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Association of All-Cause and Cause-Specific Mortality with Diabetes Mellitus in Adults: Role of Vitamin D Deficiency

Sara Saffar Soflaei[1,2*], Soheyla Jafarpour[3*], Rasoul Alimi[4], Toktam Sahranavard[2,5], Emad Ghayour-Mobarhan[6], Parsa Seyed Hosseini[1], Hossein Hatamzadeh[7], Mahmoud Ebrahimi[1,8], Mohsen Moohebati[1,8], Gordon A. Ferns[9], Habibollah Esmaily[10,11#], Majid Ghayour-Mobarhan[1,2#]

1. Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
2. International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
4. Department of Epidemiology and Biostatistics, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.
5. Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
6. Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.
7. Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
8. Department of Cardiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
9. Brighton and Sussex Medical School, Division of Medical Education, Brighton, UK.
10. Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.
11. Social Determinants of Health Research center, Mashhad University of Medical Sciences, Mashhad, Iran.

Equally contributed first author

 # Corresponding authors:

1- Habibollah Esmaily, Department of Biostatistics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: EsmailyH@mums.ac.ir

2- Majid Ghayour-Mobarhan, Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: GhayourM@mums.ac.ir

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Abstract

Background: There is increasing evidence indicating that vitamin D deficiency may contribute to the development of Type 2 Diabetes Mellitus (T2DM) by affecting insulin sensitivity, insulin secretion, and inflammation.

Objectives: We have investigated the association between vitamin D deficiency, T2DM, and mortality outcomes.

Methods: The study was conducted on a sample of 846 subjects, derived from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) cohort study. Participants were considered as vitamin D deficient with vitamin D levels of less than 20 ng/ml. Over 10 years, participants were followed up every three years. The cause of death was identified using the death register of the Iranian Ministry of Health and Education and the death cause questionnaire. The study examined the relationship between T2DM and mortality using descriptive statistics, chi-square tests, and Cox proportional hazard regression analysis.

Results: During the 10-year follow-up, 44 participants died from all causes, 15 from cancer, and 14 from cardiovascular causes. There was a significant association between diabetes and all-cause mortality, even after adjustment for age and sex yielding an HR of 2.07 (P=0.039). Vitamin D deficiency was associated with diabetes-related mortality (HR=3.16, P=0.038), but this link is not true for individuals who had vitamin D levels of more than 20 ng/ml**.** This association extends to mortality because of cancer (HR=3.64, P=0.025), but not cardiovascular mortality**.**

Conclusion: Our findings underscore the potential role of vitamin D deficiency in the mortality risk of diabetics. Future research should further explore the mechanistic links between vitamin D deficiency, T2DM, and mortality outcomes to inform targeted interventions and improve clinical management strategies.

Keywords: Mortality; Diabetes mellitus; Vitamin D deficiency; Cohort study

1. Background

Globally, chronic diseases have reached unprecedented levels in recent decades, causing the global public health systems to face challenges (1). As one of the most serious chronic diseases, type 2 diabetes mellitus (T2DM) is a leading cause for concern, exerting a significant impact both on an individual's health outcomes and the infrastructure of healthcare facilities (2). T2DM prevalence is influenced by various factors, ranging from genetics to environmental influences to socioeconomic factors (3). Lifestyle changes, including escalating obesity rates, sedentary behavior, and unhealthy dietary habits, are responsible for fueling the diabetes epidemic (4). Moreover, globalization, population aging, and urbanization have altered physical activity patterns, healthcare access, and dietary norms, all contributing to the rising prevalence of diabetes (5).

The prevalence of T2DM has progressed to a global epidemic, requiring effective prevention, early detection, and a comprehensive approach to its management (6). A diagnosis of diabetes refers to a spectrum of metabolic diseases characterized by high blood glucose levels, possibly due to an inability to produce insulin or a defect in insulin function. Type 1 diabetes mellitus is most commonly diagnosed in childhood and adolescence, and pancreatic beta cells are destroyed by the immune system, leading to the lack of insulin (7, 8). Conversely, T2DM, which accounts for the majority of diabetes cases worldwide, is caused by relative insulin deficiency and insulin resistance, usually made worse by genetics and the environment (9, 10). T2DM management involves a multidisciplinary approach to control blood glucose levels, mitigate cardiovascular risk factors, and treat associated comorbidities (11, 12). Diabetes management is largely based on lifestyle modifications, including regular physical activity, weight control, and dietary changes (13, 14).

There is emerging evidence suggesting that vitamin D deficiency may contribute to T2DM and other health outcomes (15). Traditionally recognized for its important role in calcium homeostasis and bone health, vitamin D is gaining increasing attention as a means to prevent chronic diseases (16) (17). Vitamin D deficiency is common across various populations and has been associated with several metabolic and chronic conditions, including diabetes, hypertension, dyslipidemia, and certain autoimmune and musculoskeletal disorders (18-20).

Accumulating evidence indicates that vitamin D may influence glucose metabolism through several mechanisms, including affecting of insulin sensitivity, secretion, and inflammatory pathways (21).

Recent findings have shown significant metabolic effects of vitamin D, including its association with diabetes and other cardiovascular risk factors (19, 20). In addition, vitamin D deficiency has been linked to an increased risk of diabetes and related cardiovascular risk factors, and some studies have also reported associations with higher all-cause and diabetes-related mortality (22, 23). These findings highlight the potential importance of maintaining adequate vitamin D levels for metabolic health and disease prevention (24, 25).

The novelty of the present study lies in simultaneously investigating the association between T2DM, vitamin D deficiency, and different mortality outcomes—including all-cause, cardiovascular, and cancer-related mortality—using data from a large perspective cohort. This integrated approach provides new insights into how vitamin D status may modify the impact of

diabetes on long-term health outcomes.

2. Methods and Materials

2.1. Study Design

All participants signed the written consent forms for this study. Subjects derived from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study (26). In summary, MASHAD study started in 2010 with 9704 residences of Mashhad city, the second biggest city in Iran. Baseline characteristics including demographic and socioeconomic variables as well as health-related variables were collected for all the subjects. Anthropometry along with blood pressure was performed using standard methods. After an overnight fasting blood samples were collected for measuring various biochemical factors. From the original MASHAD cohort, 846 individuals were included in the present analysis. Participants were selected based on data completeness, meaning only those with available baseline information on vitamin D levels, diabetes status, and other relevant covariates were eligible.

Inclusion criteria were: (1) adults aged ≥35 years at enrollment, (2) availability of complete baseline data (vitamin D, fasting blood glucose, anthropometric measurements including height, weight, and blood pressure, as well as demographic information) and (3) consent for follow-up. Exclusion criteria included: (1) missing baseline data on key variables, (2) untraceable or incomplete follow-up data, and (3) unclear or conflicting medical records.

T2DM is defined as either a previous clinical diagnosis, having a fasting blood glucose (FBG) of ≥126 mg/dl or taking anti-hyperglycemic medications, verified by medical records, according to ADA criteria. FBG was measured in peripheral blood samples after 14 hours of fasting. Vitamin D and all other baseline variables were measured once at the time of study enrollment (2010–2012). Vitamin D was measured as previously described with an ELISA kit (Roche Diagnostics vitamin D total assay kit; Reference Number: 06506780160, Roche Diagnostics, Mannheim, Germany) (27).

2.2. Follow Up

Over a period of 10 years, participants were followed up every three years by phone. After recognition of dead individuals, the cause of death was determined using the death register of the Iranian Ministry of Health and Education and death cause questionnaire which was asked from their spouse or their children.

For survival analysis, the time origin was defined as the date of study enrollment (2010–2012), and the endpoint was defined as the occurrence of death (all-cause, CVD, or cancer-specific) or the end of follow-up (December 2020), whichever occurred first. Participants without an event were censored at the date of last follow-up.

2.3. Statistical Analysis

Descriptive statistics were presented as several participants (percentage) for categorical variables or as mean ± standard deviation for continuous variables. Between-group comparisons were performed using chi-square or Fisher's exact test for categorical variables. Cox proportional hazard regression analysis was performed to estimate hazard ratios and 95% CIs of cancer, cardiovascular disease (CVD), and overall mortality for diabetes, with the non-diabetic category as the reference. Also, bivariate associations were assessed to determine the effect of vitamin D on the association between diabetes and mortalities.

Multivariate Cox regression analyses were used to determine the association between diabetes and outcomes of interest,

adjusted for age (continuous), sex (male, female), body mass index (BMI), hypertension status, and other potential confounders. Two-sided P values < 0.05 were regarded as statistically significant. Data was analyzed by using SPSS Statistics for Windows, Version 26.0.

3. Results

In a cohort study comprising 846 individuals, including 357 (42.2%) males and 489 (57.8%) females, with an average age of 47.29 years ± 7.90 years, the mean survival times were very close to the follow-up period, with 152.55 months for CVD, 152.68 months for cancer, and 149.57 months for all-cause mortality. The median survival times (Q1–Q3) were 154 (148–159) months for CVD, 154 (149–159) months for cancer, and 150 (145–156) months for all-cause mortality.

Five- and ten-year mortality rates were also estimated. The 5-year mortality rates (95% CI) were 2.8% (1.9–4.0) for all-cause, 1.2% (0.7–2.1) for cancer, and 1.0% (0.6–1.8) for CVD. The 10-year mortality rates (95% CI) were 6.7% (5.2–8.7) for all-cause, 3.4% (2.3–4.9) for cancer, and 2.6% (1.7–4.0) for CVD.

Analysis revealed a significant association between diabetes and all-cause mortality, with a hazard ratio (HR) of 2.64 (P=0.005). Subsequent adjustment for age and sex yielded a slightly reduced HR of 2.07 (P=0.039).

Table 1 examined the association between diabetes and mortality rates. All-cause mortality in diabetics with vitamin D deficiency was more than twice that of non-diabetics (P = 0.05), while no significant difference was observed in individuals with vitamin D levels >30. Cancer mortality in diabetic people is more than three times compared to non-diabetics after adjusting for confounding factors (P = 0.038) in all participants, while it was more than 3.5 in participants with vitamin D deficiency (P=0.025).

Table 1. Characteristics of Participants According to Diabetes and Mortality

	Vitamin D	Death	Total	T2DM	Non – T2DM	P- value for differences
All-cause mortality	**All**	Yes	44 (5.1)	11 (25.0)	33 (75.0)	**0.007**
		No	816 (94.9)	93 (11.4)	723 (88.6)	
	Deficient (D≤20 ng/mL)	Yes	39 (5.7)	10 (25.6)	29 (74.4)	**0.007**
		No	651 (94.3)	67 (10.3)	584 (89.7)	
	Sufficient (D>20 ng/mL)	Yes	5 (2.9)	1 (20.0)	4 (80.0)	**0.584**
		No	165 (97.1)	26 (15.8)	139 (84.2)	
Cancer mortality	**All**	Yes	15 (1.7)	5 (33.8)	10 (66.7)	**0.026** [a]
		No	845 (98.3)	99 (11.7)	746 (88.3)	
	Deficient (D≤20 ng/mL)	Yes	14 (2.0)	5 (35.7)	9 (64.3)	**0.014** [a]
		No	676 (98.0)	72 (10.7)	604 (89.3)	
	Sufficient (D>20 ng/mL)	Yes	1 (0.6)	0 (0.0)	1 (100.0)	**0.999** [a]
		No	169 (99.4)	27 (16.0)	142 (84.0)	
CVD mortality	**All**	Yes	14 (1.6)	3 (21.4)	11 (78.6)	**0.230** [a]
		No	846 (98.4)	101 (11.9)	745 (88.1)	
	Deficient (D≤20 ng/mL)	Yes	14 (2.0)	3 (21.4)	11 (78.6)	**0.198** [a]
		No	676 (98.0)	74 (10.9)	602 (89.1)	
	Sufficient (D>20 ng/mL)	Yes	-	-	-	-
		No	170 (100.0)	27 (15.9)	143 (84.1)	

Abbreviations: T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease [a] exact test

Cox regression modeling was utilized to determine the intensity of diabetes' effect on mortality rates while controlling for age and gender effects, with the results presented in Table 2. We considered other possible confounders such as BMI, smoking, and comorbidities, but these data were missing for a large number of participants and could not be included in the main survival models.

Table 2- Examining the role of vitamin D in the relationship between diabetes and mortality

	All	P-value	Vitamin D Deficient	P-value
All-cause Mortality				
No. of deaths	44		39	
Means for Survival Time				
Overall	149.57 (148.20 - 150.94)		145.56 (144.03 - 147.10)	
T2DM	136.01 (131.96 – 140.05)		134.57 (129.48 – 139.66)	
Non- T2DM	150.13 (148.72 – 151.53)		146.17 (144.61 – 147.74)	
Un-Adjusted HR (95% CI)	2.64 (1.33 - 5.23)	**0.005**	2.98 (1.45 – 6.12)	**0.003**
Adjusted HR[a] (95% CI)	2.07 (1.04 - 4.11)	**0.039**	2.06 (1.00 – 4.28)	**0.050**
Cancer Mortality				
No. of deaths	15		14	
Means for Survival Time				
Overall	152.68 (151.96 – 153.40)		148.79 (147.99 – 149.59)	
T2DM	139.52 (136.37 – 142.66)		138.34 (134.22 – 142.47)	
Non- T2DM	153.06 (152.42 – 153.70)		149.25 (148.56 – 149.95)	
Un-Adjusted HR (95% CI)	3.92 (1.34 -11.48)	**0.013**	4.78 (1.60 – 14.29)	**0.005**
Adjusted HR[a] (95% CI)	3.16 (1.06 – 9.37)	**0.038**	3.63 (1.18 – 11.14)	**0.025**
CVD Mortality				
No. of deaths	14		14	
Means for Survival Time				
Overall	152.55 (151-72 – 153-38)		148.47 (147.48 – 149.47)	
T2DM	141-38 (139.44 – 143.32)		140.80 (138-19 – 143.41)	
Non- T2DM	152.62 (151.73 – 153.51)		148-57 (147.51 – 149.62)	
Un-Adjusted HR (95% CI)	2.06 (0.58 7.41)	0.265	2.26 (0.63 -8.10)	0.211
Adjusted HR[a] (95% CI)	1.48 (0.41-5.35)	0.549	1.38 (0.38 – 5.02)	0.624

Abbreviations: T2DM, type 2 diabetes mellitus; CI, confidence interval; HR, hazard ratio; CVD, cardiovascular disease

[a] Adjusted for age (year) and sex

In people with vitamin D deficiency, cancer mortality in diabetic people is more than 3.5 times higher than that of non-diabetics, even after adjusting for confounding factors (P=0.025). As can be seen, this chance is higher for those who have a vitamin D deficiency than anyone else in the study. This relationship is not true for people with vitamin D levels greater than 30. Although not statistically

significant (P=0.624), diabetes also has an increasing effect on cardiovascular mortality. Adjusted cumulative hazard of mortality in diabetic and non-diabetic patients have also provided to better understanding of these differences in patients with vitamin D deficiency (Figure 1).

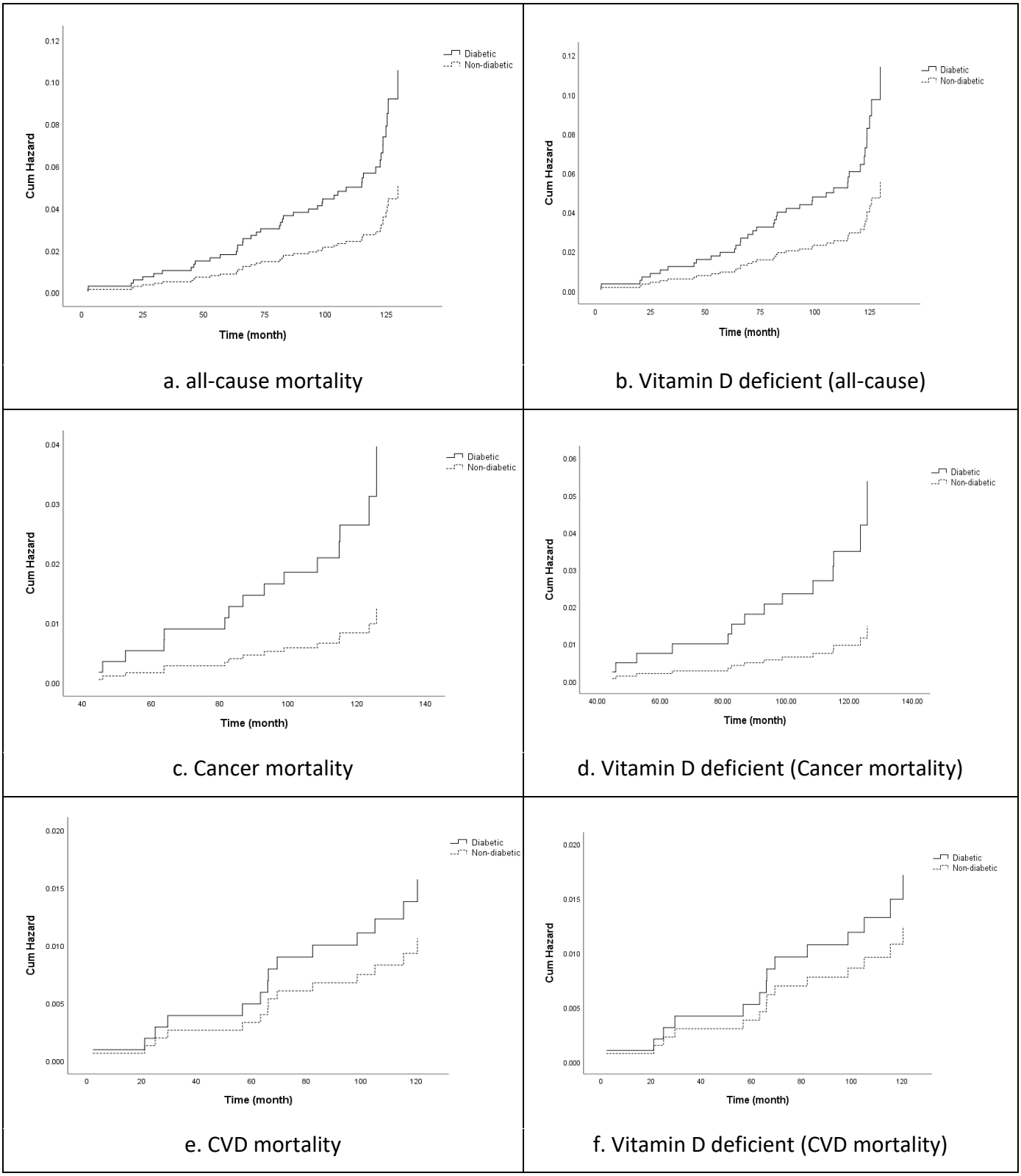

Figure 1. Adjusted cumulative hazard of mortality in diabetic and non-diabetic patients.

4. Discussion

According to the results of the current study, in individuals with vitamin d deficiency, a notable correlation emerges between diabetes and mortality, although this relationship lacks significance among those without such a deficiency. Moreover, this association extends beyond diabetes, encompassing mortality from various causes and specifically cancer-related mortality, yet it does not extend to mortality stemming from cardiovascular complications. Additionally, an incidental discovery reveals a somewhat ambiguous connection between vitamin D deficiency in individuals with diabetes and mortality rates attributed to any cause of cancer, while cardiovascular mortality does not appear to be affected. These findings underline the intricate interplay between vitamin D status, diabetes, and mortality risk, suggesting potential avenues for further exploration into the underlying mechanisms and implications for disease management and prevention strategies.

T2DM represents a formidable challenge to global public health, characterized by its escalating prevalence and profound implications for morbidity and mortality (28). As a chronic metabolic disorder, T2DM poses a substantial burden on healthcare systems worldwide, exerting a significant impact on both individual health outcomes and broader societal well-being (29). In the last few decades, T2DM has become much more common, and it is expected to keep increasing in the coming years (30, 31). This is worrying because T2DM is linked to serious health problems, like heart disease, cancer, and death from any cause (32, 33). Understanding the intricate interplay between diabetes and these deleterious outcomes is paramount for informing targeted interventions and mitigating the burgeoning burden of disease (34, 35).

The reciprocal relationship between vitamin D and diabetes with mortality involves complex pathophysiological mechanisms (36). Vitamin D plays a crucial role in modulating insulin sensitivity and secretion, and its deficiency contributes to insulin resistance and impaired glucose metabolism, hallmark features of diabetes (37, 38). Moreover, vitamin D deficiency is associated with chronic inflammation and oxidative stress, which are implicated in the progression of both diabetes and cardiovascular diseases (39, 40). The dysregulation of calcium homeostasis due to vitamin D deficiency also exacerbates vascular dysfunction, increasing the risk of cardiovascular complications in diabetic individuals (41). Conversely, diabetes-related complications such as nephropathy and neuropathy further compromise vitamin D metabolism, creating a vicious cycle of worsening metabolic control and increased mortality risk (42). This underscores the importance of addressing both vitamin D deficiency and diabetes management strategies to mitigate mortality risk effectively.

Findings from our study are consistent with prior research. For instance, da Silva Negreiros et al. reported increased T2DM-related mortality in Brazil, with risk influenced by age, sex, race, and socioeconomic status (43). Similarly, a systematic review of 26 observational studies across 30 countries showed that younger age at diabetes diagnosis was associated with greater risks of all-cause, macrovascular, and microvascular complications (44). Another large retrospective study from the U.S. Veterans Affairs Healthcare System demonstrated that diabetes significantly increased all-cause mortality despite advances in CVD risk management (45). Together, these findings align with ours, reinforcing the global relevance of diabetes as a driver of premature mortality and highlighting the modifying role of vitamin D status.

However, several limitations should be acknowledged. First, vitamin D was measured only once or twice during follow-up, which may not capture long-term fluctuations. Second, the generalizability of our findings may be limited by the characteristics of our study population. Finally, there remains potential for selection bias and unmeasured confounding, which may have influenced the observed associations. Future studies with prospective designs and randomized controlled trials are needed to validate our findings and provide stronger causal evidence.

5. conclusion

In conclusion, our study adds to the growing body of evidence suggesting an association between vitamin D deficiency, T2DM, and mortality outcomes. Utilizing data from the large MASHAD cohort study, we found significant associations between T2DM and all-cause mortality, highlighting diabetes as a strong independent risk factor. Moreover, our findings suggest that vitamin D deficiency may further modify these risks. Future research should further explore the mechanistic links between vitamin D deficiency, T2DM, and mortality outcomes to inform targeted interventions and improve clinical management strategies. Overall, our study emphasizes the need for comprehensive approaches to reduce the burden of these interconnected health conditions.

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Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interests: The authors declare no conflict of interest.

Consent for publication: Not applicable.

Ethics approval and consent to participate: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The Ethics Committee of the Mashhad University of Medical Sciences approved the study after all participants provided informed consent (IR.MUMS.MEDICAL.REC.1395.458).

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