

Vitamin D Status, Vitamin D Receptor Polymorphisms, and Risk of Microvascular Complications among Individuals with Type 2 Diabetes: A Prospective Study

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Online Supplementary Material

Supplementary Figure 1. Flowchart of the study participants

Supplementary Table 1. Least-square means of cardiometabolic markers according to levels of serum 25(OH)D among patients with T2D in the UK Biobank

Supplementary Table 2. Serum 25(OH)D concentrations according to different VDR genotypes among patients with T2D in the UK Biobank

Supplementary Table 3. Multivariable-adjusted HRs (95% CIs) for associations between VDR polymorphisms and diabetic microvascular complications among patients with T2D in the UK Biobank

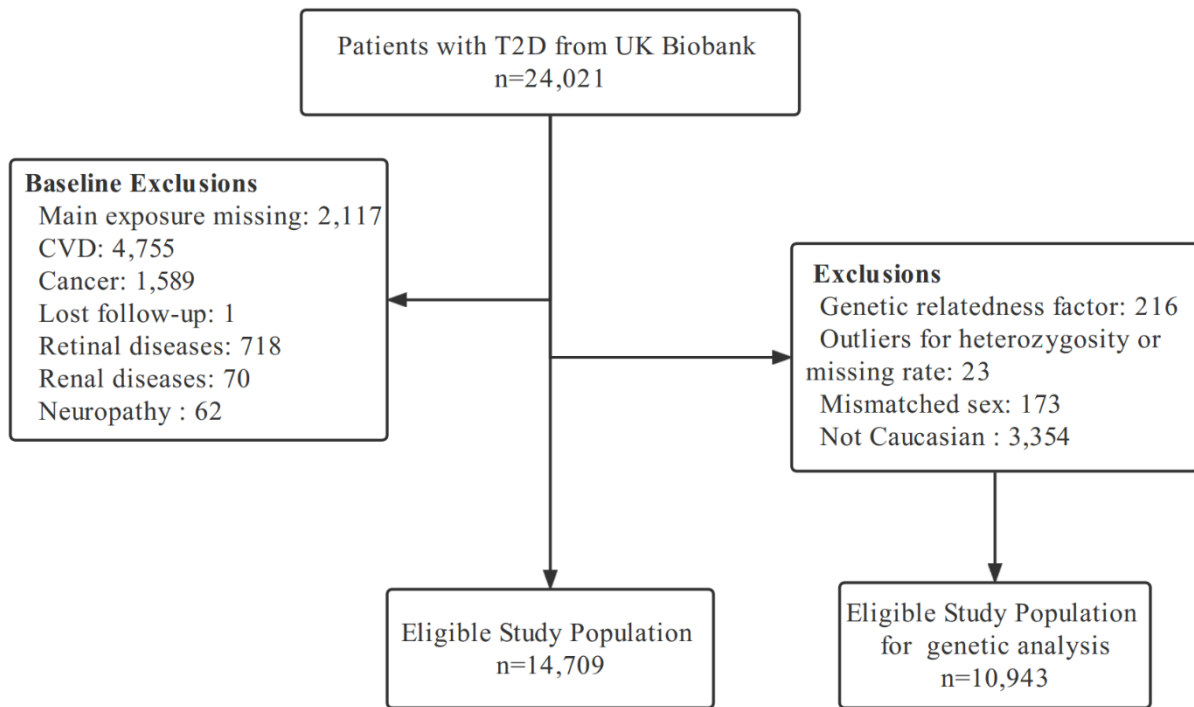
Supplementary Table 4. Multivariable-adjusted HRs (95% CIs) for associations between serum 25(OH)D concentrations and diabetic microvascular complications among patients with T2D according to different genotypes of VDR polymorphisms

Supplementary Table 5. Stratified analyses of the associations between serum 25(OH)D concentrations and composite diabetic microvascular complications among patients with T2D

Supplementary Table 6. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D after excluding outcomes occurred within 2 years of follow up

Supplementary Table 7. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D with further adjustment of CRP

Supplementary Table 8. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D with further adjustment of lipid profiles



Supplementary Figure 1. Flowchart of the study participants

Supplementary Table 1. Least-square means of cardiometabolic markers according to levels of serum 25(OH)D among patients with T2D in the UK Biobank

Characteristics	Serum 25(OH)D concentrations (nmol/L)				<i>P</i> _{trend}
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0	
Glucose (n=13,458, mmol/L)	7.82 ± 0.12	7.35 ± 0.10	7.04 ± 0.11	6.75 ± 0.15	<0.001
HbA _{1c} (n=13,891, mmol/mol)	55.31 ± 0.45	53.58 ± 0.40	52.38 ± 0.43	50.69 ± 0.58	<0.001
High density cholesterol (n=13,469, mmol/L)	1.29 ± 0.01	1.28 ± 0.01	1.29 ± 0.01	1.30 ± 0.01	0.409
Low density cholesterol direct (n=14,663, mmol/L)	2.88 ± 0.02	2.80 ± 0.02	2.70 ± 0.02	2.54 ± 0.03	<0.001
Triglyceride (n=14,681, mmol/L)	2.28 ± 0.04	1.99 ± 0.04	1.67 ± 0.04	1.35 ± 0.05	<0.001
Total cholesterol (n=14,701, mmol/L)	4.83 ± 0.03	4.68 ± 0.03	4.53 ± 0.03	4.30 ± 0.04	<0.001

The least-square mean (\pm SE) were estimated using the general linear model with the adjustment of age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, \geq 5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes/week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, \leq 90, $>$ 90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), and diabetes duration (\leq 3, 3-10 years, $>$ 10 years).

Supplementary Table 2. Serum 25(OH)D concentrations according to different VDR genotypes among patients with T2D in the UK Biobank

	Serum 25(OH)D, nmol/L	<i>P</i> value
rs7975232 (<i>Apal</i>)		0.601
CC (N=2,486)	43.4 (30.5, 58.5)	
AC (N=5,397)	43.7 (30.2, 59.1)	
AA (N=3,060)	42.9 (29.2, 58.6)	
rs1544410 (<i>BsmI</i>)		0.289
CC (N=3,831)	43.9 (30.5, 59.2)	
CT (N=5,267)	43.4 (29.9, 58.9)	
TT (N=1,845)	42.6 (29.3, 57.8)	
rs2228570 (<i>FokI</i>)		0.462
AA (N=1,667)	43.8 (30.1, 59.1)	
AG (N=5,171)	43.3 (30.1, 58.3)	
GG (N=4,105)	43.5 (30.1, 59.4)	
rs731236 (<i>TaqI</i>)		0.238
AA (N=3,882)	43.9 (30.7, 59.3)	
AG (N=5,252)	43.4 (29.8, 58.8)	
GG (N=1,809)	42.6 (29.3, 57.7)	

Data are presented as median (interquartile range).

Supplementary Table 3. Multivariable-adjusted HRs (95% CIs) for associations between VDR polymorphisms and diabetic microvascular complications among patients with T2D in the UK Biobank

	Composite microvascular complications	Diabetic retinopathy	Diabetic nephropathy	Diabetic neuropathy
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
rs7975232 (<i>Apal</i>)				
CC (n=2,486)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
AC (n=5,397)	1.03 (0.88, 1.21)	1.10 (0.85, 1.44)	0.95 (0.77, 1.17)	1.16 (0.82, 1.64)
AA (n=3,060)	1.12 (0.95, 1.33)	1.15 (0.85, 1.51)	1.11 (0.89, 1.39)	1.23 (0.84, 1.79)
rs1544410 (<i>BsmI</i>)				
CC (n=3,831)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
CT (n=5,267)	1.02 (0.89, 1.17)	1.12 (0.89, 1.41)	0.98 (0.82, 1.17)	1.08 (0.80, 1.46)
TT (n=1,845)	1.23 (1.04, 1.46)	1.16 (0.86, 1.55)	1.23 (0.99, 1.54)	1.44 (1.01, 2.05)
rs2228570 (<i>FokI</i>)				
AA (n=1,667)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
AG (n=5,171)	0.92 (0.77, 1.09)	1.01 (0.76, 1.36)	0.96 (0.76, 1.21)	1.04 (0.72, 1.52)
GG (n=4,105)	0.97 (0.81, 1.16)	1.02 (0.75, 1.38)	1.05 (0.83, 1.33)	1.07 (0.72, 1.57)
rs731236 (<i>TaqI</i>)				
AA (n=3,882)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
AG (n=5,252)	1.03 (0.89, 1.18)	1.06 (0.85, 1.33)	0.98 (0.82, 1.18)	1.09 (0.81, 1.47)
GG (n=1,809)	1.23 (1.03, 1.46)	1.17 (0.88, 1.57)	1.21 (0.97, 1.52)	1.41 (0.99, 2.02)

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥ 5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes /week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤ 90 , >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤ 3 , 3-10 years, >10 years), HbA_{1c} ($<7\%$, $\geq 7\%$ [<53 , or ≥ 53 mmol/mol]), genotype measurement batch, and ten principal components of ancestry.

Supplementary Table 4. Multivariable-adjusted HRs (95% CIs) for associations between serum 25(OH)D concentrations and diabetic microvascular complications among patients with T2D according to different genotypes of VDR polymorphisms

	Composite microvascular complications			Diabetic retinopathy			Diabetic nephropathy			Diabetic neuropathy		
	Cases	HR (95% CI) ^a	<i>P</i> _{interaction}	Case	HR (95% CI) ^a	<i>P</i> _{interaction}	Cases	HR (95% CI) ^a	<i>P</i> _{interaction}	Cases	HR (95% CI) ^a	<i>P</i> _{interaction}
rs7975232 (<i>Apal</i>)			0.841			0.959			0.552			0.406
CC (n=2,486)	224	0.85 (0.61, 1.19)		77	0.68 (0.39, 1.19)		136	0.90 (0.58, 1.39)		45	0.72 (0.34, 1.51)	
AC (n=5,397)	510	0.67 (0.54, 0.83)		193	0.76 (0.53, 1.08)		283	0.54 (0.40, 0.72)		118	0.67 (0.43, 1.04)	
AA (n=3,060)	318	0.75 (0.58, 0.99)		113	0.74 (0.47, 1.17)		191	0.61(0.43, 0.86)		74	0.84 (0.48, 1.47)	
rs1544410 (<i>BsmI</i>)			0.274			0.159			0.286			0.600
CC (n=3,831)	350	0.78 (0.60, 1.01)		121	0.65 (0.42, 1.01)		208	0.83 (0.59, 1.18)		73	0.69 (0.40, 1.21)	
CT (n=5,267)	489	0.72 (0.58, 0.90)		190	1.02 (0.71, 1.45)		275	0.52 (0.39, 0.69)		110	0.71 (0.45, 1.12)	
TT (n=1,845)	213	0.65 (0.46, 0.91)		72	0.42 (0.23, 0.75)		127	0.63 (0.41, 0.97)		54	0.74 (0.37, 1.50)	
rs2228570 (<i>FokI</i>)			0.329			0.533			0.362			0.751
AA (n=1,667)	174	0.80 (0.56, 1.16)		60	0.65 (0.35, 1.22)		97	0.67 (0.41, 1.10)		36	1.55 (0.67, 3.58)	
AG (n=5,171)	478	0.76 (0.61, 0.95)		179	0.81 (0.56, 1.16)		276	0.68 (0.50, 0.91)		110	0.65 (0.41, 1.02)	
GG (n=4,105)	400	0.70 (0.54, 0.89)		144	0.72 (0.48, 1.08)		237	0.58 (0.42, 0.79)		91	0.72 (0.43, 1.20)	
rs731236 (<i>TaqI</i>)			0.244			0.158			0.245			0.637
AA (n=3,882)	354	0.78 (0.61, 1.02)		126	0.67 (0.44, 1.03)		211	0.82 (0.58, 1.17)		74	0.73 (0.42, 1.27)	
AG (n=5,252)	491	0.71 (0.57, 0.88)		184	0.98 (0.68, 1.41)		277	0.51 (0.39, 0.68)		111	0.71 (0.45, 1.12)	
GG (n=1,809)	207	0.67 (0.47, 0.94)		73	0.45 (0.25, 0.80)		122	0.64 (0.41, 1.00)		52	0.75 (0.36, 1.55)	

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥ 5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes /week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤ 90 , >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤ 3 , 3-10 years, >10 years), HbA1c ($<7\%$, $\geq 7\%$ [<53 nmol/L, ≥ 53 nmol/L]), genotype measurement batch, and ten principal components of ancestry. ^aHR indicated the risk for per one unit increment in serum 25(OH)D concentration.

Supplementary Table 5. Stratified analyses of the associations between serum 25(OH)D concentrations and composite diabetic microvascular complications among patients with T2D

	Serum 25(OH)D concentrations (nmol/L)				<i>P</i> interaction	Natural log-transformed 25(OH)D
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0		
Age, years					0.708	
≤60	137/1,823 1 (ref.)	227/3,257 0.94 (0.75, 1.17)	69/1,572 0.59 (0.43, 0.81)	12/411 0.42 (0.23, 0.78)		0.75 (0.60, 0.92)
>60	172/1,148 1 (ref.)	407/3,402 0.77 (0.64, 0.93)	268/2,370 0.74 (0.60, 0.92)	78/726 0.71 (0.53, 0.96)		0.76 (0.65, 0.89)
Sex					0.306	
Female	123/1,248 1 (ref.)	255/2,568 0.94 (0.75, 1.17)	111/1,432 0.74 (0.56, 0.98)	29/409 0.68 (0.44, 1.05)		0.80 (0.66, 0.98)
Male	186/1,723 1 (ref.)	379/4,091 0.77 (0.64, 0.93)	226/2,510 0.68 (0.55, 0.86)	61/728 0.64 (0.47, 0.89)		0.72 (0.61, 0.85)
BMI, kg/m²					0.165	
<30	112/1,196 1 (ref.)	208/2,791 0.72 (0.56, 0.92)	157/2,030 0.68 (0.52, 0.91)	43/702 0.50 (0.34, 0.75)		0.70 (0.57, 0.85)
≥30	197/1,775 1 (ref.)	426/3,868 0.92 (0.77, 1.10)	180/1,912 0.72 (0.58, 0.91)	47/435 0.86 (0.61, 1.21)		0.80 (0.68, 0.94)
Smoking status					0.182	
Current/ past	172/1,462 1 (ref.)	344/3,406 0.79 (0.65, 0.96)	200/2,130 0.69 (0.55, 0.87)	52/633 0.61 (0.43, 0.85)		0.69 (0.59, 0.82)
Never	135/1,481 1 (ref.)	286/3,224 0.86 (0.69, 1.07)	136/1,808 0.71 (0.54, 0.93)	38/503 0.70 (0.47, 1.04)		0.80 (0.66, 0.97)

Physical activity level					0.030
<150 MET minutes/week	191/1,712	326/3,448	149/1,763	39/478	
	1 (ref.)	0.76 (0.63, 0.92)	0.66 (0.52, 0.84)	0.70 (0.48, 1.01)	0.68 (0.57, 0.81)
≥150 MET-minutes/week	83/944	228/2,586	162/1,891	47/591	
	1 (ref.)	0.90 (0.69, 1.17)	0.81 (0.60, 1.08)	0.67 (0.45, 1.00)	0.83 (0.67, 1.03)
Diabetes duration (years)					0.325
≤3	80/1,145	141/2,547	97/1,534	29/438	
	1 (ref.)	0.72 (0.54, 0.96)	0.78 (0.56, 1.10)	0.77 (0.48, 1.23)	0.77 (0.59, 0.99)
>3	215/1,620	463/3,725	226/2,210	59/632	
	1 (ref.)	0.86 (0.73, 1.02)	0.66 (0.54, 0.82)	0.62 (0.45, 0.85)	0.72 (0.62, 0.84)
HbA_{1c}					0.512
<7% (<53 nmol/L)	154/1,736	330/4,228	201/2,697	61/824	
	1 (ref.)	0.78 (0.64, 0.95)	0.71 (0.56, 0.90)	0.67 (0.48, 0.93)	0.75 (0.64, 0.90)
≥7% (≥53 nmol/L)	155/1,235	301/2431	134/1,245	28/295	
	1 (ref.)	0.89 (0.73, 1.10)	0.71 (0.54, 0.91)	0.61 (0.40, 0.94)	0.75 (0.62, 0.90)

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes /week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤90, >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤3, 3-10 years, >10 years), HbA_{1c} (<7%, ≥7% [<53 nmol/L, ≥ 53 nmol/L]). The strata variable was not included in the model when stratifying by itself.

Supplementary Table 6. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D after excluding outcomes occurred within 2 years of follow up

	Serum 25(OH)D concentrations (nmol/L)				<i>P</i> _{trend}	Natural log-transformed 25(OH)D
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0		
Composite microvascular complications	265/2,927	559/6,584	301/3,906	80/1,127		
	1 (ref.)	0.85 (0.73, 1.00)	0.74 (0.61, 0.89)	0.68 (0.52, 0.89)	<0.001	0.77 (0.68, 0.88)
Diabetic retinopathy	95/2,927	202/6,584	114/3,906	23/1,127		
	1 (ref.)	0.90 (0.70, 1.16)	0.81 (0.60, 1.10)	0.56 (0.34, 0.92)	0.023	0.76 (0.61, 0.95)
Diabetic nephropathy	162/2,927	337/6,584	174/3,906	47/1,127		
	1 (ref.)	0.80 (0.66, 0.97)	0.66 (0.52, 0.83)	0.61 (0.43, 0.87)	<0.001	0.71 (0.60, 0.85)
Diabetic neuropathy	62/2,927	101/6,584	63/3,906	14/1,127		
	1 (ref.)	0.72 (0.51, 1.00)	0.74 (0.49, 1.10)	0.59 (0.32, 1.12)	0.131	0.80 (0.60, 1.09)

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes/week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤90, >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤3, 3-10 years, >10 years), HbA_{1c} (<7%, ≥7% [<53 nmol/L, ≥ 53 nmol/L]).

Supplementary Table 7. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D with further adjustment of CRP

	Serum 25(OH)D concentrations (nmol/L)				<i>P</i> _{trend}	Natural log-transformed 25(OH)D
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0		
Composite microvascular complications	309/2,971	634/6,659	337/3,942	90/1,137		
	1 (ref.)	0.83 (0.72, 0.96)	0.71 (0.60, 0.84)	0.66 (0.51, 0.85)	<0.001	0.75 (0.66, 0.85)
Diabetic retinopathy	114/2,971	248/6,659	134/3,942	31/1,137		
	1 (ref.)	0.91 (0.72, 1.15)	0.78 (0.59, 1.04)	0.62 (0.40, 0.95)	0.014	0.75 (0.61, 0.92)
Diabetic nephropathy	182/2,971	367/6,659	183/3,942	49/1,137		
	1 (ref.)	0.78 (0.65, 0.94)	0.61 (0.48, 0.77)	0.56 (0.40, 0.79)	<0.001	0.67 (0.57, 0.79)
Diabetic neuropathy	80/2,971	128/6,659	76/3,942	14/1,137		
	1 (ref.)	0.71 (0.53, 0.96)	0.72 (0.50, 1.03)	0.49 (0.27, 0.90)	0.031	0.77 (0.59, 1.01)

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes/week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤90, >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤3, 3-10 years, >10 years), HbA_{1c} (<7%, ≥7% [<53 nmol/L, ≥ 53 nmol/L]), CRP (mg/L, continuous).

Supplementary Table 8. Multivariable-adjusted HRs (95% CIs) of diabetic microvascular complications according to serum 25(OH)D concentrations among patients with T2D with further adjustment of lipid profiles

	Serum 25(OH)D concentrations (nmol/L)				<i>P</i> _{trend}	Natural log-transformed 25(OH)D
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0		
Composite microvascular complications	309/2,971	634/6,659	337/3,942	90/1,137		
	1 (ref.)	0.84 (0.73, 0.97)	0.72 (0.61, 0.86)	0.68 (0.52, 0.88)	<0.001	0.77 (0.67, 0.87)
Diabetic retinopathy	114/2,971	248/6,659	134/3,942	31/1,137		
	1 (ref.)	0.90 (0.72, 1.14)	0.77 (0.58, 1.03)	0.61 (0.39, 0.94)	0.013	0.74 (0.60, 0.91)
Diabetic nephropathy	182/2,971	367/6,659	183/3,942	49/1,137		
	1 (ref.)	0.78 (0.65, 0.95)	0.62 (0.49, 0.79)	0.58 (0.41, 0.83)	<0.001	0.68 (0.58, 0.81)
Diabetic neuropathy	80/2,971	128/6,659	76/3,942	14/1,137		
	1 (ref.)	0.74 (0.55, 1.00)	0.78 (0.54, 1.12)	0.55 (0.30, 1.02)	0.100	0.83 (0.63, 1.10)

HR was adjusted for age (continuous), sex (female, male), ethnic (White people, non-White people [including Black people, Asian people, and multiethnic participants]), the Townsend Deprivation Index (continuous), education (College/University degree, A levels/AS levels or equivalent or O levels/GCSEs or equivalent or other professional qualifications, none of the above), employed (yes, no), smoking status (never, past, current), drinking status (never, 1-2 times/week, 3-4 times/week, ≥5 times/week), healthy diet (yes, no), use of multivitamin/mineral supplements (yes, no), total physical activity level (MET-minutes/week, continuous), time spend outdoors in summer (continuous, hours/day), season of blood drawn (March to May, June to August, September to November, December to February), estimated glomerular filtration rate (eGFR, ≤90, >90 mL/min/1.73 m²), BMI (continuous), history of hypertension (yes, no), and hypercholesterolemia (yes, no), diabetic medication (no insulin or pills, only diabetes pills, or insulin and/or others), diabetes duration (≤3, 3-10 years, >10 years), HbA_{1c} (<7%, ≥7% [<53 nmol/L, ≥ 53 nmol/L]), LDL (mmol/L, continuous), HDL (mmol/L, continuous), triglyceride (mmol/L, continuous).