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Vitamin and Mineral Combined in Diabetes: Modulating HbA1c Across Different Demographics

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Abstract. The increasing incidence of diabetes and the serious complications it causes has become a major global health problem. This issue demonstrates the need for society to develop effective nutrition strategies in the area of public health. The study used data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES) to examine how vitamin and mineral supplements could be combined to help prevent and manage diabetes. By looking at the effects of these supplement combinations on glycosylated hemoglobin (HbA1c) levels, the study found that calcium can enhance the role of vitamin D in lowering glycosylated hemoglobin levels, and in addition, vitamin B12 and vitamin D together have a strong effect in reducing these levels. The study highlights that certain combinations of vitamins and minerals, particularly calcium, caffeine, alcohol, vitamin B12, vitamin C, and vitamin D, are most effective at restoring HBA1c levels to normal.

Keywords: Diabetes, Vitamin, Mineral, Supplementation, HbA1c, Nutritional interventions

1. Introduction

Diabetes is a chronic metabolic disease characterized by elevated blood sugar levels, can lead to serious complications, such as cardiovascular disease, neuropathy, kidney disease and retinopathy [1]. At present, the prevention and management of diabetes has become an important public health priority around the world. According to the World Health Organization (WHO), the number of people with diabetes increased from 108 million in 1980 to 422 million in 2014, with low-income and middle-income countries growing faster than high-income countries [2]. By 2021, the number had surged to an alarming 529 million worldwide. Diabetes, meanwhile, is a leading cause of blindness, kidney failure, heart attack, stroke and lower limb amputation. Diabetes-related deaths increased by 3 percent between 2000 and 2019, with diabetes and related kidney disease causing an estimated 2 million deaths in 2019 [2].

Given the rising prevalence and serious complications of diabetes, nutritional interventions have become a worthy focus of research. Minerals and trace elements, as essential and indispensable trace elements in human activities, maintain the normal operation of the human body [3]. And nutritional interventions, including vitamin and mineral supplementation, have received significant attention due to their potential role in influencing diabetes and its associated underlying psychiatric disorders, helping to regulate glucose homeostasis, and improving diabetes-related outcomes [4].

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Vitamins and minerals can play a crucial role in many physiological processes, including insulin secretion and sensitivity, oxidative stress and inflammation, which are related to the pathophysiology of diabetes [5]. While it has been established that single nutrient deficiencies are associated with adverse metabolic outcomes, emerging evidence suggests that combinations of vitamins and minerals may have synergistic effects and therefore be more beneficial in diabetes management and prevention than single nutrients alone [6].

This study wanted to investigate how various combinations of vitamins and minerals work together to affect the prevention and treatment of diabetes. The data used in the study came from the 2017-2018 NHANES survey. The hope is to be able to determine the most effective combination of vitamins and minerals to treat diabetes by analyzing the combined effects of single nutritional supplements and complex nutritional supplements. The study also explored whether the effectiveness of these combinations varied across age groups, gender and ethnic backgrounds, and what combinations were optimal.

By examining how different combinations of micronutrients affect diabetes-related health indicators, this study can provide valuable insights into personalized nutrition strategies for managing and preventing diabetes. By understanding how these nutrients interact, the findings could help public health agencies develop targeted intervention strategies for different populations. This can meet the specific needs of different populations, and ultimately strengthen the practical role of public health.

2. Material and Methods

2.1. Study Design and Setting

The study was conducted in the United States. As an ecological analysis, different combinations of vitamins and minerals are studied to explore how they affect diabetes-related outcomes. The main purpose of this study was to investigate whether combined vitamin and mineral supplements have a greater impact on diabetes management than individual nutritional deficiencies. To find the best drug delivery plan. In addition, the study sought to determine which combinations would work best for which different demographic groups. These differences include differences in age, gender and race.

2.2. Study Population and Dataset Description

The study used data from the NHANES 2017-2018 dataset. This dataset is a project run by the National Center for Health Statistics (NCHS), part of the CDC. NHANES wants to be able to assess the health and nutrition status of Americans by collecting different data through interviews and physical exams. The dataset is comprehensive and includes a wide variety of demographic, diet, and health information. This diverse information provides a comprehensive basis for analyzing the effects of vitamin and mineral combinations on diabetes outcomes.

In the sampling process of NHANES, a complex multi-stage probabilistic sampling design is implemented. This ensures that the sample is representative of the non-institutionalized U.S. civilian population. They select participants through a combination of stratification, clustering, and oversampling to ensure adequate representation of key subgroups such as specific age groups and ethnic minorities.

2.3. Key Variables Explanation

Predictors: The main predictors are various combinations of vitamin and mineral intake. These include, but are not limited to vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, calcium, magnesium, and zinc. These vitamin and mineral intake levels were collected through 24-hour dietary recall interviews, where participants reported all foods and beverages consumed in the previous 24 hours, so intake levels were measured in milligrams, and we take that as their daily intake of these substances.

Outcome variable: The primary outcome variable was diabetes-related outcomes, particularly the level of glycated hemoglobin A1c (HbA1c). Blood samples from participants were collected during physical exams and analyzed at a CDC laboratory.

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Additional Covariates: Additional variables considered in the analysis included age, gender, ethnicity, body mass index (BMI), physical activity, smoking status, and overall dietary intake. These variables were collected through standardized NHANES interviews and examinations.

2.4. Statistical Analysis

2.4.1. Preliminary Screening Univariate linear regression: Initial univariate linear regression analysis was performed to identify significant associations between individual vitamins and minerals and HbA1c levels. The predictive variables with high correlation coefficients and significant p-values ($p < 0.05$) were selected for further analysis.

2.4.2. Combined Analysis Multiple linear regression:Vitamin D, vitamin B12, and calcium were selected to establish a multiple linear regression model. The quartile method was employed to group each variable (vitamin D, vitamin B12, and calcium) separately, and the relationships between the other variables and HbA1c were examined at different levels of each individual predictor. The models included adjustments for potential confounding factors such as age, gender, ethnicity and BMI.

2.4.3. Comparative Analysis Multiple linear regression: High-impact vitamins and minerals are selected from three to seven in turn as compositions. A multiple linear regression model was then used to assess the effect of each combination on HbA1c levels.

Stepwise regression analysis: Systematically introduced variables sequentially and conducted feature extraction based on their explanatory power. An F-test was performed at each step to assess the effectiveness of different variables and to identify the optimal combination of predictors for analysis. Additionally, subgroup analyses were conducted to determine the most effective variable combinations for specific populations, stratified by age, sex, and ethnicity.

3. Results

3.1. Single and Combined Effects of Vitamins and Minerals

3.1.1. Single Effect Initial linear regression analysis of all unstratified data showed that certain individual vitamins and minerals were significantly associated with HbA1c levels. Notably, vitamin D, vitamin C, niacin, vitamin B12, caffeine, calcium, vitamin B6, Zinc, Phosphorus and vitamin E showed a significant correlation.

Table 1. Linear Regression Results of Various Vitamins and Minerals on Glycated Hemoglobin

Description	Slope (10^{-3})	Correlation Coefficient	95% CI (10^{-3})
Vitamin D	0.150	0.074	[-0.046, 0.346]
Vitamin C	-8.625	-0.068	[-8.821, -8.429]
Niacin	-0.253	-0.060	[-0.449, -0.057]
Vitamin B12	-1.681	-0.056	[-1.877, -1.485]
Caffeine	0.025	0.055	[-0.171, 0.221]
Calcium	-0.006	-0.052	[-0.202, 0.190]
Alcohol	-0.264	-0.052	[-0.460, -0.068]
Vitamin B6	-2.139	-0.051	[-2.335, -1.943]
Zinc	-0.393	-0.039	[-0.589, -0.197]
Phosphorus	-0.004	-0.037	[-0.200, 0.192]
vitamin E	-0.385	-0.036	[-0.581, -0.189]

Note: This table shows the significant results of vitamins and minerals on glycated hemoglobin.

After grouping and stratifying the data, Table 1 shows that different vitamins and minerals had different correlations for different groups. In this study, the relationships between the levels of vitamin

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D, vitamin B12, and calcium with various factors were analyzed. Overall, there was a significant weak positive correlation between vitamin D levels and HbA1c ($r = 0.0995$, $p < 0.0001$). The correlation between vitamin D and HbA1c varied across different groups. There was a stronger positive correlation in males ($p < 0.0001$), Mexican Americans ($p = 0.0003$), non-Hispanic Whites ($p < 0.0001$), non-Hispanic Blacks ($p = 0.0009$), and non-Hispanic Asians ($p < 0.0001$), with the strongest positive correlation observed in non-Hispanic Asians. For different age groups, younger age group ($p < 0.0001$) and older age group ($p = 0.0105$) exhibited varying degrees of negative correlation with vitamin D levels.

Vitamin B12 exhibited a weak negative correlation with HbA1c overall ($p = 0.0015$). In the racial analysis, significant negative correlations between vitamin B12 levels and HbA1c were found in Mexican Americans ($p = 0.0052$), other Hispanics ($p = 0.0327$), and non-Hispanic Asians ($p = 0.0449$).

Calcium levels showed a weak negative correlation with HbA1c overall ($p = 0.0026$). A stronger negative correlation was observed in males ($p< 0.0001$). Racial analysis indicated a significant weak negative correlation between calcium levels and HbA1c in non-Hispanic Whites ($r = -0.0616$, $p = 0.0276$). In other groups, the correlation between calcium levels and HbA1c was weaker, but further analysis revealed interactions between calcium, vitamin D, and vitamin B12.

Table 2. Pearson Correlation Coefficients and p-values for Different Groups

	Vitamin D		Vitamin B12		Calcium	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Total	0.0995	<0.0001	−0.0563	0.0015	−0.0499	0.0026
male	0.1122	<0.0001	−0.0632	0.0136	−0.1033	<0.0001
female	0.0863	0.0001	−0.0362	0.1387	−0.0174	0.4514
Mexican American	0.1502	0.0003	−0.1329	0.0052	−0.0130	0.7666
Other Hispanic	0.0613	0.1775	−0.1298	0.0327	−0.0485	0.3878
Non-Hispanic White	0.1392	<0.0001	0.0439	0.1402	−0.0616	0.0276
Non-Hispanic Black	0.1103	0.0009	−0.0089	0.8036	−0.0450	0.1905
Non-Hispanic Asian	0.2370	<0.0001	−0.1027	0.0449	−0.0216	0.6437
Non-Hispanic Asian	0.0749	0.2592	−0.0113	0.8796	−0.0918	0.1872
BMI (<23.2)	0.0787	0.0130	−0.0281	0.4291	−0.0696	0.0365
BMI (23.2-27.2)	0.0934	0.0038	−0.0476	0.1842	−0.0485	0.1478
BMI (27.3-32.0)	0.1021	0.0014	−0.0570	0.1115	−0.0683	0.0410
BMI (>32.0)	0.1066	0.0009	−0.0878	0.0141	−0.0372	0.2670
Age (<27)	-0.1286	<0.0001	−0.0091	0.7241	−0.0388	0.2344
Age (27-46)	-0.0813	0.0105	−0.0446	0.2183	0.0047	0.8871
Age (47-63)	-0.0406	0.1938	−0.0029	0.9310	−0.0070	0.8289
Age (>63)	-0.0763	0.0189	−0.1387	0.4346	−0.0308	0.3689

Note: A p-value less than 0.01 indicates a significant correlation. When the absolute value of the correlation coefficient is less than 0.1, it is generally considered to reflect a weak correlation; a value greater than 0.1 indicates a strong correlation.

3.1.2. Combined Effects Furthermore, the study focused on vitamin D, vitamin B12, and calcium.This study analyzed the relationships between vitamin D, vitamin B12, and calcium, as well as their synergistic effects on reducing HbA1c.

Table 2 presents the correlations and p-values between vitamin D, vitamin B12, and calcium with HbA1c at different levels of vitamin D, vitamin B12, and calcium.In the medium-high vitamin D group, vitamin B12 showed a significant negative correlation with HbA1c ($r = -0.148$, $p = 0.00$), indicating that vitamin B12 may exert its effects by lowering HbA1c levels. Similarly, in the medium-high calcium

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Table 3. Parameter Estimates (p-values) for the Association of Vitamin D, Vitamin B12, and Calcium with A1c Levels by Quartile Analysis

	Calcium Quartiles			
	First	Second	Third	Fourth
Vitamin D*	-0.08(0.019)	-0.044(0.177)	-0.148(0.00)	-0.019(0.613)
Vitamin B12*	-0.038(0.731)	-0.167(0.111)	0.042(0.635)	-0.113(0.117)

	Vitamin D Quartiles			
	First	Second	Third	Fourth
Calcium*	-0.027(0.271)	0.004(0.868)	-0.043(0.124)	-0.034(0.192)
Vitamin B12*	-0.012(0.895)	-0.186(0.036)	-0.067(0.473)	-0.129(0.176)

	Vitamin B12 Quartiles			
	First	Second	Third	Fourth
Calcium*	-0.023(0.482)	-0.001(0.981)	-0.002(0.928)	-0.024(0.232)
Vitamin D*	-0.076(0.038)	-0.068(0.075)	-0.047(0.738)	-0.104(0.004)

*Model: HbA1c = β_1Calcium + β_2Vitamin D + β_3Vitamin B12 + β_4Age + β_5Ethnicity + β_6BMI + β_7Gender and in calcium model calcium variable is excluded, in Vitamin D model Vitamin D variable is excluded, in Vitamin B12 model Vitamin B12 variable is excluded.

group, vitamin D demonstrated a significant negative correlation with HbA1c (r = -0.186, p = 0.036), further supporting the role of calcium in enhancing the regulatory effect of vitamin D on HbA1c. Additionally, in the high vitamin B12 group, vitamin D showed a significant negative correlation with HbA1c (r = -0.104, p = 0.004), suggesting a potential synergistic effect between vitamin B12 and vitamin D in reducing HbA1c levels.

3.1.3. Impact of Multiple Vitamins and Minerals on HbA1c Levels Table 3 looking at the effects of multivitamin and mineral combinations on glycosylated hemoglobin (HbA1c) levels have used multiple linear regression analysis, which is very comprehensive. The study initially focused on three groups and was later expanded to include seven groups of vitamins and minerals.

The analysis identified the most useful results. The results included seven key substances: calcium, caffeine, alcohol, vitamin B12, vitamin C, and vitamin d. In the results, it was clear that this combination had the most significant effect on HbA1c levels. Not only that, this combination not only shows superior performance compared to other combinations, but also consistently performs as the most efficient combination in various analyses. This suggests that these nutrients play an irreplaceable role in controlling HbA1c levels.

The study further found that an approach combining multiple vitamins and minerals worked better than a single nutritional supplement. The synergistic effect of using multiple vitamins and minerals at the same time resulted in a significant improvement in HbA1c levels. Essentially, the more nutrients used in the synergy, the greater the positive effect on HbA1c. This suggests that a holistic approach that combines multivitamins and minerals may be more effective in optimizing diabetes management.

3.2. Effectiveness for Specific Populations

3.2.1. Age Groups The effects of the nutritional combinations significantly differ across various age groups. Figure 1 shows the results of these four groups.

Young Adults (age $<$ 26): In this demographic, significant determinants of glycated hemoglobin include Vitamin D2 and different forms of Vitamin D3. Specifically, Vitamin D2 (p = 0.0043) exhibits a significant positive impact on glycated hemoglobin, indicating that increased levels of Vitamin D2 correlate with higher glycated hemoglobin levels. Conversely, one form of Vitamin D3 (p = 0.0056) has a significant negative impact, suggesting that its increased levels lead to a decrease in glycated hemoglobin, while another form of Vitamin D3 (p = 0.0065) shows a significant positive impact. Additionally, although the impact of Vitamin C (p = 0.0915) on glycated hemoglobin is not significant, it trends negatively.

Prime in life (27 $<$ age$<$ 46): In this age group, the significant factors affecting glycated hemoglobin are Vitamin B6, niacin, Vitamin C, and Vitamin D3. Vitamin B6 (p = 0.023) shows a significant positive influence, meaning that higher levels of Vitamin B6 lead to an increase in glycated hemoglobin. Niacin (p = 0.0073), on the other hand, has a significant negative impact, indicating that increased niacin levels result in lower glycated hemoglobin. Although Vitamin C (p = 0.106) does not significantly influence glycated hemoglobin, it shows a negative trend. Vitamin D3 (p = 0.0012) significantly decreases glycated hemoglobin levels.

Middle-Aged Adults (47 $<$ age $<$ 63): For middle-aged adults, significant factors include Vitamin C and Vitamin D3. Specifically, Vitamin C (p = 0.0078) has a significant negative effect on glycated hemoglobin, implying that higher Vitamin C levels lead to lower glycated hemoglobin. Similarly, Vitamin D3 (p = 0.0093) also shows a significant negative impact.

Elderly (age $>$ 63): In the elderly population, key factors influencing glycated hemoglobin (HbA1c) levels include caffeine, alcohol, Vitamin C, and Vitamin D3. Each of these substances showed significant negative effects on HbA1c, with p-values of 0.0305 for caffeine, 0.0085 for alcohol, 0.0083 for Vitamin C, and 0.0093 for Vitamin D3. This suggests that higher intake of these nutrients is associated with lower HbA1c levels in older adults.

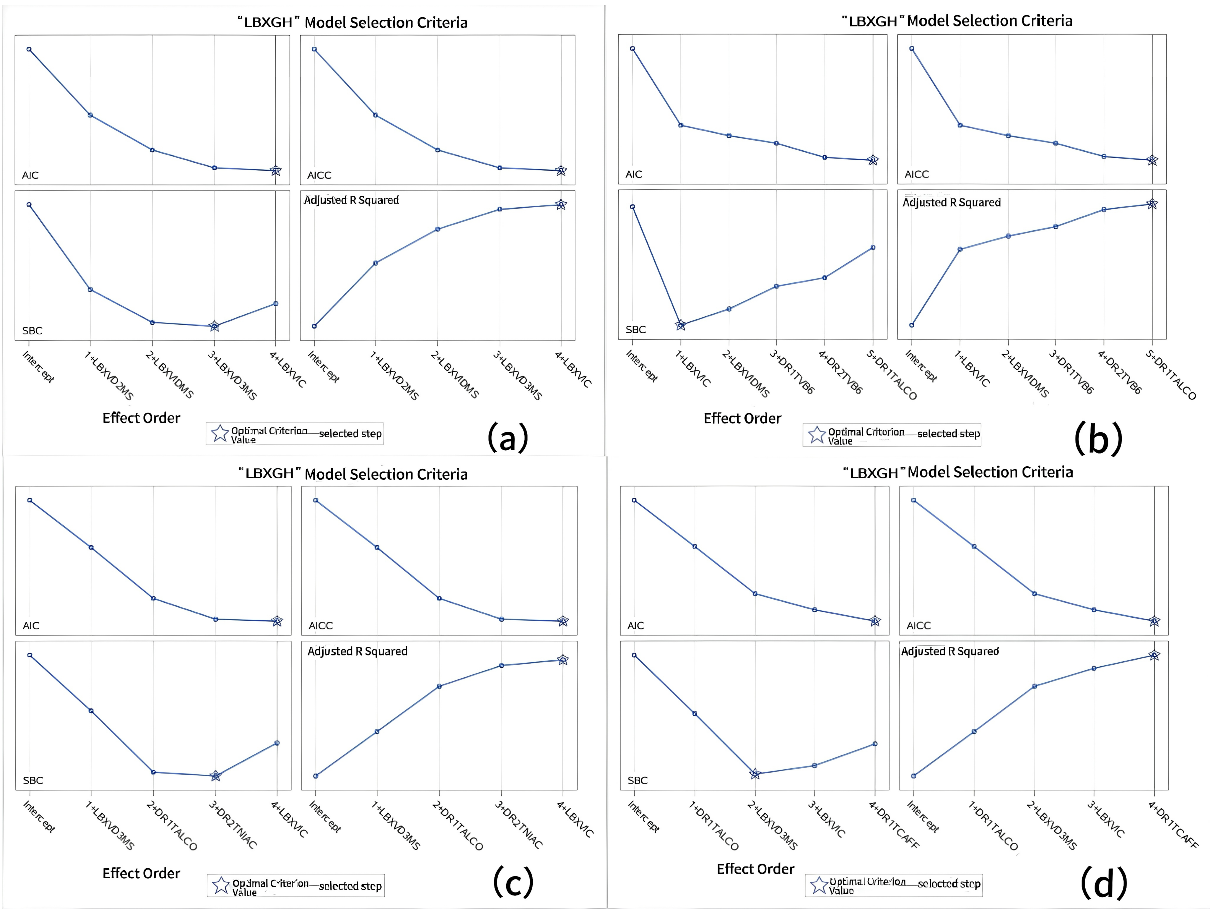
3.2.2. Gender Male Population: In males, key factors influencing glycated hemoglobin (HbA1c) levels include calcium, caffeine, alcohol, niacin, Vitamin B6, Vitamin C, and Vitamin D. Calcium (p = 0.0009) and niacin (p = 0.0003) both significantly lower HbA1c levels, while Vitamin C (p = 0.0436) also shows a significant negative effect. Conversely, caffeine (p = 0.0474) and Vitamin B6 (p = 0.0167) have significant positive impacts, and alcohol (p = 0.0015) has a significant negative effect. Vitamin D3 (p = 0.0234) also significantly affects HbA1c levels positively.

Female Population: For females, significant determinants of HbA1c include calcium, alcohol, Vitamin B12, Vitamin C, and Vitamin D. Alcohol (p ¡ 0.0001) has a notably strong negative effect on HbA1c, suggesting that higher alcohol intake is associated with lower HbA1c levels. Vitamin B12 (p = 0.0377) also shows a significant negative effect, as does calcium (p = 0.0028). Vitamin C (p $<$ 0.0001) has a significant negative impact on glycated hemoglobin. In contrast, both Vitamin D2 (p $<$ 0.0001) and Vitamin D3 (p = 0.0139) demonstrate significant positive effects.

These results indicate that the significant determinants of glycated hemoglobin differ between males and females. However, Vitamin C and Vitamin D are important factors in both groups. Additionally, the negative impacts of calcium and alcohol on glycated hemoglobin are significant in both males and females.

3.2.3. Ethnicity The analysis of significant factors affecting glycated hemoglobin (HbA1c) across different racial groups reveals varied roles of vitamins and minerals. However, certain key nutrients like caffeine, Vitamin C, and Vitamin D demonstrate importance across multiple racial groups.

Non-Hispanic White Population: Significant factors affecting HbA1c include caffeine, alcohol, niacin, Vitamin C, and Vitamin D2. Specifically, caffeine (p = 0.0216) shows a significant positive



Note: In Figures A to D, four groups are Young adults, Prime in life, Middle-aged adults and Elderly. Represents the performance comparison using the AIC and SBC metrics. The horizontal axis indicates the model type, while the vertical axis represents the effectiveness metrics.

Figure 1. A fitting map of the optimal combination of vitamins and minerals at four ages

impact on HbA1c, indicating that increased caffeine levels correlate with higher HbA1c. Alcohol (p = 0.0361) and niacin (p = 0.0015) both have significant negative impacts. Vitamin C (p = 0.0400) also exhibits a significant negative effect, while Vitamin D2 (p = 0.0002) shows a significant positive impact.

Non-Hispanic Black Population: For this group, significant factors include calcium and caffeine. Calcium (p = 0.0426) has a significant negative impact on HbA1c, indicating that increased calcium levels result in lower HbA1c. Although caffeine (p = 0.0731) does not significantly affect HbA1c, it shows a positive trend.

Mexican American Population: Significant determinants include calcium, caffeine, alcohol, Vitamin C, and Vitamin D2. Calcium (p = 0.0136) shows a significant negative impact on HbA1c. Caffeine (p = 0.0814), although not significant, trends positively. Alcohol (p = 0.0083) has a significant negative impact, while Vitamin C (p = 0.0245) also shows a significant negative effect. Both Vitamin D2 (p = 0.0053) and Vitamin E (p = 0.0157) exhibit significant positive impacts.

Other Hispanic Population: Vitamin B6, caffeine, alcohol, Vitamin B12, Vitamin C, and Vitamin D. Vitamin B6 (p = 0.0015) has a significant positive impact. Caffeine (p = 0.0615), while not significant, trends positively. Alcohol (p = 0.0094) shows a significant negative impact, and Vitamin B12 (p = 0.0732) trends negatively, though not significantly. Vitamin C (p ¡ 0.0001) has a significant negative effect, whereas Vitamin D3 (p = 0.0004) shows a significant positive impact.

Other Race/Multi-Racial Population: Significant determinants include caffeine, Vitamin B6, Vitamin C, and Vitamin D3. Caffeine ($p = 0.0417$) shows a significant positive impact. Vitamin B6 ($p = 0.0015$) exhibits a significant negative effect. Vitamin C ($p = 0.0955$), while not significant, trends negatively, and Vitamin D3 ($p = 0.0003$) has a significant positive impact.

Non-Hispanic Other, Including Multi-Racial Population: The only significant factor for this group is alcohol, which, although not significant ($p = 0.1161$), trends negatively in its impact on HbA1c.

These findings underscore the differing significant determinants of glycated hemoglobin among various racial groups. However, the importance of Vitamin C and Vitamin D is evident across multiple groups. Additionally, the negative impacts of calcium and alcohol on HbA1c are significant in several racial demographics.

4. Discussion

Our research confirms that vitamins and minerals indeed have an impact on glycated hemoglobin (HbA1c) levels, consistent with the findings of [7]. In this study, we first observed the effects of individual vitamins and minerals. We found that the positive correlation between vitamin D and HbA1c was significant across multiple groups, particularly among males, females, Mexican Americans, non-Hispanic Whites, non-Hispanic Blacks, and non-Hispanic Asians. Biologically, this positive correlation may seem paradoxical, as vitamin D deficiency is generally associated with increased insulin resistance and diabetes risk [8]. This positive correlation can be explained by several possible mechanisms and factors. First, vitamin D levels may reflect certain health behaviors or lifestyles that are also associated with higher HbA1c levels. For example, some individuals may take vitamin D supplements to improve their health because of existing diabetes or high risk, leading to increased vitamin D levels that reflect already high HbA1c levels rather than vitamin D directly causing diabetes [9].Regarding vitamin B12, its weak negative correlation with HbA1c was significant among Mexican Americans, other Hispanics, and non-Hispanic Asians. This may be related to the crucial role of vitamin B12 in carbon metabolism and DNA synthesis. Vitamin B12 deficiency can lead to elevated homocysteine levels, thereby increasing oxidative stress and insulin resistance risk [10]. Differences in vitamin B12 intake and metabolism among different racial groups may explain the significance of these correlations. Mexican Americans and other Hispanic groups may be more prone to vitamin B12 deficiency due to dietary habits or socioeconomic factors, affecting their HbA1c levels [11, 12]. The overall weak negative correlation between calcium levels and HbA1c, and the significant negative correlation in males, suggest the importance of calcium in glucose metabolism. Calcium plays a key role in signaling within pancreatic cells, directly influencing insulin secretion through changes in calcium ion concentration [13]. Low calcium intake may lead to insufficient insulin secretion and insulin resistance, thus affecting blood glucose control. The significant negative correlation observed in males may reflect gender differences in calcium and glucose metabolism.

Furthermore, our comparative study found that the combination of vitamins and minerals had a more pronounced effect on HbA1c levels than individual nutrients. This aligns with findings in other disease fields, suggesting that micronutrients can have synergistic effects, thereby enhancing their collective efficacy in controlling diabetes [14–17]. Previous studies have mentioned that lifestyle changes, including diet and exercise, and comprehensive nutritional approaches, such as time-restricted feeding and personalized interventions incorporating genetics, epigenetics, and metagenomics, can better address the complex metabolic disturbances in diabetes [18–20]. This is consistent with our findings on the benefits of multiple vitamins and minerals. However, previous studies have only suggested that the application of combined vitamins and minerals might be more effective than individual use without fully testing which combinations are optimal [21]. Our research further explores this by identifying that the combination of calcium, caffeine, alcohol, vitamin B12, vitamin C, vitamin D, and 25-hydroxyvitamin D3 is most effective in reducing HbA1c levels. The consistent presence of these nutrients in the optimal combinations highlights their key roles in diabetes management, likely due to their involvement in various physiological processes related to glucose metabolism, insulin sensitivity, and oxidative stress

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reduction. [22] suggested that combinations of these micronutrients can enhance each other's effects, providing stronger improvements in blood glucose control than individual intake, which aligns with our results. Therefore, we believe that synergistic management and supplementation of vitamins and minerals to standard levels is highly necessary and influential.

This study also explored the combined effects of vitamin D, vitamin B12, and calcium levels on HbA1c levels, finding significant differences in the correlation of these nutrients at different levels. Medium to high levels of calcium enhance the effects of vitamin B12 and vitamin D, medium to high levels of vitamin D enhance the effects of vitamin B12, and high levels of vitamin B12 enhance the effects of vitamin D. While the role of vitamin D and calcium in regulating calcium homeostasis and bone health has been studied, their synergistic effect in glucose metabolism has received less attention. Vitamin D, through its active form 1,25-dihydroxyvitamin D3, binds to the vitamin D receptor (VDR) and regulates gene expression related to calcium absorption, bone metabolism, and insulin secretion [23, 24]. Vitamin D promotes intestinal absorption of calcium, maintaining serum calcium levels, and thus indirectly influencing insulin secretion [25]. Calcium is a critical secondary messenger in insulin secretion, with its concentration changes directly affecting pancreatic beta-cell depolarization and insulin release [26]. At high calcium levels, vitamin D, through VDR, enhances calcium signaling and promotes insulin secretion efficiency [27]. Specific mechanisms include vitamin D regulating genes such as calbindin through VDR to increase calcium absorption in the intestine [28] and calcium acting as a signaling molecule in pancreatic beta cells to participate in insulin secretion [29]. Vitamin B12, as a coenzyme in methylation reactions, is involved in homocysteine (Hcy) metabolism. High Hcy levels are associated with insulin resistance and type 2 diabetes [30]. Vitamin B12 can lower Hcy levels, reducing insulin resistance. Vitamin D, through its anti-inflammatory effects and regulation of insulin signaling pathways, improves insulin sensitivity [31]. At high vitamin D levels, the Hcy-lowering effect of vitamin B12 is amplified, possibly due to the anti-inflammatory action of vitamin D reducing the interference of inflammatory mediators on insulin signaling pathways [32]. Specific mechanisms include vitamin D downregulating the nuclear factor kappa B (NF-κB) pathway to reduce the release of inflammatory factors [33] and vitamin D promoting insulin receptor gene expression through VDR, improving insulin sensitivity [34]. The role of calcium in insulin secretion is well established, and vitamin B12 regulates calcium homeostasis through methylation actions. Vitamin B12 deficiency may lead to osteoporosis, indirectly affecting calcium metabolism [35]. At high calcium levels, vitamin B12 reduces Hcy levels, decreasing damage to insulin signaling pathways and enhancing insulin efficacy [36]. Specific mechanisms include vitamin B12 promoting bone cell health, indirectly affecting calcium absorption and metabolism [37] and calcium and vitamin B12 jointly improving the integrity and function of insulin signaling pathways [38].

Compared to previous studies focusing on specific populations [39] or the general human population, our results emphasize the significant differences in the effectiveness of these nutrient combinations across different age groups, genders, and ethnicities. This highlights the necessity of personalized nutritional interventions in diabetes management. We introduced multiple stratifications to categorize the data, allowing for the exploration of the specificity of each combination. By dividing the age groups into young, adult, middle-aged, and elderly, we found that prime in life (26 to 43 years old) benefit most from vitamin B6 and niacin, while the elderly (63 years and older) show significant effects from vitamin C and vitamin D3. These age-specific differences may reflect the different metabolic needs and nutritional deficiencies commonly present at different life stages. Thus, we recommend that different age groups pay attention to the vitamins that most influence their own health. Similarly, gender-specific analysis showed that although both males and females benefit from common nutrients such as vitamin C and vitamin D, the extent of these benefits varies. For example, vitamin D shows a negative correlation with HbA1c levels in both sexes but is more pronounced in males. These differences highlight the importance of considering gender in dietary recommendations and the necessity for further research to understand the underlying mechanisms. Ethnicity-specific analysis also revealed different patterns, suggesting that genetic and cultural factors may influence the efficacy of certain nutrient combinations. For example,

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vitamin D shows a negative correlation with HbA1c levels in Mexican Americans, while niacin and calcium are beneficial for most ethnic groups. This supports the concept that tailored nutritional strategies considering ethnic-specific dietary habits and genetic predispositions can optimize diabetes management.

Our research confirms that vitamins and minerals indeed have an impact on glycated hemoglobin (HbA1c) levels, consistent with the findings of previous studies. However, while this study provides valuable insights, several limitations must be acknowledged. The ecological analysis nature of this study means that causality cannot be firmly established; associations observed between vitamin and mineral intake and HbA1c levels do not confirm direct causal relationships. The reliance on self-reported dietary intake data from NHANES may be subject to recall bias and inaccuracies, affecting the reliability of the data on vitamin and mineral intake. Additionally, the cross-sectional nature of the NHANES dataset limits the ability to observe changes over time and determine long-term effects of vitamin and mineral supplementation on HbA1c levels. Although the study adjusted for several potential confounders, there may be other unmeasured confounders that could influence the results. The findings may not be generalizable to populations outside the United States or to individuals not represented in the NHANES sample, as variations in diet, lifestyle, and genetic factors across different populations may affect the applicability of the results. Furthermore, while the study examines combinations of vitamins and minerals, it does not account for all possible interactions between different nutrients, and some combinations may have synergistic or antagonistic effects that were not fully explored. Laboratory measurements of HbA1c levels and nutrient biomarkers, though standardized, may still be subject to measurement errors. The effectiveness analysis across different age, gender, and ethnic subgroups may also suffer from reduced statistical power due to smaller sample sizes in these stratified groups, limiting the robustness of subgroup-specific conclusions. These limitations highlight the need for further research using longitudinal and interventional study designs to better understand the causal relationships and long-term effects of vitamin and mineral combinations on diabetes management across diverse populations. Understanding these limitations is crucial for contextualizing the findings and guiding future research directions.

5. Conclusion

The aim of this study was to investigate the effects of combined vitamin and mineral supplementation on HbA1c levels and to provide strategies for diabetes management in different populations. The results showed that specific nutrient combinations, particularly calcium, caffeine, alcohol, vitamin B12, vitamin C, and vitamin D, were associated with significant improvements in HbA1c levels. However, these effects varied by age group, gender, and ethnicity, suggesting that the benefits of supplements were not consistent across all populations. For example, younger people benefit more from vitamin D3, while middle-aged and older people respond positively to vitamin C and vitamin D3. Similarly, sex-specific and race-specific patterns highlighted unique responses to these nutrient combinations, with calcium and niacin being particularly effective for men, and vitamins B12 and C having a greater impact on women.

These findings highlight the importance of personalized nutrition interventions in diabetes management, providing a basis for tailored dietary recommendations that take into account population differences. This approach could improve the effectiveness of public health strategies aimed at controlling diabetes and its complications in diverse populations.

However, the study still has some limitations. The cross-sectional nature of the NHANES dataset limits the ability to establish causality, and reliance on self-reported dietary intake may introduce recall bias. In addition, the sample was limited to the U.S. population, which may affect the generality of the findings. Future research should focus on longitudinal and interventional studies to validate these results and explore other potential nutritional interactions in diabetes management.

All in all, this study contributes to our understanding of how combined micronutrient supplementation contributes to blood sugar control and highlights the potential for population-specific dietary strategies in diabetes prevention and management.

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