

Supplementary Online Content

Liu Y, Geng T, Wan Z, et al. Associations of serum folate and vitamin B₁₂ levels with cardiovascular disease mortality among patients with type 2 diabetes. *JAMA Netw Open*. 2022;5(1):e2146124. doi:10.1001/jamanetworkopen.2021.46124

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Associations Between Serum Folate With All-Cause Mortality in Various Subgroups Among Patients With T2D in NHANES III and NHANES 1999-2014

	Quartiles of serum folate, nmol/L				<i>P</i> interaction
	Q1: <16.2	Q2: 16.2-27.4	Q3: 27.5-44.0	Q4: ≥44.1	
Age, years					.85
<60	1.00 (0.74, 1.35)	1.00 (ref.)	0.87 (0.61, 1.24)	1.09 (0.69, 1.73)	
≥60	1.16 (0.97, 1.38)	1.00 (ref.)	1.06 (0.86, 1.30)	1.28 (1.04, 1.57)	
Sex					.91
Female	1.07 (0.88, 1.30)	1.00 (ref.)	0.88 (0.67, 1.17)	1.12 (0.90, 1.40)	
Male	1.26 (1.00, 1.58)	1.00 (ref.)	1.10 (0.88, 1.38)	1.00 (0.77, 1.29)	
Race					.83
White	1.19 (0.98, 1.46)	1.00 (ref.)	1.08 (0.84, 1.39)	1.07 (0.86, 1.34)	
Other	1.21 (0.96, 1.53)	1.00 (ref.)	0.89 (0.69, 1.14)	1.15 (0.88, 1.49)	
BMI, kg/m²					.02
<30	1.31 (0.96, 1.81)	1.00 (ref.)	1.39 (1.05, 1.86)	1.27 (0.96, 1.67)	
≥30	1.36 (0.99, 1.86)	1.00 (ref.)	0.98 (0.73, 1.31)	1.25 (0.93, 1.68)	
Smoking status					.10
Never	1.02 (0.81, 1.30)	1.00 (ref.)	1.03 (0.77, 1.37)	1.23 (0.97, 1.57)	
Ever or current	1.25 (1.03, 1.52)	1.00 (ref.)	0.99 (0.79, 1.23)	0.94 (0.75, 1.18)	
Drinking status					.18
Non-drinkers	1.03 (0.86, 1.25)	1.00 (ref.)	0.97 (0.75, 1.26)	1.11 (0.88, 1.39)	
Drinkers	1.35 (1.06, 1.71)	1.00 (ref.)	1.06 (0.84, 1.33)	1.04 (0.83, 1.31)	
Duration, years					.07
<10	1.28 (0.98, 1.69)	1.00 (ref.)	1.118 (0.81, 1.54)	1.02 (0.76, 1.36)	
≥10	1.17 (0.79, 1.72)	1.00 (ref.)	1.104 (0.77, 1.59)	1.43 (1.00, 2.03)	
Physical activity					.04
Inactive	1.18 (0.91, 1.54)	1.00 (ref.)	1.06 (0.81, 1.38)	1.15 (0.86, 1.54)	
Active	1.48 (0.97, 2.26)	1.00 (ref.)	1.29 (0.96, 1.73)	1.29 (0.90, 1.85)	
HbA1c					.40
<7.0%	1.36 (1.00, 1.85)	1.00 (ref.)	1.16 (0.80, 1.68)	1.18 (0.87, 1.62)	
≥7.0%	1.21 (0.87, 1.68)	1.00 (ref.)	1.07 (0.83, 1.38)	1.18 (0.82, 1.69)	
Hypertension					.27
Yes	1.43 (1.08, 1.89)	1.00 (ref.)	1.20 (0.90, 1.60)	1.29 (1.02, 1.64)	
No	1.04 (0.72, 1.50)	1.00 (ref.)	0.97 (0.66, 1.41)	1.10 (0.77, 1.56)	
Hypercholesterolemia					.11
Yes	1.21 (0.86, 1.70)	1.00 (ref.)	1.14 (0.85, 1.54)	1.20 (0.86, 1.67)	
No	1.27 (0.97, 1.67)	1.00 (ref.)	1.13 (0.81, 1.59)	1.24 (0.91, 1.68)	

HRs (95% CIs) were adjusted for age (continuous), sex (male, or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, or active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes or no), self-reported hypercholesterolemia (yes or no). The strata variable was not included when stratifying by itself.

eTable 2. Associations Between Serum B₁₂ With All-Cause Mortality in Various Subgroups Among Patients With T2D in NHANES III and NHANES 1999-2014

	Quartiles of serum vitamin B ₁₂ , pmol/L				P _{interaction}
	Q1: <272.3	Q2: 272.3-373.3	Q3: 373.4-519.0	Q4: ≥519.1	
Age, years					.48
<60	1.13 (0.74, 1.73)	1.00 (ref.)	1.78 (1.13, 2.81)	1.71 (1.05, 2.77)	
≥60	1.07 (0.91, 1.25)	1.00 (ref.)	1.10 (0.86, 1.40)	1.14 (0.92, 1.41)	
Sex					.75
Female	1.09 (0.83, 1.44)	1.00 (ref.)	1.42 (1.06, 1.89)	1.23 (0.88, 1.70)	
Male	1.11 (0.86, 1.43)	1.00 (ref.)	1.30 (0.94, 1.79)	1.36 (1.01, 1.82)	
Race					.97
White	1.01 (0.83, 1.22)	1.00 (ref.)	1.43 (1.08, 1.88)	1.27 (0.94, 1.71)	
Other	1.48 (1.09, 2.01)	1.00 (ref.)	1.28 (0.95, 1.71)	1.40 (0.99, 1.98)	
BMI, kg/m²					.53
<30	0.87 (0.66, 1.13)	1.00 (ref.)	1.11 (0.84, 1.48)	1.19 (0.89, 1.59)	
≥30	1.33 (1.01, 1.76)	1.00 (ref.)	1.59 (1.18, 2.15)	1.29 (0.93, 1.80)	
Smoking status					.85
Never	1.08 (0.79, 1.48)	1.00 (ref.)	1.44 (1.05, 1.97)	1.34 (0.95, 1.89)	
Ever or current	1.15 (0.91, 1.45)	1.00 (ref.)	1.36 (1.01, 1.83)	1.25 (0.95, 1.66)	
Drinking status					.17
Non-drinkers	1.15 (0.91, 1.46)	1.00 (ref.)	1.40 (1.06, 1.85)	1.19 (0.91, 1.56)	
Drinkers	1.06 (0.80, 1.41)	1.00 (ref.)	1.33 (0.97, 1.81)	1.29 (0.92, 1.80)	
Duration, years					.58
<10	1.18 (0.92, 1.50)	1.00 (ref.)	1.46 (1.13, 1.90)	1.54 (1.15, 2.07)	
≥10	1.07 (0.80, 1.44)	1.00 (ref.)	1.29 (0.92, 1.81)	1.09 (0.80, 1.48)	
Physical activity					.97
Inactive	1.24 (1.00, 1.54)	1.00 (ref.)	1.51 (1.20, 1.90)	1.42 (1.14, 1.77)	
Active	0.86 (0.62, 1.20)	1.00 (ref.)	1.19 (0.83, 1.72)	1.18 (0.81, 1.71)	
HbA1c					.84
<7.0%	1.05 (0.84, 1.32)	1.00 (ref.)	1.17 (0.86, 1.59)	1.27 (0.94, 1.70)	
≥7.0%	1.18 (0.90, 1.55)	1.00 (ref.)	1.48 (1.09, 2.02)	1.27 (0.92, 1.76)	
Hypertension					.29
Yes	0.95 (0.71, 1.28)	1.00 (ref.)	1.10 (0.80, 1.52)	1.19 (0.85, 1.67)	
No	1.21 (0.86, 1.70)	1.00 (ref.)	1.10 (0.76, 1.59)	1.53 (1.13, 2.09)	
Hypercholesterolemia					.16
Yes	2.10 (1.12, 3.91)	1.00 (ref.)	2.04 (1.06, 3.93)	2.45 (1.35, 4.44)	
No	1.50 (0.90, 2.52)	1.00 (ref.)	1.57 (0.87, 2.83)	2.51 (1.47, 4.29)	

HRs (95% CIs) were adjusted for age (continuous), sex (male, or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, or active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes or no), and self-reported hypercholesterolemia (yes or no). The strata variable was not included when stratifying by itself.

eTable 3. HRs (95% CIs) of CVD Mortality According to Serum Folate and Vitamin B₁₂ Levels After Excluding T2D Patients With Less Than 2 Years of Follow-up

	Serum folate concentrations (nmol/L)				Serum vitamin B ₁₂ concentrations (pmol/L)			
	Q1: <16.2	Q2: 16.2-27.4	Q3: 27.5-44.0	Q4: ≥44.1	Q1: <272.3	Q2: 272.3-373.3	Q3: 373.4-519.0	Q4: ≥519.1
CVD mortality								
No. deaths/total	306/1802	149/1737	138/1730	90/1656	114/1064	72/1069	96/1061	104/1032
Model 1 ^a	1.47 (1.00, 2.17)	1.00 (ref.)	1.31 (0.94, 1.83)	1.12 (0.79, 1.58)	1.85 (1.13, 3.00)	1.00 (ref.)	1.69 (1.07, 2.65)	2.88 (1.88, 4.41)
Model 2 ^b	1.48 (1.03, 2.12)	1.00 (ref.)	1.44 (1.05, 1.98)	1.21 (0.86, 1.71)	1.89 (1.23, 2.91)	1.00 (ref.)	1.96 (1.27, 3.02)	2.78 (1.84, 4.20)

a Adjusted for age (continuous), sex (male, or female), and race (non-Hispanic white, non-Hispanic black, Mexican American, or other).

b Model 1+ BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes, no), and self-reported hypercholesterolemia (yes, no).

eTable 4. HR (95% CIs) of CVD Mortality According to Quintiles of Serum Folate and Vitamin B₁₂ Concentrations Among Patients With T2D

	Serum folate concentrations (nmol/L)					Serum B ₁₂ concentrations (pmol/L)				
	Q1 (<13.9)	Q2 (13.9-22.7)	Q3 (22.8-33.0)	Q4 (33.1-49.9)	Q5 (≥50.0)	Q1 (<253)	Q2 (253-332)	Q3 (333-421)	Q4 (422-564)	Q5 (≥565)
CVD mortality										
No. deaths/total	302/1544	164/1536	122/1537	117/1545	94/1538	115/974	74/970	94/974	82/970	102/972
Model 1 ^a	1.41 (1.07, 1.85)	1.00 (ref.)	0.85 (0.61, 1.18)	0.97 (0.71, 1.33)	0.86 (0.63, 1.16)	2.14 (1.33, 3.44)	1.00 (ref.)	1.84 (1.22, 2.78)	1.43 (0.97, 2.11)	2.88 (1.91, 4.36)
Model 2 ^b	1.46 (1.09, 1.96)	1.00 (ref.)	0.90 (0.63, 1.29)	1.06 (0.77, 1.45)	0.96 (0.70, 1.33)	2.05 (1.32, 3.19)	1.00 (ref.)	1.85 (1.24, 2.76)	1.49 (1.01, 2.21)	2.66 (1.75, 4.04)

a Adjusted for age (continuous), sex (male, or female), and race (non-Hispanic white, non-Hispanic black, Mexican American, or other).

b Model 1+ BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, or active), HEI (continuous), duration of diabetes (≤3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes or no), self-reported hypercholesterolemia (yes or no).

eTable 5. HRs (95% CIs) of CVD Mortality According to Serum Folate and Vitamin B₁₂ Levels Among T2D Patients With Further Adjustment of Several Biomarkers and Dietary Factors

	N	Serum folate concentrations (nmol/L)				N	Serum B ₁₂ concentrations (pmol/L)			
		Q1: <16.2	Q2: 16.2-27.4	Q3: 27.5-44.0	Q4: ≥44.1		Q1: <272.3	Q2: 272.3-373.3	Q3: 373.4-519.0	Q4: ≥519.1
No. deaths/total		345/1929	180/1921	159/1925	115/1925		138/1213	88/1216	117/1216	124/1215
Model 1	770 0	1.43 (1.04, 1.98)	1.00 (ref.)	1.17 (0.88, 1.57)	1.03 (0.74, 1.44)	486 0	1.74 (1.20, 2.52)	1.00 (ref.)	1.79 (1.19, 2.71)	2.32 (1.60, 3.35)
Model 2	484 1	1.72 (1.03, 2.87)	1.00 (ref.)	1.27 (0.85, 1.89)	1.01 (0.62, 1.65)	484 1	1.69 (1.15, 2.47)	1.00 (ref.)	1.80 (1.18, 2.74)	2.44 (1.61, 3.72)
Model 3	548 0	1.53 (1.00, 2.34)	1.00 (ref.)	1.22 (0.82, 1.81)	1.20 (0.76, 1.91)	348 1	1.54 (0.93, 2.56)	1.00 (ref.)	1.85 (1.04, 3.29)	2.71 (1.60, 4.62)
Model 4	605 1	1.54 (0.92, 2.61)	1.00 (ref.)	1.24 (0.79, 1.92)	1.26 (0.80, 1.98)	324 3	1.98 (1.04, 3.79)	1.00 (ref.)	2.08 (1.15, 3.76)	3.31 (1.89, 5.78)
Model 5	284 9	1.40 (1.01, 1.94)	1.00 (ref.)	1.23 (0.91, 1.67)	1.11 (0.78, 1.59)	184 2	1.63 (1.10, 2.43)	1.00 (ref.)	1.69 (1.11, 2.58)	2.22 (1.49, 3.30)
Model 6	311 6	1.34 (0.76, 2.37)	1.00 (ref.)	1.34 (0.89, 2.01)	1.05 (0.62, 1.78)	310 9	1.54 (1.00, 2.37)	1.00 (ref.)	1.74 (1.12, 2.71)	2.44 (1.63, 3.65)
Model 7	706 6	1.41 (0.93, 2.04)	1.00 (ref.)	1.37 (0.95, 1.98)	1.16 (0.73, 1.83)	482 5	1.67 (1.12, 2.50)	1.00 (ref.)	1.78 (1.18, 2.70)	2.25 (1.52, 3.33)
Model 8	759 0	1.38 (0.97, 1.95)	1.00 (ref.)	1.30 (0.97, 1.74)	1.15 (0.80, 1.65)	483 1	1.61 (1.05, 2.47)	1.00 (ref.)	1.56 (1.03, 2.38)	2.28 (1.53, 3.41)
Model 9	367 1	1.56 (1.06, 2.12)	1.00 (ref.)	1.61 (1.10, 2.57)	1.34 (0.83, 2.17)	237 8	1.98 (1.07, 3.66)	1.00 (ref.)	1.43 (0.73, 2.79)	3.05 (1.59, 5.83)

Model 10	770 0	1.53 (1.01, 2.30)	1.00 (ref.)	1.38 (0.94, 2.01)	1.14 (0.72, 1.79)	486 0	1.71 (1.16, 2.51)	1.00 (ref.)	1.79 (1.19, 2.70)	2.27 (1.56, 3.32)
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Model 1: Adjusted for age (continuous), sex (male, or female), and race (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes, no), self-reported hypercholesterolemia (yes, no).

Model 2: Model 1 + mutually adjustment of serum folate and vitamin B12.

Model 3: further excluded participants who had CVD history at baseline based on Model 1.

Model 4: Model 1 + CRP.

Model 5: Model 1 + triglycerides, LDL, and HDL.

Model 6: Model 1 + homocysteine.

Model 7: Model 1 + AST, ALT, GGT, LDH.

Model 8: Model 1 + GFR.

Model 9: Model 1 + vitamin B12 supplements and folate supplements.

Model 10: Model 1 + dietary vitamin B12 and folate intake.

eTable 6. HRs (95% CIs) of CVD Mortality According to Serum Vitamin B₁₂ Levels Among Patients With T2D in NHANES III and NHANES 1999-2014

	Serum vitamin B12 concentrations (pmol/L)				
	<272.3	272.3-373.3	373.4-519.0	519.1-701.0	≥701.1
CVD mortality					
No. deaths/total	138/1213	88/1216	117/1216	78/708	46/507
Model 1 ^a	1.80 (1.16, 2.78)	1.00 (ref.)	1.67 (1.08, 2.56)	2.63 (1.69, 4.10)	2.25 (1.45, 3.49)
Model 2 ^b	1.73 (1.19, 2.53)	1.00 (ref.)	1.77 (1.17, 2.67)	2.63 (1.72, 4.05)	1.84 (1.14, 2.98)

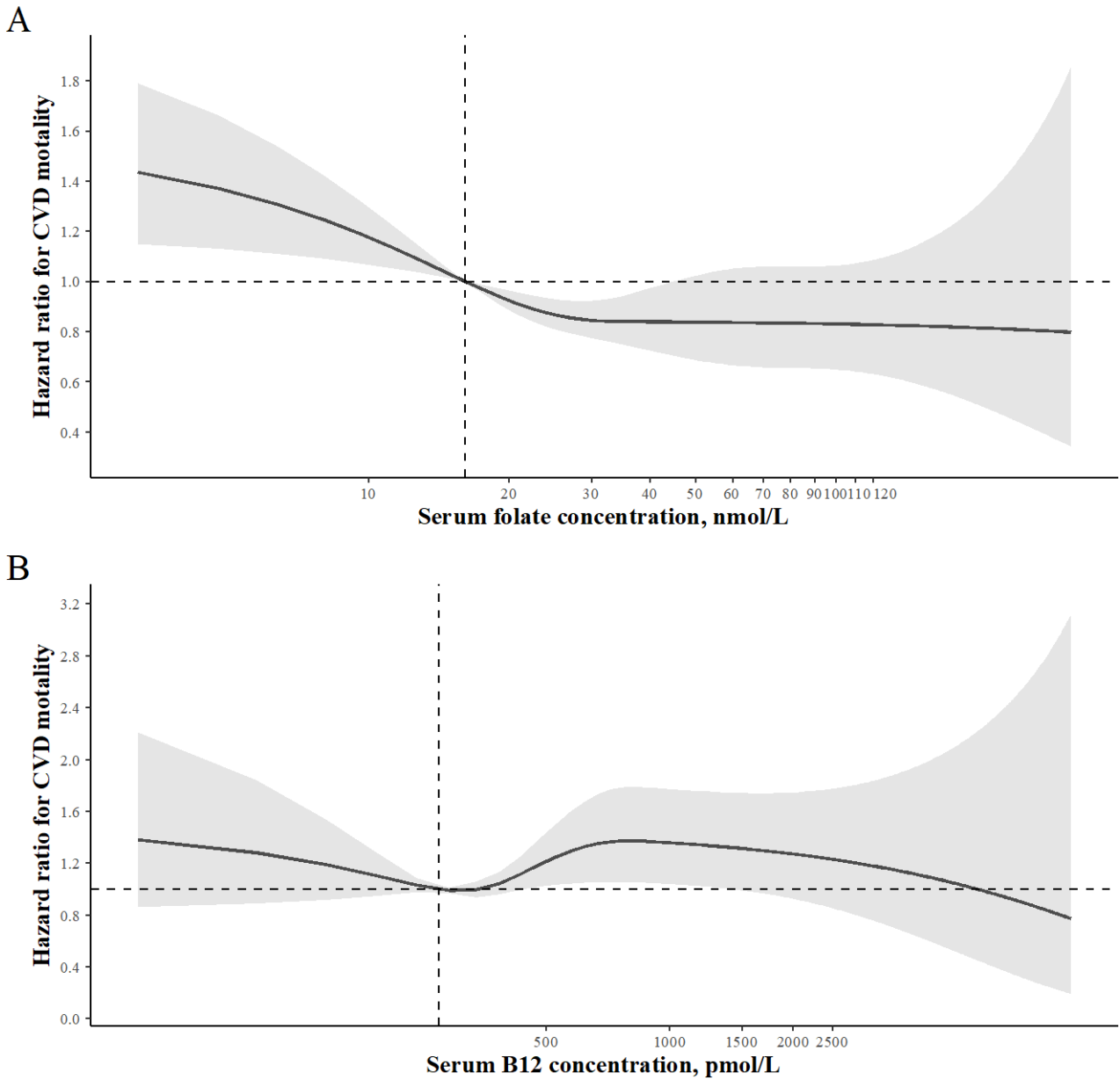
^a Adjusted for age (continuous), sex (male, or female), and race (non-Hispanic white, non-Hispanic black, Mexican American, or other).

^b Model 1+ BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes, no), and self-reported hypercholesterolemia (yes, no).

eTable 7. Spearman Correlation of Baseline Serum Folate and B₁₂ With Age, BMI, HbA1c, CRP, Triglycerides, LDL, HDL, and Homocysteine Among Patients With T2D

		Serum folate	Serum vitamin B12
Age (years)		0.18**	-0.02
	N	7700	4860
BMI (kg/m²)		-0.02	-0.08**
	N	7700	4860
HbA1c (%)		0.01	0.07**
	N	7678	4852
CRP (mg/dL)		-0.15**	0.07**
	N	6051	3243
Total cholesterol (mmol/L)		-0.19**	0.02
	N	7649	4849
Triglyceride (mmol/L)		-0.02*	-0.06**
	N	7616	4838
LDL (mmol/L)		-0.17**	0.02
	N	2880	1853
HDL (mmol/L)		0.09**	0.09**
	N	7613	4831
Homocysteine (umol/L)		-0.09**	-0.22**
	N	3116	3109

P*<.05, *P*<.01



eFigure. Association of Serum Folate (A) and Vitamin B₁₂ (B) With CVD Mortality Among Patients With T2D

HRs (95% CIs) were adjusted for age (continuous), sex (male, or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (<25.0, 25.0-29.9, or ≥30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income level (lower, normal, higher), smoking status (never smoker, ever smoker, or current smoker), drinking status (never drinker, ever drinker, or current drinker), physical activity (inactive, active), HEI (continuous), duration of diabetes (<3, 3-10, or >10 years), diabetes medication use (none, only diabetes pills, only insulin, or diabetes pill and insulin), HbA1c (<7%, ≥7%), self-reported hypertension (yes, no), and self-reported hypercholesterolemia (yes, no). P-nonlinearity=.02 in A. P-nonlinearity=.04 in B.