 19 (3): 325–41.

[60] Jennifer F. Bobb, 2022, bkmr: Bayesian Kernel Machine Regression. From URL: https://cran.r-project.org/web/packages/bkmr/index.html

[61] Lee, Soo Chan; Ristaino, Jean B.; Heitman, Joseph (13 December 2012). "Parallels in Intercellular Communication in Oomycete and Fungal Pathogens of Plants and Humans". PLOS Pathogens. 8 (12): e1003028. doi:10.1371/journal.ppat.1003028

[62] WebMD. "Find a Vitamin or Supplement – Beta Carotene". Retrieved 29 May 2012. Stargrove, Mitchell (20 December 2007). Herb, nutrient, and drug interactions : clinical implications and therapeutic strategies (1 ed.). Mosby. ISBN 978-0323029643.

[63] Ahmad, A., Riaz, S., Shahzaib Nadeem, M., Mubeen, U., & Maham, K. (2022). Role of Carotenoids in Cardiovascular Disease. IntechOpen. doi: 10.5772/intechopen.102750

[64] Chen J, He J, Hamm L, Batuman V, Whelton PK. Serum antioxidant vitamins and blood pressure in the United States population. Hypertension. 2002 Dec;40(6):810-6. doi: 10.1161/01.

[65] Karppi J, Kurl S, Mäkikallio TH, Ronkainen K, Laukkanen JA. Serum β-carotene concentrations and the risk of congestive heart failure in men: a population-based study. Int J Cardiol. 2013 Oct 3;168(3):1841-6. doi: 10.1016/j.ijcard.2012.12.072. Epub 2013 Jan 17. PMID: 23333366.

[66] Karppi J, Laukkanen JA, Mäkikallio TH, Kurl S. Low serum lycopene and β-carotene increase risk of acute myocardial infarction in men. Eur J Public Health. 2012 Dec;22(6):835-40. doi: 10.1093/eurpub/ckr174.

[67] Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chemistry & Biology. March 2014, 21 (3): 319–29, doi:10.1016/j.chembiol.2013.12.016

[68] Zhang Y, Kong J, Deb DK, Chang A, Li YC. Vitamin D receptor attenuates renal fibrosis by suppressing the renin-angiotensin system. J Am Soc Nephrol. 2010; 21: 966–973.

doi:10.6342/NTU202400005

[69] Young EW, Morris CD, Holcomb S, McMillan G, McCarron DA. Regulation of parathyroid hormone and vitamin D in essential hypertension. Am J Hypertens. 1995; 8: 957–964.

[70] Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, Liu Y, Li W, Li X. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. Prev Chronic Dis. 2020 Jan 9;17:E03. doi: 10.5888/pcd17.190307. PMID: 31922371

[71] Joukar F, Naghipour M, Hassanipour S, Salari A, Alizadeh A, Saeidi-Saedi H, Mansour-Ghanaei F. Association of Serum Levels of Vitamin D with Blood Pressure Status in Northern Iranian Population: The PERSIAN Guilan Cohort Study (PGCS). Int J Gen Med. 2020;13:99-104. https://doi.org/10.2147/IJGM.S244472

[72] Wu, Y., Li, S. & Zhang, D. Circulating 25-hydroxyvitamin D levels and hypertension risk. Eur J Epidemiol 28, 611–616 (2013). https://doi.org/10.1007/s10654-013-9817-8

[73] Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ Health Perspect. 2020 Apr;128(4):47004. doi: 10.1289/EHP5838.

[74] Liang M, Guo X, Ding X, Song Q, Wang H, Li N, Su W, Liang Q, Sun Y. Combined effects of multiple metals on hearing loss: A Bayesian kernel machine regression approach. Ecotoxicol Environ Saf. 2022 Dec 1;247:114279. doi: 10.1016/j.ecoenv.2022.114279.

[75] Varadharaj S, Kelly OJ, Khayat RN, Kumar PS, Ahmed N, Zweier JL. Role of Dietary Antioxidants in the Preservation of Vascular Function and the Modulation of Health and Disease. Front Cardiovasc Med. 2017 Nov 1;4:64. doi: 10.3389/fcvm.2017.00064.

doi:10.6342/NTU202400005