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RESEARCH

Using nutrigenomics to guide personalized nutrition supplementation for bolstering immune system

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Abstract

Immunity refers to the ability of the human immune system to resist pathogen infection. Immune system has the basic functions of immune defense, immune self stabilization and immune surveillance. Balanced nutrition is the cornerstone of the immune system to play its immune function, and nutritional intervention is also an important means to maintain and improve immunity. Previous studies have confirmed that T cells have individual differences in recognizing viral antigens of virus infected cells, and the body's response to antigens is controlled by a variety of genetic genes, such as human leukocyte antigen (HLA) genes, immune response (Ir) genes, etc. In this paper, through immunity genetic testing, we screen out genetically susceptible people with low immunity and people with the risk of nutrient metabolism disorders; through using lifestyle questionnaire and physical examination results, we analyze people's physical condition, dietary habits, and exercise habits to evaluate people's nutrient deficiency degree. Then, combining multi-dimensional health data, we evaluate users' immune status and nutritional deficiency risk comprehensively, further, we implemented personalized nutrition intervention on the types and doses of nutritional supplements to improve immunity. We also validated the effectiveness of our personalized nutrition solution through a population-based cohort study.

Keywords: Immunity, Precision nutrition, Nutrigenetics, DNA testing, Physical examination

Introduction

Immune organs mainly include thymus, lymph nodes, bone marrow, spleen and tonsil, which are the places where immune cells are generated, matured and concentrated. Immune cells are cells involved in or related to immune response, mainly including phagocytes and lymphocytes (T lymphocytes, B lymphocytes), which participate in cellular immunity and humoral immunity through effector T cells and plasma cells, respectively. Immune molecules, including cytokines, antibodies and lysozymes, act a significant role in the occurrence, regulation and effect of immune response.

Immune system mainly relies on three lines of defense against the attack of pathogens: (1) skin and mucosa, (2) bactericidal substances in phagocytes and body fluids, (3) immune organs and immune cells.

Individual immunity is affected by genetic factors. The polymorphism of immunity related genes will affect individual's response to antigens, affect individual's risk of autoimmune diseases, and affect individual's immune surveillance function.

Over-nutrition or under-nutrition will also affect the immune system to exert its immune function. Nutritional balance is an important means to enhance immunity. However, individuals have differences in nutrient digestion, absorption, metabolism and so on.

To boost immune system effectively, we proposed a personalized nutrition solution [1] based on individual's genetic, lifestyle, and physical examination data. "Balanced nutrition and immune system" section explains the relation between nutrition and immunity, "Immune function and genes" section introduces how genes affect immune function, "Personalized nutrition for bolstering

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immune system" section introduces our personalized solution for boosting immune system, "Validation" section validates the effectiveness of our model through a population based cohort study, "Conclusions" section concludes the paper and discusses our future research topics.

Balanced nutrition and immune system

Immune system is the defense and monitoring system of body and an important guarantee for survival and health. However, immunity is a "double-edged sword", too weak will cause repeated infection, too strong will cause autoimmune diseases.

Balanced nutrition is the cornerstone of immunity. Many nutrients not only directly affect the function of immune organs and participate in the differentiation and maturation of immune cells, but also act a significant role in immune regulation, cell proliferation and anti-inflammatory.

At present, the diseases such as obesity, hyperlipidemia, diabetes and obese cancer, which pose the greatest threat to health, have been proved to be inflammatory and autoimmune diseases caused by over nutrition [2]. When over-nutrition reaches the limit of self storage, it will stimulate cells, especially immune cells, to consume the excess nutrition (causing infectious diseases or autoimmune disease), inhibit continuous storage (causing insulin resistance) and directly expel nutrition (causing diabetes), or activate cell proliferation (causing hyperimmunity or cancer occurrence and development), or continue to tolerate nutrition accumulation (causing obesity or cardiovascular and cerebrovascular diseases) [3].

Lack of nutrition will affect the immune system to play its immune function. For example, copper deficiency can cause thymus atrophy and impaired antibody synthesis. Iron deficiency can lead to anemia, leukopenia and reduced bactericidal capacity, inhibit antibody production, and reduce the response to infection. Zinc deficiency or excess will lead to immune deficiency, reduce white blood cells and lymphocytes; zinc supplementation can shorten the course of disease, reduce symptoms and significantly improve immune function. Vitamin A deficiency will weaken antibody response and mucosal barrier function. Vitamin C supplementation can enhance the function of epithelial barrier, enhance the function of phagocytes, and promote the production of antibodies. Vitamin E supplementation can improve the division speed of T cells and B cells.

Therefore, supplementing balanced nutrition is essential for strengthening immune system.

Immune function and genes

Lots of genes are connected with human immune system. For instance, the human leukocyte antigen (HLA) genes have the function of antigen presentation, participate in the activation and differentiation of T cells, participate in the regulation of immune response, and participate in antigen processing. The polymorphism of these genes determines the different immune responses of individuals to the same antigen.

HLA genes are closely related to the susceptibility to a variety of autoimmune diseases [4, 5]. *HLA-DR3* is associated with myasthenia gravis, systemic lupus erythematosus, exophthalmos goiter, and type 1 diabetes; HLA-DR2 is associated with pulmonary hemorrhagic nephritis syndrome and multiple sclerosis; *HLA-DR5* is associated with hashimoto thyroiditis.

As an immune modulator, vitamin D is associated with the occurrence of a variety of autoimmune diseases [6], such as systemic lupus erythematosus, multiple sclerosis and type 1 diabetes [7]. Vitamin D deficiency can also lead to a significantly increased risk of autoimmune thyroid disease (AITD), and supplementing vitamin D can reduce its incidence rate. *VDR* gene's polymorphism changes the structure and quantity of VDR through gene regulation, and then affects the biological function of VDR, indicating that *VDR* gene's polymorphism is associated with the genetic susceptibility of AITD [8, 9].

Vitamin A is an important fat soluble vitamin, which acts a significant role in cell differentiation, proliferation, immune function, eye function and reproductive function [10]. According to the WHO survey [11], there are about 100 million preschool children worldwide who are vitamin A deficient, of which more than 30 million children show clinical symptoms, which are mainly related to immune response, such as respiratory infection and low immunity. Vitamin A supplementation can improve children's immune function [12, 13].

Individuals with *BCMO1* gene's mutations have low plasma vitamin A level and are prone to vitamin A deficiency (VAD) [14]. VAD limits the function of innate cells to phagocytize pathogens and activate natural killer T cells to exert immune regulation, affecting the immune function of respiratory mucosa. VAD interferes with the proliferation and maturation of epithelial cells, induces keratinization of epithelial cells, inhibits the secretion of secretory immunoglobulin A (sIgA) from respiratory mucosa, and affects humoral immune function [15].

Personalized nutrition for bolstering immune system

Immunity DNA testing

To evaluate individual's genetic risk of low immunity and nutrient metabolism disorders, we implemented a

genetic testing service for immunity. Through collecting individual's saliva, our laboratory extracts DNA and sequences the DNA, then we analyze the DNA data using bioinformatic pipelines, finally we use genetic interpretation database to interpret the DNA data. Figure 1 is the homepage of the strengthen immunity DNA testing report. In Fig. 1 left, the "Testing Results Radar Chart" part uses a radar chart to demonstrate the immune capacity of an individual; correspondingly, the "Testing Results Five Dimensional Summarization" part summarizes the testing results. Figure 1 middle and right, list the five genetic testing categories:

- Anti-infection ability, contains the DNA testing items of: Influenza A virus infection, chronic sinus infection, *Staphylococcus aureus* infection, urinary tract infection, and yeast infection.

For example, chronic sinusitis infection is a common nasal disease, which can lead to chronic sinusitis and cause great trouble to patients. Chronic sinusitis is a chronic suppurative inflammation of the paranasal sinuses, often involves multiple paranasal sinuses at the same time. Chronic sinusitis affects the quality of life of patients, aggravates the respiratory tract infection symptoms of patients, and in severe cases, may cause cranioocular pulmonary complications, leading to visual changes, and even death due to aggravated infection.

The coding product of *AFF3* gene is a tissue restricted nuclear transcription activator preferentially expressed in lymphoid tissue, which may play a role in lymphoid development and tumorigenesis. Genome wide association studies (GWAS) indicated that the polymorphism of the *AFF3* gene would affect the susceptibility of individuals to chronic sinus infection [5].

- Antibody response level, contains the DNA testing items of: IgG level after *Chlamydia pneumonia* infection, the level of IgG after human herpesvirus 8 infection, cytomegalovirus (CMV) antibody response, and thyroid peroxidase antibody level.

For example, CMV can cause congenital infection. People with low immunity, such as tumors, organ transplantation, AIDS, etc., can cause latent CMV activation, leading to serious CMV infection throughout the body, manifested as interstitial pneumonia, hepatitis, and can lead to death.

The encoding product of *AGBL1* gene is glutamic acid decarboxylase, research has shown that the polymorphism of the *AGBL1* gene is closely connected to the antibody response of CMV [16].

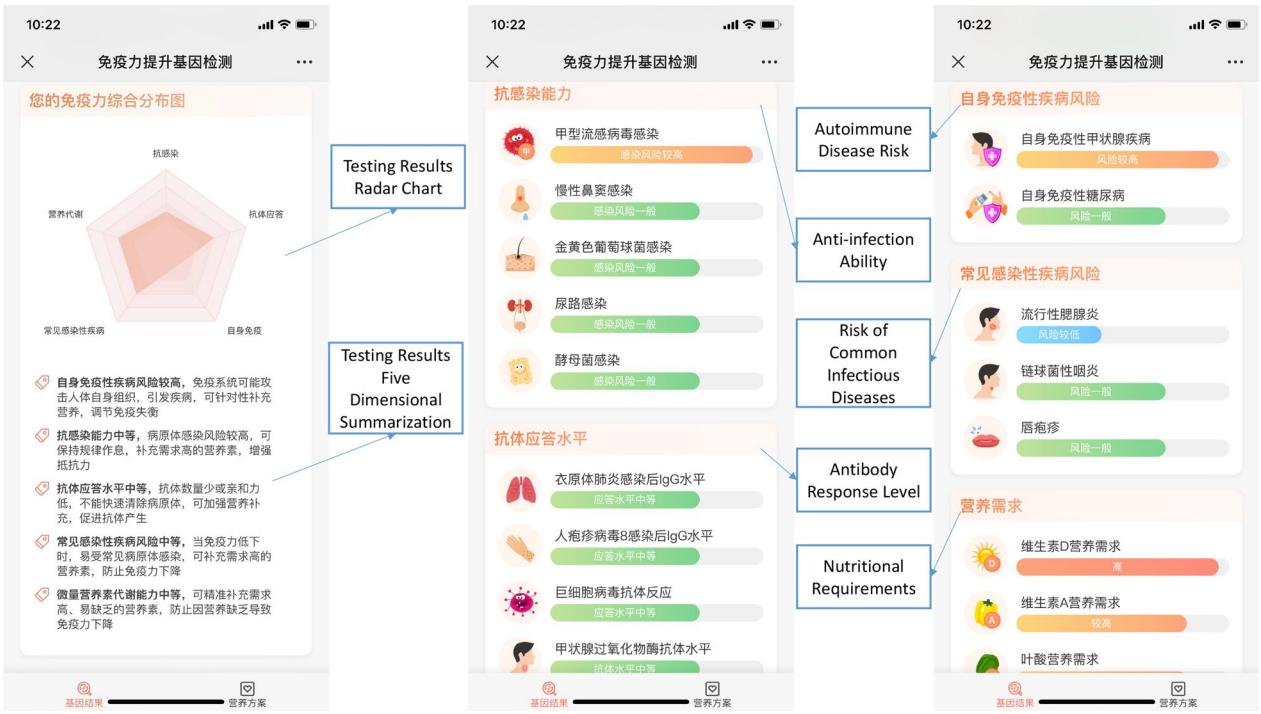

Fig. 1 The screen shots of the homepage of the strengthen immunity DNA testing report

- Autoimmune disease risk, contains the DNA testing items of: autoimmune thyroid disease, and autoimmune diabetes mellitus.

  For example, thyroid gland is an important endocrine organ of human body. It can appear some autoimmune diseases under the influence of autoimmunity. Patients with autoimmune thyroid disease can have other autoimmune diseases at the same time or successively, such as myasthenia gravis, type 1 diabetes, pernicious anemia, atrophic gastritis, etc.

  BACH2 is a protein coding gene, *BACH2* affects the diseases of immunodeficiency, chronic myeloid leukemia and etc. Research indicated that the polymorphism of the *BACH2* gene has close connection with the susceptibility to autoimmune thyroid disease. Individuals carrying the A allele at the key locus of this gene have a higher risk of autoimmune thyroid disease [17].
- Risk of common infectious diseases, contains the DNA testing items of: epidemic parotitis, streptococcal pharyngitis, and Herpes labialis.

  For example, epidemic parotitis/mumps is a common respiratory infectious disease in children and adolescents. It is an acute and systemic infection caused by mumps virus. After infection with mumps, fever and headache will appear, and then the parotid glands centered on the earlobes on one or both sides will swell, the face will swell and ache, and the pain will intensify when eating, making it difficult to open mouth.

  HLA-A belongs to HLA class I heavy chain analogues, which are composed of heavy chains and light chains (β-2 microglobulin). Research has shown that the *HLA-A* gene is connected to mumps. Individuals carrying the C allele of the key locus of this gene have weak immunity and high susceptibility to mumps [5].
- Nutritional requirement, contains the DNA testing items of: vitamin A, vitamin D, vitamin E, vitamin C, vitamin B_6, folic acid, magnesium, iron, zinc, selenium, DHA.

  For example, iron is one of the essential elements of human physiological metabolism and an important component of hemoglobin and many enzymes. Iron is involved in maintaining normal immune function, participating in the production of antibodies, and increasing the phagocytosis of neutrophils and phagocytes. Iron deficiency will increase the chance of infection, reduce the bactericidal capacity of leukocytes, and damage the function of lymphocytes. Excessive iron will promote bacterial growth, which is unfavorable to the resistance to bacterial infection.

  The encoding product of *TMPRSS6* gene is membrane-bound serine protease, which can inhibit the expression of ferritin. Research showed that the *TMPRSS6* gene's polymorphism has connection with iron deficiency anemia and affects the content of hemoglobin and ferritin [18].

Click the genetic testing item name in Fig. 1 middle or right, a second level page will pop out as described in Fig. 2. In Fig. 2 left, the "Testing Result and Explanations" module gives the testing result, explanation and suggestions (e.g., the testing result of "Chronic Sinus Infection" is medium); the "Item Introduction" module introduces the association between the testing item and the immune system; the "Testing Loci" module gives the genotypes of the tested gene loci. In Fig. 2 right, the "Scientific Evidences" module explains the connections between the tested genes and immunity; the "Lifestyle (Preventive) Guidelines" module provides lifestyle suggestions to prevent the happening of diseases; the "Scientific References" module makes a list of the published scientific and clinical papers.

Physical examination data

Physical examination generally includes but not limited to the test items of: chemistry panel, blood pressure, complete blood count, heart rate, urinalysis, respiration rate, throat, sinuses, eyes, lymph nodes, thyroid, and etc.

To understand the current physical condition and relevant indicators of individuals, we combine individual's physical examination result into our personalized nutrition data model. Individuals can upload their physical examination report in PDF format to our online system or fill their physical examination result to our online form, then our system will extract the required test items to our data model. Figure 3 is the physical examination report accessed in mobile phone. In Fig. 3 left, the "Key Attention Items and Explanations" module summarizes the items that should pay attention, the "General Examination Items" module lists the general examination items (such as body mass index (BMI), systolic blood pressure (SBP), etc.) and their results. In Fig. 3 right, the "Biochemical Tests" module gives the biochemical tests items (such as triglyceride level, total cholesterol level, etc.) and their results.

Click the physical examination item name in Fig. 3, a second level page will pop out as shown in Fig. 4. In Fig. 4 left, the "Testing Result" module gives an item's testing result (e.g., the "Total Cholesterol" level is medium); the "Trend Chart" lists the indicators of the test items in different periods. In Fig. 4 middle, the "Friendly Reminder" module provides some friendly health reminders and explains how total cholesterol affects health; the "Introduction" module explains the test item in details (for example, explains what is total cholesterol and the factors affecting total cholesterol); the "Matters Need Attention"

Fig. 2 The screen shots of the second level page of the strengthen immunity genetic testing report

module provides the matters that need to pay attention. In Fig. 4 right, the "Diagnosis Evidences" module explains the test item's diagnosis evidences; the "Scientific References" module lists the reference papers.

Lifestyle evaluation

Balanced nutrition supplementation is necessary for a healthy immune system. Additionally, other factores such as appropriate sport and adequate sleep also benefit immune system. We developed an online food frequency questionnaires [19] to assess individual's lifestyle including diet, sleeping, sports, medical history and etc. The online food frequency questionnaires can be accessed and answered from computer or mobile phone conveniently, and the questions are dynamic that the latter question will be different based on individual's answer to the previous question.

Boosting the immune system

Combining DNA testing, physical examination, and lifestyle evaluation results together, we developed a data model to compute personalized nutrition solutions for boosting the immune system.

Figure 5 is the homepage of a personalized nutrition solution. In Fig. 5 left, the "Nutrition Facts" module lists the nutrition facts tailored for each individual. In Fig. 5 middle, the "Core Nutrients Requirement for Supplementation" module lists the nutrients tailored for supplementation to boost immunity. Click the nutrient name, more information concerning the nutrient will be shown in Fig. 5 right, in which, the "Nutrient Name" part explains why should supplement the nutrient (such as magnesium); the "Immune Functions" part describes how the nutrient affects immune system; the "Evaluation and Suggestions" part, demonstrates the immune capacity evaluation evidences based on DNA testing, physical examination, and lifestyle evaluation results; the "Food Sources" part suggests the foods that are rich in the corresponding nutrient (such as hickory contains 306mg magnesium per 100g edible part).

We need to emphasize that a daily balanced diet includes ensuring that each meal contains carbohydrates, protein, fat, fiber, and it is not recommended to eat only meat or only vegetables at each meal, is the cornerstone

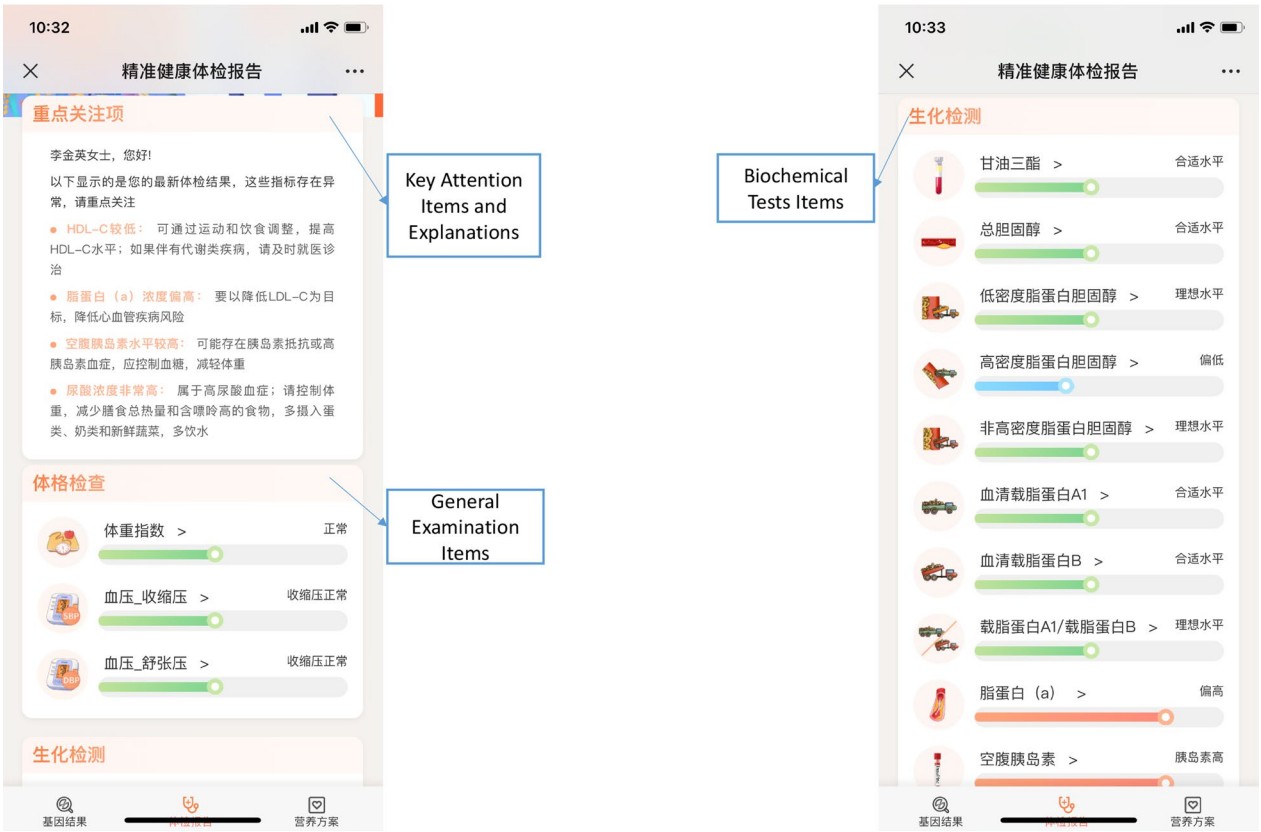

Fig. 3 The screen shots of the homepage of the physical examination report

Fig. 4 The screen shots of the second level page of the physical examination report

Fig. 5 The screen shots of the homepage of the personalized nutrition report

of maintaining good health. Therefore, when it is found that an individual is prone to deficiencies in certain nutrients through testing and assessment, we give those foods rich in certain nutrients in the "Food Sources" in the Personalized Nutrition report (in Fig. 5 right), so that individual can supplement nutrients through the corresponding foods. But even so, affected by geography, eating habits, lifestyle and other factors, some foods can not be obtained reliable, some foods cannot be guaranteed to be eaten enough every day, which will lead to the deficiency of some nutrients, so we need to supplement the lacked nutrients through dietary supplements. Compared with the traditional one size fits all solution, personalized supplements can better meet the health needs of individuals.

Relying on the personalized nutrition solution for boosting immune system, individual can place order for tailored daily nutrition box, then our intelligent nutrition production plant will produce personalized nutrition box for each individual.

Validation

We collaborated with a physical examination center to evaluate the effectiveness of our personalized nutrition solution. The evaluation was aimed to validate the personalized vitamin D supplementation solutions based on genetic testing, metabolism and lifestyles, were beneficial to reduce the risk of vitamin D deficiency for people. Serum 25 hydroxyvitamin D (25(OH)D) concentration is clinically used as a marker of vitamin D status.

Study population

The validation was conducted at a health checkup center, in Fujian Province, China. We recruited 90 adults (aged 22–76 years); pregnant women, lactating women and individuals with severe chronic diseases (e.g., cardiovascular disease, diabetes) were excluded for safety consideration, but people who were overweight or obese were allowed to participate. Participants need to be able to fill out questionnaires online using mobile phones.

The characteristics of the 90 participants are described in Table 1, from which we can see that, the participants' mean baseline serum 25(OH)D concentration is 42.1 $\pm$ 14.9 nmol/L, 66.7% of the participants had vitamin D deficiency (serum 25(OH)D concentration $<$ 50 nmol/L). There was nearly no difference in the rate of vitamin D deficiency between men and women (64.7% vs. 67.8%, P $=$ 0.764); the mean concentration of serum 25(OH)D between men and women was different, but the difference was not significant (45.9 nmol/L vs. 38.9 nmol/L, P $=$ 0.0766). Other parameters, such as body mass index (BMI), systolic blood pressure (SBP),

Table 1 The descriptive characteristics of the participants at first visit

	Female	Male	All
Number	56	34	90
Age (years)	41.3 (23–76)	43.3 (22–74)	42.0(22–76)
BMI (kg/m^2)	22.2 ± 2.9	25.2 ± 3.0	23.3 ± 3.2
SBP (mmHg)	115.7 ± 12.3	124.4 ± 11.6	118.9 ± 12.7
DBP (mmHg)	74.9 ± 8.0	69.2 ± 8.6	71.2 ± 8.6
Serum TG (mmol/L)	1.05 ± 0.51	1.90 ± 1.03	1.37 ± 0.85
Serum TC (mmol/L)	4.76 ± 0.96	5.02 ± 1.05	4.88 ± 1.00
Serum LDL-C (mmol/L)	2.88 ± 0.87	3.32 ± 0.89	3.06 ± 0.90
Serum HDL-C (mmol/L)	1.60 ± 0.28	1.22 ± 0.25	1.46 ± 0.32
Serum homocysteine (mol/L)	8.40 ± 1.93	11.23 ± 3.01	9.51 ± 2.78
Serum 25(OH)D (nmol/L)	38.9 ± 15.5	45.9 ± 13.3	42.1 ± 14.9
Serum 25(OH)D < 50 nmol/L	67.8 (38)	64.7 (22)	66.7 (60)
Current smoker	0	44.1 (15)	16.7 (15)
Drinking frequency ≥ 1 times/week	23.2 (13)	73.5 (25)	42.2 (38)
Physical activity ≥ 3 times/week	7.1 (4)	23.5 (8)	13.3 (12)

Values are means (range), means ± SD, or % (n)

BMI body mass index, *SBP*, systolic blood pressure, *DBP* diastolic blood pressure, *TG* total triglyceride, *TC* total cholesterol, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol

diastolic blood pressure (DBP), total triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), homocysteine, proportion of smokers, frequency of drinking, number of physical activities, were significantly different between men and women.

Please note that in this validation, we mainly verified the influence of three main factors, namely gene, diet and serum 25(OH)D level, on vitamin D supplementation. The participants selected in the study are generally healthy people, so the other baseline data in Table 1 are intended to include/exclude participants.

Follow-up plan

After introduction and training, all the participants signed the informed consent form for personalized nutrition validation, then:

- each participant collected 2 mL saliva used for genetic testing;
- each participant filled in food frequency questionnaires on-line;
- the nurses collected the participants' upper arm venous blood (5 mL + 5 mL) for routine blood tests (including total triglyceride, total cholesterol, homocysteine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, etc.), and serum 25(OH)D concentration test;
- the nurses took physical measurements of the participants, including weight, systolic blood pressure, diastolic blood pressure, and etc. (Table 2).

Genes and serum 25(OH)D concentration

According to some of the published genes that have a greater impact on serum 25(OH)D concentration, we analyzed the association between different genotypes of these genes and their serum 25(OH)D concentration (see Table 3). Among them, different genotypes of *CYP2R1* (rs10741657) and *GC* (rs7041) have a greater impact on serum 25(OH)D concentration, although the difference is not significant (P values are 0.249 and 0.168, respectively).

GRS and serum 25(OH)D concentration

The loci rs10741657 and rs7041 were included in the genetic risk score (GRS) for predicting serum 25(OH)D concentration, in our study, the GRS was the sum of the number of risk alleles for the SNPs rs10741657 (G allele, major allele) and rs7041 (A allele, major allele) (range: 0–4). The more risk alleles the participants carried, the higher the score. In our study, individuals with 0–2 risk alleles (GRS 0–2) were assigned to the low-risk group of vitamin D deficiency, and individuals with 3–4 risk alleles (GRS 3–4) were assigned to the high-risk group of vitamin D deficiency. The serum 25(OH)D concentration in the high-risk group was 5.1 nmol/L lower than that in the low-risk group (95% CI − 1.8, 12.0, P = 0.147), but the difference was not significant. The risk of vitamin D deficiency in the high-risk group was 1.77 times higher than that in the low-risk group (OR = 1.77, 95% CI 0.63, 4.97, P = 0.294) (Table 4).

Table 2 Follow-up plan in the study

Follow-up plan	First visit	Nutrition intervention	Second visit	Third visit
Study progress	Sample collection and testing	Personalized nutrition intervention	Sample collection and testing	Sample collection and testing
Timeline	Day 0	Day 30	Day 60	Day 90

Table 3 Association between individual locus and serum 25(OH)D concentration

Gene	Locus	Genotype	Serum 25(OH)D (nmol/L)	P value	Percentage of 25(OH)D < 50 nmol/L
CYP2R1	rs10741657	AA	49.4 ± 15.8	0.249	66.7
		AG	41.6 ± 15.1		77.1
		GG	41.4 ± 15.1		73.0
CYP27B1	rs4646536	GG	42.8 ± 8.0	0.942	73.7
		AG	41.8 ± 15.5		73.5
		AA	42.3 ± 15.8		83.3
GC	rs7041	CC	48.6 ± 28.1	0.168	76.9
		AC	40.2 ± 14.5		80.0
		AA	42.6 ± 16.4		58.8
	rs1155563	TT	43.7 ± 15.9	0.695	50.0
		CT	41.5 ± 15.5		80.6
		CC	40.8 ± 13.0		73.2
NADSYN1	rs7944926	AA	45.1 ± 14.2	0.711	76.9
		AG	37.5 ± 14.2		80.0
		GG	47.0 ± 16.2		58.8
	rs3829251	AA	45.4 ± 5.4	0.815	83.3
		GA	39.7 ± 14.6		80.0
		GG	43.8 ± 16.5		67.6

P value is the probability of t test of serum 25(OH)D concentration of low-risk homozygotes and high-risk homozygotes of a gene

Table 4 Association between GRS and serum 25(OH)D concentration

Risk level	GRS score	Serum 25(OH)D (nmol/L)	Percentage of 25(OH)D < 50 nmol/L	P value
Low risk	0–2	45.3 ± 13.6	67.8	0.147
High risk	3–4	40.2 ± 15.4	78.8	

CI confidence Interval, *OR* odds ratio

Effects of personalized vitamin D supplementation

Relying on the participants' GRS, physical examination and food frequency questionnaire data, we developed a personalized vitamin D supplementation program. After 3 months of personalized nutritional intervention, the participants' serum 25(OH)D concentration increased from 42.1 to 56.3 nmol/L, with an average increase of 14.2 nmol/L (95% CI 8.4, 23.5, P < 0.0001) (see Table 5).

By analyzing the supplementation effects with different vitamin D supplementation doses for the participants

Table 5 Association between personalized vitamin D supplementation effects and genotypes/GRS

Locus or GRS	Genotype or GRS score	Vitamin D supplementation (μg)	Serum 25(OH)D (nmol/L)		Difference after supplementation (95% CI)	P value
			Pre-supplementation	Post-supplementation		
Total		5.96 ± 2.22	42.1 ± 14.9	56.3 ± 13.9	14.2 (8.4, 23.5)	< 0.0001
rs10741657	AA	5.86 ± 1.61	51.5 ± 24.6	51.9 ± 18.9	− 0.3 (− 49.9, 49.4)	0.9871
	AG	6.17 ± 2.56	38.5 ± 14.8	59.3 ± 14.9	20.8 (10.1, 31.5)	0.0004
	GG	5.59 ± 1.79	40.0 ± 13.0	53.2 ± 12.0	13.2 (2.1, 24.3)	0.0224
rs7041	CC	3.36 ± 0.03	50.1 ± 3.0	69.8 ± 9.6	19.7 (− 10.8, 50.2)	0.1091
	AC	6.40 ± 2.92	41.0 ± 14.5	57.7 ± 11.0	16.7 (5.8, 27.6)	0.0043
	AA	6.04 ± 1.65	38.7 ± 16.4	53.6 ± 16.1	14.9 (3.8, 26.7)	0.0145
GRS	0–2	5.64 ± 2.68	45.4 ± 15.6	59.2 ± 12.2	13.8 (2.5, 25.2)	0.0193
	3–4	6.25 ± 1.77	36.5 ± 13.9	54.1 ± 15.4	17.6 (7.3, 27.8)	0.0014

with different genotypes and GRS, the results showed that for different genotypes at rs10741657 locus, the participants with low-risk homozygous (AA genotype) have no significant difference in the change of serum 25(OH)D concentration after supplementation, the serum 25(OH)D concentration of the participants with high-risk homozygous (GG genotype) increased significantly after supplementation ($P < 0.05$).

The average supplementation dose of vitamin D of different genotypes at rs7041 locus was different (CC genotype 3.36 μg vs. AA genotype 6.04 μg). The serum 25(OH)D concentration of low-risk homozygotes (CC genotype) increased after supplementation, but the difference was not significant ($P = 0.1091$). The serum 25(OH)D concentration of high-risk homozygotes (GG genotype) increased significantly after supplementation ($P < 0.05$). There was a difference in vitamin D supplementation dose between GRS low-risk group and high-risk group (5.64 μg vs. 6.25 μg). The concentration of serum 25(OH)D increased significantly after supplementation ($P < 0.05$).

The participants were separated into three groups according to the baseline serum 25(OH)D concentration. By analyzing the supplementation effects with different vitamin D supplementation doses for the participants with different baseline vitamin D status, the results showed that, the mean baseline serum 25(OH)D concentration of the participants in lower tertile was only 24.4 nmol/L, which was 41.4% of the participants (59.0 nmol/L) in upper tertile. The mean vitamin D supplementation doses for the participants in the lower tertile and upper tertile were 6.92 μg and 5.16 μg, respectively. After supplementation, the mean serum 25(OH)D concentration of the participants in lower tertile reached 51.9 nmol/L, increased 113%; The mean serum 25(OH)D concentration of the participants in upper tertile reached 64.6 nmol/L, increased 9.5% (see Table 6).

66.7% of the participants' baseline serum 25(OH)D concentrations were less than 50.0 nmol/L. After 3 months of supplementation, the proportion of participants with serum 25(OH)D concentration less than 50.0 nmol/L decreased to 35.3%. In particular, for the participants in the lower tertile of baseline vitamin D (all with vitamin D deficiency), after personalized supplementation, their average serum 25(OH)D concentration reached 51.9 nmol/L, the vitamin D deficiency rate decreased 37.5%. From Fig. 6, we can see that, after personalized supplementation, the serum 25(OH)D concentration of all the participants was > 30.0 nmol/L; and after personalized vitamin D supplementation, the variability of serum 25(OH)D concentration among individuals decreased.

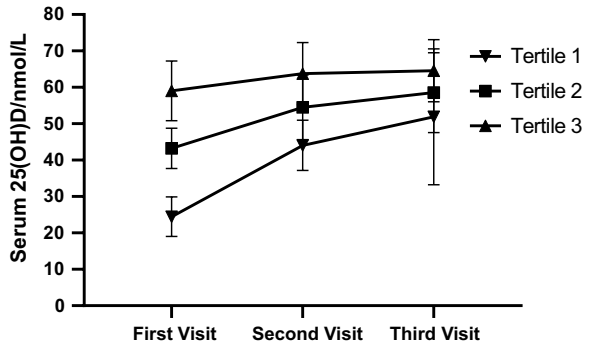

Fig. 6 Baseline serum 25(OH)D status before (first visit) and after (second visit and third visit) personalized nutrition supplementation

Discussion

This study's purpose was to verify the procedure and effects of our personalized nutrition intervention. Our study population came from the southeast coastal cities in China, including three study follow-up visits of 90 participants within 4 months. The small size of samples may lead to the failure to show the association between some SNPs and serum 25(OH)D concentration. Although there are differences between different genotypes and 25(OH)D concentration, they are not significant. In addition, the short follow-up time made it difficult to evaluate the personalized nutrition intervention's long-term effect. There are differences in the personalized supplementation doses of vitamin D, however, the difference is not

Table 6 Association between personalized vitamin D supplementation effects and baseline serum 25(OH)D concentration

Baseline tertile (nmol/L)	Vitamin D supplementation (μg)	Serum 25(OH)D (nmol/L)		Difference after supplementation (95% CI)	P value
		Pre-supplementation	Post-supplementation		
Total	5.96 ± 2.22	42.1 ± 14.9	56.3 ± 13.9	14.2 (8.4,23.5)	< 0.0001
Lower tertile (< 30)	6.92 ± 2.30	24.4 ± 5.4	51.9 ± 18.7	27.4 (12.8,42.2)	0.0013
Middle tertile (30–50)	5.75 ± 1.75	43.2 ± 5.5	58.5 ± 11.0	15.3 (6.0,24.6)	0.0034
Upper tertile (≥ 50)	5.16 ± 2.60	59.0 ± 8.2	64.6 ± 8.5	5.5 (− 3.5,14.5)	0.2086

significant, especially for the participants with the highest GRS score and the lowest serum 25(OH)D concentration, they should consider supplementing higher doses of vitamin D in order to quickly reach an adequate level of serum 25(OH)D concentration. Our next studies should include more samples and longer follow-up time to evaluate: the effects of more genes and GRS on the prediction of serum 25(OH)D concentration, and the effects of personalized vitamin D supplementation.

The inter individual variability of serum 25(OH)D concentration may also be related to factors such as age, sex, BMI, season, skin color, length of time of skin exposure to sunlight, geographic latitude, physical activity, smoking and drinking, but we cannot quantitatively assess their impacts on serum 25(OH)D at this moment, so we have not included these factors in our personalized nutrition model. We will further study these factors later, and gradually incorporated these factors into our model.

Balanced nutrition and sufficient physical exercise are important ways for boosting immunity. Kumar et al. [20] and Iddir et al. [21] explained the importance of vitamins and minerals for strengthening immune system in COVID-19, Galmes et al. [22] reviewed the effects of some micronutrients on immunity based on the nutritional data from 10 European countries (including France, Germany, Spain, Italy, Portugal, Belgium, Denmark, Finland, The Netherlands, and the United Kingdom) and emphasized that genetic factors must be considered for personalized nutrition supplementation, however none of them gave practical personalized nutrition solutions; compared with them, we have taken an important step in the field of personalized nutrition.

Conclusions

Different from the other one-size-fits-all immune boosting strategies, in this paper, we proposed a novel personalized nutrition solution considering the genetic factor, physical examination result, and lifestyle assessment data of different individuals, so that to bolster immunity personally-tailored and effectively.

We validated the effect of our personalized vitamin D supplementation solution based on GRS, physical examination and lifestyles, we found that personalized vitamin D supplementation helped to reduce the risk of vitamin D deficiency, reduce the variability of serum 25(OH)D concentration among individuals, and especially reduce the concentration difference of serum 25(OH)D between different genetic risk groups. The study showed that GRS was helpful to identify individuals with genetic tendency of low serum 25(OH)D concentration, and personalized vitamin D supplementation based on GRS can benefit people at higher risk of vitamin D deficiency a lot.

Concerning future work, through cooperation with hospitals or physical examination centers, we will establish more population cohort studies to further prove the effectiveness of our personalized nutrition model by validating more nutrients such as vitamin C, folic acid and etc. Meanwhile, we will continue to optimize our personalized nutrition solution for boosting immune system by integrating more data to our model. For example, wearable devices such as smart watches and smart bands, are commonly worn for monitoring the physiological indicators including heart rate, sleep, blood oxygen, steps, oxygen uptake, and etc. [23]. Therefore, we will consider to combine the indicators that are validated mature (e.g. heart rate) to our personalized nutrition model [24] in the near future. Pregnant women, lactating women and individuals with severe chronic diseases were excluded in our personalized nutrition model as well as in our validation experiments, we plan to extend our model to provide personalized nutrition service for those special population groups, and we already have solution for pregnant women, but for people with chronic diseases, we need to give different personalized nutrition solutions for different diseases based on clinical diagnosis results and clinicians knowledge [25], which is very challenging.

Additionally, we plan to extend our personalized nutrition solution to other areas, such as considering both the clock genes [26] and a customer's sleep status [27], we can find personalized nutrition solution to improve customer's sleep quality; through evaluating the genetic factors affected diabetic eye disease [28], and detecting the diabetic eye disease in early stage [29–31], we can try to find personalized nutrition solution to reduce the risk of vision impairment; combining genetic [32] and IoT [33] data, we can use personalized nutrition solution to reduce the risk of cardiac arrhythmia; by analyzing the epilepsy genetic[34] testing data and epilepsy detection [35] result data, we can help to support the clinical-decision as well as provide personalized nutrition recommendations.

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Declarations

Conflicts of interest

The author declares no conflict of interest.

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