

Review

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Review

Dietary Vitamin K Intake and Insulin Resistance: Implications for Early Diabetes Risk in U.S. Adults (NHANES 2001-2018)

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Abstract

Background: Vitamin K (VK) has emerging roles beyond coagulation, including potential involvement in glucose metabolism. While large cohorts report inverse associations between VK status and incident type 2 diabetes, less is known about its relationship with insulin resistance in general populations. **Methods:** We conducted a cross-sectional analysis of 23,247 adults from the National Health and Nutrition Examination Survey (NHANES) 2001-2018. Dietary VK intake was assessed using a 24-h recall and modeled as energy-adjusted nutrient density ($\mu\text{g}/1000 \text{ kcal}$). Fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), fasting glucose, and HbA1c were analyzed using survey-weighted linear regression; models were adjusted for demographic, socioeconomic, lifestyle, and adiposity-related factors. Effect modification by baseline metabolic status was evaluated, and sensitivity analyses assessed robustness. **Results:** Higher energy-adjusted VK intake was independently associated with lower fasting insulin and HOMA-IR, but not with fasting glucose or HbA1c. Each SD increase in VK intake was associated with 1.4% lower fasting insulin (95% CI -2.4% to -0.4%) and 1.3% lower HOMA-IR (95% CI -2.3% to -0.3%) in fully adjusted models. Associations were attenuated but remained significant after adjustment for adiposity. Effect modification by baseline metabolic status was observed, with stronger associations among normoglycemic individuals. Findings were robust across sensitivity analyses. **Conclusions:** In this nationally representative sample of U.S. adults, higher VK intake was modestly associated with lower insulin resistance markers. Dietary VK intake may contribute to maintenance of insulin sensitivity, particularly in metabolically intact states. Prospective studies incorporating comprehensive VK biomarkers and dynamic measures of insulin sensitivity are warranted.

Keywords: vitamin K; insulin resistance; HOMA-IR; fasting insulin; glucose metabolism; NHANES; type 2 diabetes

1. Introduction

Vitamin K (VK), traditionally recognized for its role in coagulation, is increasingly implicated in extrahepatic processes, including metabolic regulation [1–3]. These extrahepatic roles require higher VK status than needed to maintain normal hemostasis, and a substantial proportion of the population is thought to have subclinical VK deficiency – a state in which coagulation is preserved but VK availability may be insufficient to support its broader physiological roles [4–8]. Observational evidence links lower VK status to adverse metabolic outcomes, including insulin resistance and type 2 diabetes (T2D) [9–11], greater adiposity [12–17], elevated inflammatory markers [6,10,18–23], and less favorable lipid profiles [6,10,24,25].

Insulin resistance is a key pathophysiological process in the development of T2D and often precedes overt hyperglycemia by many years [26,27]. Identifying modifiable dietary factors associated with insulin sensitivity in the general population may therefore provide insight into early strategies for diabetes prevention. Mechanistic studies support a role for VK in glucose metabolism; in pancreatic β -cells, VK contributes to preservation of cellular integrity through regulation of endoplasmic reticulum calcium handling and cAMP-dependent signaling [28,29]. In peripheral tissues, VK enhances insulin sensitivity via SIRT1/AMPK activation and anti-inflammatory pathways [30–36]. Consistent with these mechanisms, observational studies report inverse associations between VK status and risk of T2D [9–11]. Supplementation trials, however, remain heterogeneous: effects on fasting glucose are limited [6,37–40], whereas improvements in insulin sensitivity indices are more consistently observed, particularly among individuals with prediabetes or diabetes [41–43]. These findings suggest that VK exerts context-dependent effects on glucose metabolism. Whether these associations primarily reflect direct modulation of insulin signaling, mediation through adiposity or inflammation, or other mechanisms is unclear; it is also uncertain whether VK plays a predominantly preventive role – supporting maintenance of metabolic homeostasis – or whether its effects are more pronounced in metabolically impaired states. Although recent NHANES analyses have linked VK intake to dyslipidemia, with insulin resistance proposed as a mediator [24], a comprehensive evaluation of dietary VK in relation to glycemic markers in this large population-based sample is lacking.

Here, we examined the association between dietary VK intake and glycemic markers among adults using data from NHANES 2001–2018. The use of a large, nationally representative sample with standardized laboratory measurements allowed evaluation of these associations at the population level. Additionally, we assessed effect modification by baseline metabolic status and quantified attenuation by adiposity, providing insight into the metabolic contexts in which VK may influence insulin resistance.

2. Materials and Methods

Study Population

We analyzed data from the National Health and Nutrition Examination Survey (NHANES). NHANES is a program of cross-sectional studies conducted by the National Center for Health Statistics (NCHS), which assesses the health and nutritional status of a nationally representative sample of U.S. population. We pooled nine consecutive NHANES cycles (2001–2018) because they included concurrent measurements of dietary VK intake and fasting glycemic markers. Among adults aged ≥ 18 years, we excluded participants with missing dietary VK data, fasting laboratory measurements, or survey design variables. The final analytic sample included 23,247 adults; sample sizes varied slightly by outcome due to missing laboratory data (HbA1c: $N = 22,321$; fasting glucose: $N = 22,249$; fasting insulin: $N = 21,820$; HOMA-IR: $N = 21,795$). NHANES protocols were approved by the NCHS Ethics Review Board, and all participants provided written informed consent [44].

Assessment of Dietary VK intake

VK intake ($\mu\text{g}/\text{day}$) was assessed using the Day 1 24-h dietary recall collected via the USDA Automated Multiple-Pass Method. VK intake was energy-adjusted using the nutrient density method (μg per 1000 kcal). For primary analyses, it was categorized into survey-weighted quartiles (Q1–Q4), with Q1 representing the lowest intake. For continuous analyses, VK density was modeled per SD increase (1 SD = 102.5 $\mu\text{g}/1000$ kcal).

Assessment of Glycemic Markers

Blood samples were collected as part of the NHANES examination protocol during the participant's examination visit after an overnight fast and processed according to standardized NHANES laboratory protocols.

Primary outcomes were fasting insulin and insulin resistance estimated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), calculated as:

$$\text{HOMA-IR} = (\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mg/dL)}) / 405.$$

Fasting insulin and HOMA-IR were natural log-transformed in all analyses due to right-skewed distributions. Secondary outcomes included fasting glucose and glycated hemoglobin (HbA1c); they were analyzed on their original scale.

Covariates

We selected covariates based on biological plausibility and prior evidence. These included: age (years, continuous); sex (male/female); race/ethnicity; poverty-income ratio (continuous); smoking status (current/non-current smoker); alcohol use (ever/never drinker); total energy intake (kcal/day); body mass index (BMI, kg/m²); and waist circumference (cm).

Statistical Analysis

All analyses followed NHANES Analytic and Reporting Guidelines and used sampling weights to account for oversampling and the complex hierarchical, multistage, clustered sampling design. The weighted sample is representative of the U.S. adult population [45]. The full prespecified analysis plan is shown in Supplementary Figure S2.

We summarized descriptive statistics across quartiles of energy-adjusted VK intake using weighted percentages for categorical variables and survey-weighted means $\pm$ standard deviations (SD) for continuous variables, except for energy-adjusted VK intake, insulin, and HOMA-IR, which were presented as median (interquartile range) due to right-skewed distributions.

We used survey-weighted linear regression models to examine associations between energy-adjusted VK intake and glycemic markers. VK intake was analyzed in quartiles, with the lowest quartile (Q1) serving as reference; linear trends were assessed by modeling median intake within each quartile as a continuous variable. VK intake was also modeled continuously per SD increase in VK density (1 SD = 102.5 $\mu\text{g}/1000$ kcal). All glycemic markers were modeled as continuous outcomes. For each outcome, analyses were restricted to participants with non-missing values for that specific marker, and all covariates included in the corresponding model (complete-case analysis). Insulin and HOMA-IR were natural log-transformed, and results are presented as percent differences.

Three models were specified: Model 1 (unadjusted); Model 2, adjusted for age, sex, race/ethnicity, poverty-income ratio, smoking status, alcohol use, and total energy intake; and Model 3, additionally adjusted for BMI and waist circumference. To quantify the contribution of adjustment for adiposity to observed associations, percent attenuation was calculated as the proportional change in β coefficients between sequential models.

We evaluated potential nonlinearity using survey-weighted restricted cubic spline models (3 degrees of freedom), with Wald tests used to assess overall association and nonlinearity.

Sensitivity analyses included additional adjustment for overall diet quality (HEI-2020) and vigorous physical activity; exclusions of implausible energy intake, extreme VK intake (1st-99th percentiles), or diabetes; alternative specifications of adiposity (BMI or waist circumference modeled separately); and modeling VK intake as a continuous exposure on the natural logarithmic scale.

We assessed effect modification by testing interaction terms between continuous energy-adjusted VK intake (per SD) and baseline metabolic status (normal vs impaired glucose metabolism, defined as fasting glucose 100-125 mg/dL or HbA1c 5.7-6.4%), obesity status (BMI <30 kg/m² vs. $\geq$ 30 kg/m²) and sex; interaction significance was assessed using Wald tests.

All analyses were performed using R (version 4.5.2) with the survey package. Two-sided p-values <0.05 were considered statistically significant.

3. Results

Study Population Characteristics

The analytic sample included 23,247 adults from NHANES 2001-2018. Survey-weighted characteristics by quartiles of energy-adjusted VK intake are shown in Table 1. Participants in higher VK quartiles were older, more often female, had higher poverty-income ratios, and were less likely to be current smokers. Total energy intake was lower in the highest quartile, whereas BMI and waist circumference were similar across quartiles. The prevalence of diabetes increased slightly across quartiles. Unadjusted fasting insulin and HOMA-IR were lower across increasing VK quartiles, whereas fasting glucose and HbA1c differed modestly.

Table 1. Survey-weighted characteristics of study population according to quartiles of energy-adjusted vitamin K intake (NHANES 2001-2018).

Variable	Total (N = 23,247)	Q1 (N = 6,055)	Q2 (N = 5,905)	Q3 (N = 5,755)	Q4 (N = 5,531)
Vitamin K intake, µg/1000 kcal	29.4 (18.0, 53.9)	13.0 (9.8, 15.6)	23.2 (20.5, 26.1)	38.7 (33.7, 45.1)	89.5 (67.1, 143.4)
Age, years	46.0 (17.4)	42.1 (16.8)	44.6 (17.1)	47.6 (17.5)	49.5 (17.2)
Sex					
Male	48%	55%	53%	48%	38%
Female	52%	45%	47%	52%	62%
Race/ethnicity					
Mexican American	8.4%	9.1%	11%	8.1%	5.8%
Other Hispanic	5.3%	5.3%	5.5%	5.6%	4.6%
Non-Hispanic White	68%	67%	67%	69%	70%
Non-Hispanic Black	11%	13%	11%	10%	9.9%
Other race	6.9%	5.1%	5.4%	6.9%	10%
Poverty-income ratio	3.0 (1.6)	2.7 (1.6)	2.9 (1.6)	3.0 (1.6)	3.3 (1.6)
Energy intake, kcal/day	2,190.3 (992.9)	2,249.6 (1,102.6)	2,325.7 (1,027.9)	2,214.5 (942.9)	1,971.4 (844.0)
BMI, kg/m²	28.8 (6.9)	28.6 (6.8)	29.1 (7.0)	28.9 (6.7)	28.6 (7.0)
Waist circumference, cm	98.3 (16.5)	97.8 (16.5)	99.3 (16.9)	98.8 (16.3)	97.4 (16.3)
Fasting insulin	9.1 (5.9, 14.8)	9.4 (5.9, 15.3)	9.5 (6.2, 15.7)	9.2 (6.0, 15.0)	8.3 (5.4, 13.3)
HOMA-IR	2.3 (1.4, 3.9)	2.3 (1.4, 4.0)	2.4 (1.5, 4.1)	2.3 (1.4, 4.0)	2.0 (1.3, 3.5)
Fasting glucose, mg/dL	104.7 (29.4)	103.1 (29.3)	105.0 (28.9)	105.9 (30.5)	104.9 (28.9)
HbA1c, %	5.6 (0.9)	5.5 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)
Smoking status					
Current smoker	21%	30%	21%	18%	14%
Non-smoker	79%	70%	79%	82%	86%
Alcohol use					
Drinker	78%	78%	77%	78%	77%
Non-drinker	22%	22%	23%	22%	23%
Diabetes	12%	11%	12%	13%	14%

Notes: Values are survey-weighted means ± standard deviations (SD) for continuous variables and weighted percentages for categorical variables, except for energy-adjusted vitamin K intake, insulin, and HOMA-IR, which are presented as median (interquartile range). Sample sizes (N) are unweighted. Quartiles were defined using survey-weighted cutpoints of energy-adjusted vitamin K intake (µg/1000 kcal). Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin.

Association Between Dietary Vitamin K Intake and Glycemic Markers

Associations between energy-adjusted VK intake and glycemic markers are presented in Tables 2 and 3. In crude models (Model 1), higher VK intake was negatively associated with fasting insulin and HOMA-IR, and it was positively associated with fasting glucose and HbA1c.

After multivariable adjustment, associations with fasting glucose and HbA1c were no longer significant. In contrast, higher VK intake remained inversely associated with insulin resistance markers. In fully adjusted models (Model 3), participants in the highest quartile of VK intake had 6.6% lower fasting insulin and 6.2% lower HOMA-IR compared with the lowest quartile (both P for trend <0.001).

When modeled continuously (per 1 SD increase in energy-adjusted VK intake), no associations were observed for fasting glucose or HbA1c. However, each SD increase in VK intake was associated with a 1.4% lower fasting insulin (95% CI -2.4% to -0.4%; P = 0.0067) and a 1.3% lower HOMA-IR (95% CI -2.3% to -0.3%; P = 0.014). Adjustment for demographic and lifestyle factors modestly attenuated associations (13-19%), while additional adjustment for adiposity explained 44-49% of the remaining association (Supplementary Table S4).

Table 2. Associations between quartiles of energy-adjusted vitamin K intake and glycemic markers.

Model/Quartile	Insulin (% difference)	HOMA-IR (% difference)	Glucose (mg/dL)	HbA1c (%)
Model 1: unadjusted				
Q2 vs Q1	3.8% (-0.6, 8.3)	5.8% (0.9, 10.8)*	1.85 (0.56, 3.14)*	0.07 (0.03, 0.10)*
Q3 vs Q1	0.3% (-3.2, 3.9)	2.9% (-1.1, 6.9)	2.74 (1.39, 4.09)*	0.10 (0.06, 0.14)*
Q4 vs Q1	-8.7% (-12.1, -5.2)*	-7.0% (-10.9, -3.0)*	1.81 (0.44, 3.19)*	0.09 (0.05, 0.13)*
Model 2: lifestyle-adjusted				
Q2 vs Q1	1.3% (-3.2, 6.1)	2.1% (-2.9, 7.4)	0.64 (-0.79, 2.08)	0.03 (-0.01, 0.08)
Q3 vs Q1	-0.6% (-4.3, 3.2)	0.1% (-3.9, 4.3)	0.75 (-0.67, 2.18)	0.03 (-0.01, 0.08)
Q4 vs Q1	-8.4% (-12.0, -4.6)*	-8.1% (-12.2, -3.8)*	0.15 (-1.39, 1.69)	0.02 (-0.03, 0.06)
Model 3: adiposity-adjusted				
Q2 vs Q1	-0.8% (-4.3, 2.7)	-0.3% (-4.0, 3.5)	0.32 (-1.12, 1.75)	0.02 (-0.02, 0.06)
Q3 vs Q1	-0.4% (-3.3, 2.6)	0.4% (-2.7, 3.7)	0.85 (-0.57, 2.27)	0.04 (-0.01, 0.08)
Q4 vs Q1	-6.6% (-9.5, -3.6)*	-6.2% (-9.4, -3.0)*	0.16 (-1.29, 1.61)	0.02 (-0.02, 0.06)
P for trend (model 3)	<0.001*	<0.001*	0.971	0.681

Notes: Values are survey-weighted linear regression coefficients (β) with 95% confidence intervals. β represents the difference in glycemic measures compared with the lowest quartile (Q1) of energy-adjusted vitamin K intake. Insulin and HOMA-IR estimates represent percent differences derived from log-transformed models. P for trend was calculated by modeling quartile medians as an ordinal variable in Model 3. P-values < 0.05 are denoted by (*). Abbreviations: HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 3. Associations between energy-adjusted vitamin K intake (per SD increase) and glycemic markers (Model 3).

Outcome	β (95% CI)	P value
Insulin, % difference	-1.4% (-2.4, -0.4)	0.0067*
HOMA-IR, % difference	-1.3% (-2.3, -0.3)	0.014*
Glucose, mg/dL	0.13 (-0.16, 0.43)	0.365
HbA1c, %	0.00 (-0.02, 0.01)	0.740

Notes: Values are survey-weighted linear regression coefficients (β) with 95% CI from fully adjusted models (Model 3). β represents the change in glycemic measures per SD increase in energy-adjusted vitamin K intake. Insulin and HOMA-IR estimates represent percent differences derived from log-transformed models. P-values < 0.05 are denoted by (*). Abbreviations: CI, confidence intervals; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance.

Effect Modification by Baseline Metabolic Status, Obesity, and Sex

Associations differed significantly by baseline glucose metabolism status (P for interaction = 0.0052 for insulin; 0.0062 for HOMA-IR) (Table 4). In normoglycemic participants, each SD increase in energy-adjusted VK intake was associated with a 3.4% lower fasting insulin (95% CI -5.2% to -1.6%) and 3.4% lower HOMA-IR (95% CI -5.2% to -1.5%), whereas in participants with impaired glucose metabolism associations were attenuated but remained statistically significant (insulin -0.8%; HOMA-IR -0.7%).

No significant interactions were observed by obesity status or by sex (all P for interaction >0.05; Supplementary Table S6).

Table 4. Effect modification of the association between energy-adjusted vitamin K intake and insulin resistance by baseline metabolic status.

Baseline metabolic status	Fasting insulin (% difference)	HOMA-IR (% difference)
Normoglycemic (N = 6925)	-3.4% (-5.2, -1.6)*	-3.4% (-5.2, -1.5)*
Impaired (prediabetes) (N = 6892)	-0.8% (-1.2, -0.3)*	-0.7% (-1.1, -0.2)*
P for interaction	0.0052*	0.0062*

Notes: Impaired glucose metabolism (prediabetes) was defined as fasting glucose 100-125 mg/dL or HbA1c 5.7-6.4%. Unweighted N represents the analyzed (complete-case) sample size for this model. Values are survey-weighted linear regression coefficients (β) with 95% confidence intervals from fully adjusted models (Model 3). β represents the percent difference in insulin and HOMA-IR per 1 SD increase in energy-adjusted vitamin K intake (μg/1000 kcal), derived from log-transformed models. P for interaction derived from multiplicative interaction terms. P-values < 0.05 are denoted by (*). Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance.

Sensitivity Analyses

Associations between energy-adjusted VK intake and insulin resistance markers were robust across sensitivity analyses (Supplementary Tables S1-S3). Additional adjustment for overall diet quality (HEI-2020) moderately attenuated effect sizes, but associations remained statistically significant (insulin -1.1% vs -1.4% in the primary analysis; HOMA-IR -0.9% vs -1.3%). Adjustment for vigorous physical activity resulted in a modest attenuation (insulin -1.3%; HOMA-IR -1.2%). Exclusion of extreme VK intake values strengthened the associations (insulin -2.3%; HOMA-IR -2.2%), whereas exclusion of participants with implausible energy intake or diabetes, as well as alternative adiposity specifications, did not materially change results (Supplementary Tables S1-S2). Modeling VK intake on natural log scale strengthened the associations (insulin -2.6%; HOMA-IR -2.4%; Supplementary Table S3).

Restricted cubic spline analyses supported an overall association between energy-adjusted VK intake and fasting insulin (P<0.001) and HOMA-IR (P=0.0044), with no evidence of non-linearity (P for non-linearity=0.132 and 0.184, respectively). No overall association was observed for fasting glucose. HbA1c showed a statistically significant but small and non-linear association (Supplementary Table S4).

4. Discussion

Key Findings

In this nationally representative sample of 23,247 U.S. adults, higher energy-adjusted dietary VK intake was independently associated with lower fasting insulin and HOMA-IR, but not with fasting glucose or HbA1c. Each SD increase in VK intake was associated with 1.4% lower fasting insulin and 1.3% lower HOMA-IR in fully adjusted models. Adjustment for adiposity attenuated nearly half of the association, and effect modification by baseline glycemic status was observed, with stronger associations among normoglycemic participants. Although the magnitude of association was modest

– consistent with effect sizes typically observed in population-based nutritional epidemiology – findings were robust across multiple sensitivity analyses.

Mechanistic Considerations

Several biological mechanisms may explain the observed association between dietary VK intake and markers of insulin resistance. In pancreatic β -cells, VK-dependent regulation of endoplasmic reticulum calcium handling preserves glucose-stimulated insulin secretion under metabolic stress [29]; VK also modulates cAMP-dependent pathways involved in insulin secretion, including Epac2 signaling [28].

In peripheral tissues, animal models demonstrate that VK activates SIRT1-dependent pathways in liver and skeletal muscle, improving insulin signaling and mitochondrial function [35,36]. Beyond direct effects on insulin signaling, VK reduces oxidative stress [46–48], modulates inflammatory pathways [30–34], and alters gut microbiota composition, including increased butyrate production – a metabolite linked to improved insulin sensitivity [49].

Collectively, these mechanisms support a model in which adequate VK availability enhances insulin signaling and peripheral glucose disposal. Because insulin resistance typically precedes overt hyperglycemia, such effects would be expected to reduce compensatory hyperinsulinemia and HOMA-IR in individuals with preserved β -cell function, without necessarily altering fasting glucose [50].

Effect Modification by Baseline Metabolic Status

We observed stronger associations between VK intake and insulin resistance markers in individuals with normoglycemia than in those with impaired glucose metabolism. These findings suggest that, within typical dietary intake levels, VK may primarily support the maintenance of insulin signaling rather than reverse established dysfunction.

One possible explanation is that, at usual intake levels, extrahepatic VK-dependent pathways involved in inflammatory and oxidative stress regulation, β -cell preservation, and peripheral glucose uptake are only partially activated [6–8]. Within this limited activation range, variation in VK intake may meaningfully influence insulin sensitivity when intracellular signaling and β -cell function remain largely intact. In contrast, once metabolic dysfunction becomes established, chronic inflammatory and structural changes may reduce the responsiveness and relative contribution of these pathways, thereby attenuating associations detectable at habitual intake levels. Consistent with this interpretation, longitudinal studies report inverse associations between VK intake or status and incident T2D [9–11], supporting a role for VK in preventing metabolic deterioration.

Importantly, this interpretation applies to dietary exposure. Supplementation trials suggest a different dynamic at higher doses. In individuals with prediabetes or diabetes, VK supplementation has more consistently improved insulin resistance markers [41–43], whereas effects in healthy populations have generally been limited [6,37–40]. Pharmacologic and highly bioavailable VK doses used in these trials allow for fuller activation of extrahepatic VK-dependent pathways involved in insulin sensitivity [6–8]. In metabolically healthy individuals – where these pathways already function near physiological sufficiency – additional activation may yield minimal benefit. In contrast, in metabolically impaired states, it may exert more pronounced effects by partially restoring disrupted signaling.

Taken together, these observations suggest that VK operates across two exposure ranges: within physiological intake levels, VK sufficiency may primarily maintain insulin sensitivity through partial pathway activation, whereas higher doses may partially correct metabolic impairment through fuller engagement of extrahepatic VK-dependent pathways. Although this framework remains hypothetical, it provides a biologically plausible explanation for the divergence between observational associations and supplementation trial outcomes.

Attenuation After Adjustment for Adiposity

Adjustment for BMI and waist circumference attenuated nearly half of the association, underscoring the complex relationship between adiposity, VK status, and glucose metabolism. While adiposity is a well-established driver of insulin resistance, its relationship with VK status is more complex. As a lipophilic vitamin, VK can be sequestered in adipose tissue, potentially reducing its bioavailability in individuals with higher body fat [13]; this supports a role for adiposity as a confounder. Conversely, several population-based analyses have reported inverse associations between VK intake or status and measures of adiposity, particularly visceral fat [12–14,16,17]; these findings raise the possibility that adiposity may lie on the causal pathway linking VK intake to insulin resistance.

Given the cross-sectional design, confounding cannot be distinguished from mediation, and adiposity-adjusted models likely represent conservative estimates of the association between VK intake and insulin resistance.

Exposure Assessment Considerations

Importantly, dietary VK intake may be a weak proxy for biologically relevant VK exposure. Experimental studies demonstrating effects on β -cell function and insulin resistance used high-dose, chemically pure VK, whereas a single 24-hour recall captures mostly short-term phyloquinone intake and does not account for the variability in VK absorption, tissue distribution, or conversion to menaquinone-4 [51]. Although this limitation would be expected to attenuate associations, results remained statistically significant.

On the other hand, phyloquinone is abundant in leafy green vegetables and may reflect overall dietary quality. Higher VK intake could therefore act as a marker of healthier dietary patterns rather than an independent exposure [51]. Consistent with this notion, further adjustment for overall diet quality (HEI-2020) attenuated the associations by 24–29%, but they remained statistically significant (Supplementary Table S1). While residual confounding by unmeasured or imperfectly measured dietary factors cannot be excluded, the persistence of the association after adjustment suggests that overall diet quality does not fully account for the observed relationship.

Clinical and Preventive Implications

These findings may have relevance for metabolic risk reduction at both clinical and public health levels. Insulin resistance is a central driver of T2D and often develops years before overt hyperglycemia becomes clinically detectable [26,27]. Identifying dietary exposures associated with insulin sensitivity may therefore provide insight into strategies aimed at delaying metabolic deterioration. Our results, together with prospective cohort studies reporting lower incidence of T2D among individuals with higher VK intake or status [9–11], suggest that VK availability may represent one such factor. Notably, subclinical VK insufficiency appears to be relatively common in the general population [4–8]. Although VK intake often reflects consumption of green leafy vegetables – foods already recommended within cardiometabolic prevention frameworks – other dietary sources, including fermented foods and certain dairy products, also contribute substantially to VK exposure [10,52]. These observations support further investigation of VK status as a potentially modifiable determinant of metabolic risk and the role of dietary strategies or supplementation in diabetes prevention.

Strengths and Limitations

This study has several limitations. First, the cross-sectional design precludes conclusions about causality or the direction of the observed associations. Second, VK intake was assessed using a single 24-hour dietary recall, which may not reflect habitual intake and is subject to measurement error and recall bias. Third, NHANES does not include biomarkers of VK status, such as circulating phyloquinone or undercarboxylated VK-dependent proteins, which would better capture

physiological VK exposure than dietary intake alone [51]. Fourth, although models were adjusted for key determinants of glycemic status, residual confounding by other factors cannot be excluded. Fifth, glycemic outcomes were limited to fasting measures; dynamic indices of insulin sensitivity, which may better reflect extrahepatic insulin resistance, were not available. Finally, the modest magnitude of association warrants careful interpretation of clinical implications.

Despite these limitations, this study has notable strengths. It is, to our knowledge, the first NHANES analysis to directly examine dietary VK intake in relation to insulin resistance markers. The use of a large, nationally representative sample of U.S. adults, standardized laboratory measurements, sequential covariate adjustment, multiple sensitivity analyses, spline modeling, and formal assessment of effect modification all enhance the validity and generalizability of the findings presented here.

5. Conclusions

In this nationally representative sample of U.S. adults, higher energy-adjusted dietary VK intake was independently associated with lower fasting insulin and HOMA-IR, but not with fasting glucose or HbA1c. The stronger associations observed among normoglycemic individuals suggest that VK may contribute to the maintenance of insulin sensitivity in metabolically intact states. Prospective studies incorporating comprehensive assessments of VK status and dynamic measures of insulin sensitivity are needed to clarify its role in prevention of metabolic dysfunction.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Supplementary Figure S1. Directed acyclic graph (DAG) illustrating conceptual relationships between vitamin K status and glycemic markers. Supplementary Figure S2. Prespecified analytical strategy for evaluating associations between energy-adjusted vitamin K intake and glycemic markers. Supplementary Table S1. Sensitivity analyses of the association between energy-adjusted vitamin K intake (per SD) and fasting insulin and HOMA-IR. Supplementary Table S2. Sensitivity analysis using alternative adiposity specifications. Supplementary Table S3. Association between log-transformed energy-adjusted vitamin K intake and glycemic markers (Model 3). Supplementary Table S4. Percent attenuation of associations between energy-adjusted vitamin K intake and fasting insulin and HOMA-IR across sequential adjustment models. Supplementary Table S5. Survey-weighted restricted cubic spline analysis of energy-adjusted vitamin K intake and glycemic markers. Supplementary Table S6. Effect modification of associations between energy-adjusted vitamin K intake and fasting insulin and HOMA-IR by sex and obesity status.

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Abbreviations

The following abbreviations are used in this manuscript.:

NHANES	National Health and Nutrition Examination Survey
HOMA-IR	Homeostatic Model Assessment - Insulin Resistance
DM2	Type 2 diabetes
VK	Vitamin K

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