Supplementary materials

MMA measurement

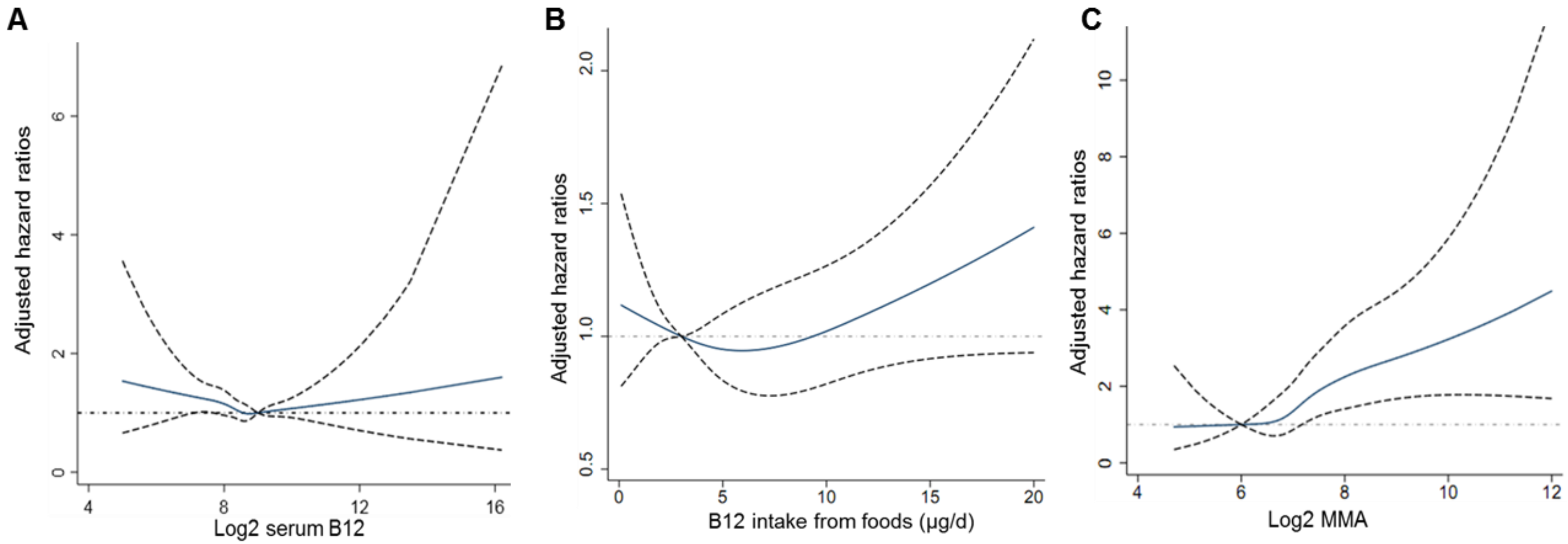
MMA was measured in venous plasma and/or serum by gas chromatography-mass spectrophotometry (GC/MS) in NHANES 1999-2004 and measured by liquid chromatography-mass spectrophotometry (LC-MS/MS) in NHANES 2011-2014 after butanol derivatization. According to the in-house comparison for the measurement of MMA (n = 326), The LC-MS/MS assay showed excellent correlation (r = 0.99) and agreement (Deming regression, Bland-Altman analysis) compared to the prior GC/MS method. MMA concentrations in pairs of serum and plasma were comparable. The protocols have been described before (*Anal Bioanal Chem. 2015;407(11):2955-64*).

According to the GC/MS method, High-performance GC/MS (Model 6890 GC system and Model 5973 mass selective detector) was procured from Hewlett-Packard, San Fernando, CA. DB-5MS capillary GC column, 0.25mm x 30m, 0.25-μm (J&W Scientific, Folsom, CA) was used for chromatographic separation. In brief, 275 μL specimens with internal standard solution supplemented by isotope-labeled methyl-d^3-malonic acid (d^3MMA) were extracted and subsequently derivatized with cyclohexanol to produce a dicyclohexyl ester. After derivatization and separation (chromatographic run time, 15 min.), the effluent part from the GC column was monitored with a mass selective detector by the selected ion monitoring process. MMA levels were quantitated using the peak area ratios of MMA and the internal standard, isotope-labeled d^3MMA. There was a favorable linear pattern for MMA in the range of 50-2000 nmol/L. Samples with MMA concentrations > 400 nmol/L were repeatedly analyzed. The total CV was 4-10% and the mean recovery rate was 96.0±1.9%, as described in MMA GC-MS protocols (https://wwwn.cdc.gov/nchs/data/nhanes/1999-2000/labmethods/lab06_met_methylmalonic_acid.pdf).

Because GC/MS method required 275 μL of sample and had a low throughput (36 samples/run), Ekaterina and colleagues developed and validated an LC-MS/MS method for MMA detection in NHANES 2011-2014. Compared to GC/MS procedures, LC-MS/MS method required less sample volume (75ul), and had shorter run time (6 min), higher sensitivity (the limit of detection 22.1 nmol/L), and higher throughput (160 samples/run). Thermo-Electron HPLC System and Thermo-Electron TSQ triple quadrupole mass spectrometer were purchased from Thermo Scientific, West Palm Beach, FL. The Hypersil Gold C18 column (2.1 mm × 50 mm, 1.9 μm particle size, Thermo Fisher Scientific) was selected because it allowed an excellent separation between MMA and succinic acid (SA) with relatively short chromatography run time, narrow analyte peaks, and excellent service life. MMA is extracted from 75 μL of sample along with an added internal standard (d3-MMA) via liquid-liquid extraction method with tert-butylmethylether. Then, the extracted organic acid is derivatized with butanol to form a dibutylester. The butanol is evaporated under vacuum and the derivatized sample is reconstituted in acetonitrile/water (v/v 50/50). MMA was chromatographically separated from SA using isocratic mobile phase (0.1% acetic acid: methanol 40:60 (v/v), 0.4 mL/min, 35 ℃) within 6 min (retention time 3.47min for SA and 4.25 min for MMA). Multiple reaction monitoring (MRM) was performed in positive electrospray ionization mode, with two transitions each for MMA (m/z 231 → 119 and 175.1) and for d3-MMA (m/z 234.1 → 122.1 and 178.1). According to the in-house comparisons of aqueous calibration and calibration in serum, slopes for the two calibration curves (serum vs. water) were equivalent (less than ± 5% difference), suggesting a minor matrix effect. The sum of the two signals was used for quantitation. The method is linear in the range of 25 to 2500 nmol/L. The total coefficient of variation was 4.9–7.9%, and the recovery rate was 94.0 ±5.5%. The detailed protocols were publicly available (https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/labmethods/MMA_G_MET.pdf).

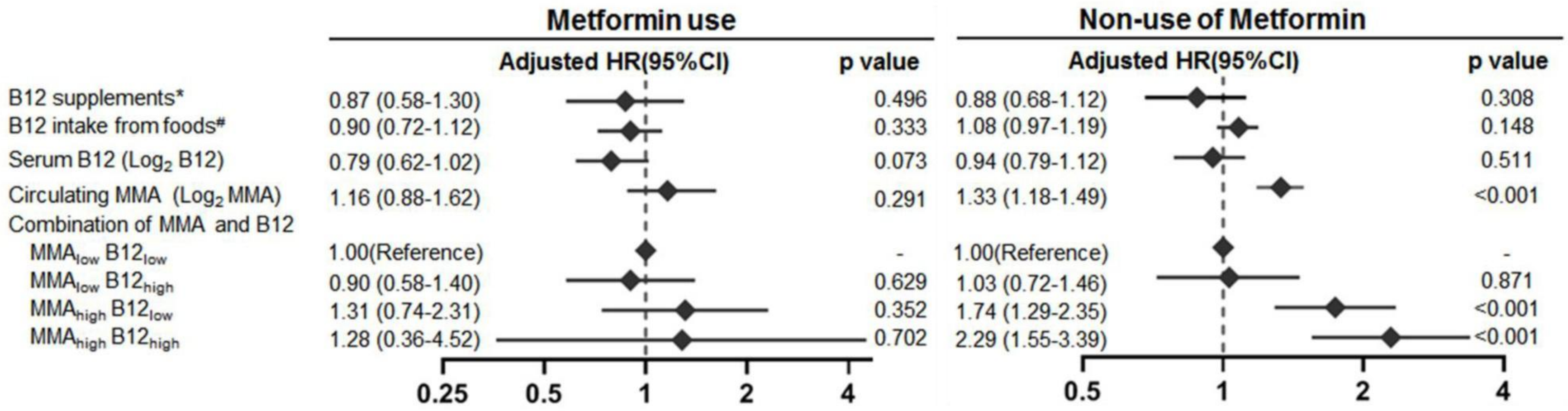
Supplementary Figure and Tables

Supplementary Figure 1. The association of all-cause mortality with serum B12, B12 intake from foods, circulating MMA visualized by restricted cubic spline curves



Restricted cubic spline curve showed the adjusted hazard ratios of **(A)** log2 transformed serum B12, **(B)** B12 intake from foods, **(C)** log2 MMA for all-cause mortality based on Cox regression model. Knots included the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the exposure factor. The model was fully adjusted for age, sex and race/ethnicity, smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum B12 (only for MMA model), B12 supplements (only for B12 intake from foods model), eGFR, HbA1c, metformin, duration of diabetes, UACR, and diabetic complications. The solid line represented point estimates, and dashed lines represented 95% CIs.

Supplementary Figure 2. Associations of all-cause mortality with serum and dietary cobalamin, MMA, and sensitivity to cobalamin in metformin users or nonusers



The associations of all-cause mortality with cobalamin, MMA and decreased cobalamin sensitivity stratified by metformin use. *vitamin B12 supplement use versus nonuse, # cobalamin intake from foods increase per 5 μg/d. HR (95% CI) was estimated by weighted Cox regression analyses after adjustment for age, sex and race/ethnicity, smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum cobalamin (only for MMA model), eGFR, HbA1c, duration of diabetes, UACR, and diabetic complications. The model for cobalamin supplements was further adjusted for cobalamin intake from foods and vice versa.

Supplementary Table 1. Baseline characteristcs across the tertiles of serum B12 among diabetic patients

	Serum vitamin B12 (pmol/L)			
	Tertile 1	**Tertile 2**	**Tertile 3**	**p trend**
Serum B12 (pg/ml)	597.4 ± 19.3	582.2 ± 17.0	617 ± 18.6	-
Age (year)	59.6 ± 0.5	58.1 ± 0.6	60.3 ± 0.4	0.325
Male (%)	53.38	54.21	46.89	0.028
Race/ethnicity (%)				
Non-Hispanic White	67.17	58.57	56.33	<0.001
Non-Hispanic Black	10.63	16.24	19.00	<0.001
Hispanic-Mexican	7.60	9.82	9.01	0.258
Other Ethnicity	14.61	15.37	15.66	0.603
Smoking status (%)				
Never	49.3	48.62	44.51	0.097
Former	33.76	32.81	37.95	
Current	16.94	18.57	17.54	
BMI (kg/m2)	33.7 ± 0.4	32.5 ± 0.3	31.9 ± 0.4	<0.001
TC/HDL-C ratio	2.6 ± 0.1	2.3 ± 0.1	2.2 ± 0.2	0.071
Hypertension (%)	71.16	66.99	69	0.384
Cancer (%)	27.06	23.67	24.07	0.151
CVD (%)	14.59	14.2	15.62	0.638
eGFR (mL/min per 1.73m²)	85.3 ± 0.9	87.5 ± 1	81.5 ± 1.1	0.014
UACR (mg/g)	101.2 ± 12.9	149 ± 24.9	154.8 ± 23.9	0.031
HbA1c (%)	7.3 ± 0.1	7.5 ± 0.1	7.6 ± 0.1	0.002
HbA1c (mmol/mol)	55.8 ± 0.8	58.2 ± 0.8	59.3 ± 0.8	0.002
Duration of diabetes (year)	8.7 ± 0.5	8.4 ± 0.4	9.5 ± 0.4	0.161
Diabetic complications (%)	25.23	29.78	27.28	0.291
Retinopathy (%)	13.15	16.38	16.33	0.064
Foot ulcer/sore (%)	3.87	3.06	3.61	0.755
Peripheral neuropathy (%)	14.53	16.92	13.89	0.777
Metformin (%)	46.41	38.14	32.84	<0.001
B12 supplements (%)	25.21	32.3	52.39	<0.001
B12 intake from foods (μg/d)	4.5 ± 0.3	4.9 ± 0.2	4.9 ± 0.2	0.324
Circulating MMA (nmol/L)	256.3 ± 18.9	169.9 ± 4.8	170.2 ± 6.3	<0.001

Data are represented as weighted percentage or mean (SE). P trend was estimated by weighted linear or logistic regression. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; TC, total cholesterol; UACR, urinary albumin-creatinine ratio.

Supplementary Table 2. Baseline characteristics across the tertiles of B12 intake from foods in patients with T2DM

	Vitamin B12 intake from foods (μg/d)			
	Tertile 1	Tertile 2	Tertile 3	p trend
B12 intake from foods (μg/d)	1.4 ± 0.1	3.4 ± 0.1	8.6 ± 0.3	-
Age (year)	59.5 ± 0.5	59.5 ± 0.5	58.7 ± 0.7	0.297
Male (%)	37.66	51.22	63.93	<0.001
Race/ethnicity (%)				
Non-Hispanic White	53.51	61.4	68.95	<0.001
Non-Hispanic Black	18.91	14.67	11.67	<0.001
Hispanic-Mexican	8.842	9.197	7.698	0.279
Other Ethnicity	18.74	14.73	11.69	0.001
Smoking status (%)				
Never	51.15	46.01	45.33	0.097
Former	29.59	35.27	38.72	
Current	19.26	18.72	15.95	
BMI (kg/m2)	32.1 ± 0.3	32.9 ± 0.3	33.3 ± 0.5	0.051
TC/HDL-C ratio	2.2 ± 0.1	2.2 ± 0.1	2.7 ± 0.1	0.018
Hypertension (%)	70.64	67.85	69.29	0.693
Cancer (%)	28.99	23.59	24.08	0.056
CVD (%)	14.96	13.64	16.27	0.582
eGFR (mL/min per 1.73m^2)	83.2 ± 1.1	85.5 ± 1	85.9 ± 1	0.079
UACR (mg/g)	123.4 ± 19.4	138.1 ± 19.5	121.2 ± 18	0.901
HbA1c (%)	7.3 ± 0.1	7.5 ± 0.1	7.4 ± 0.1	0.364
HbA1c (mmol/mol)	56.2 ± 0.7	58.9 ± 1	57.4 ± 0.8	0.364
Duration of diabetes (year)	9.1 ± 0.5	8.4 ± 0.5	8.9 ± 0.4	0.846
Diabetic complications (%)	28.43	26.05	27.21	0.696
Retinopathy (%)	16.92	14.81	12.66	0.019
Foot ulcer/sore (%)	2.97	3.214	4.454	0.124
Peripheral neuropathy (%)	15.93	13.67	17	0.575
Metformin (%)	36.05	37.3	43.84	0.023
B12 supplements(%)	36.01	32.24	39.85	0.162
Serum B12 (pg/ml)	597.4 ± 19.3	582.2 ± 17	617.0 ± 18.6	0.407
Circulating MMA (nmol/L)	211.1 ± 13.6	210.8 ± 18.9	184.3 ± 6.2	0.078

Data are represented as weighted percentage or mean (SE). P trend was estimated by weighted linear or logistic regression. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; TC, total cholesterol; UACR, urinary albumin-creatinine ratio.

Supplementary Table 3. Baseline characteristics in patients with T2DM with or without B12 supplement use

	Vitamin B12 supplements		
	Non-use	**Use**	**p value**
Age (year)	58 ±0.4	61.6 ±0.5	<0.001
Male (%)	51.93	51.22	0.719
Race/ethnicity (%)			
Non-Hispanic White	55.81	70.34	
Non-Hispanic Black	16.90	11.70	
Hispanic-Mexican	10.78	5.15	<0.001
Other Ethnicity	16.51	12.80	
Smoking status (%)			
Never	48.16	46.63	0.001
Former	31.94	39.70	
Current	19.9	13.67	
BMI (kg/m2)	33.2 ±0.3	31.9 ±0.3	<0.001
TC/HDL-C ratio	2.4 ±0.1	2.4 ±0.1	0.895
Hypertension (%)	67.3	72.38	0.031
Cancer (%)	24.48	26.00	0.512
CVD (%)	13.28	17.44	0.012
eGFR (mL/min per 1.73m^2)	86.4 ±0.8	82.1 ±0.9	0.001
UACR (mg/g)	148.2 ± 15	106.2 ± 18.1	0.081
HbA1c (%)	7.6 ± 0.1	7.1 ± 0.1	<0.001
HbA1c (mmol/mol)	59.4 ± 0.6	54.5 ± 0.8	<0.001
Duration of diabetes (year)	8.9 ± 0.3	8.7 ± 0.4	0.636
Diabetic complications (%)	27.11	27.81	0.699
Retinopathy (%)	15.38	14.84	0.696
Foot ulcer/sore (%)	3.59	3.41	0.839
Peripheral neuropathy (%)	14.84	15.63	0.635
Metformin (%)	39.04	40.43	0.590
B12 intake from foods (μg/d)	4.7 ± 0.2	4.8 ± 0.2	0.842
Serum B12 (pg/ml)	535.4 ± 11.2	714.2 ± 19.9	<0.001
Circulating MMA (nmol/L)	196.4 ± 4.6	210.6 ± 17.9	0.439

Data are represented as weighted percentage or mean (SE). P trend was estimated by weighted t-student or chi-square test. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; TC, total cholesterol; UACR, urinary albumin-creatinine ratio.

Supplementary Table 4. Baseline characteristcs across the tertiles of circulating MMA among diabetic patients

	Circulating MMA (nmol/L)			
	Tertile 1	**Tertile 2**	**Tertile 3**	**p trend**
Circulating MMA (nmol/L)	96.1 ± 0.9	148.7 ± 0.8	361.5 ± 20.7	-
Age (year)	53 ± 0.5	59.2 ± 0.5	65.6 ± 0.5	<0.001
Male (%)	51.51	51.14	52.41	0.765
Race/ethnicity (%)				
Non-Hispanic White	48.95	62.78	71.1	<0.001
Non-Hispanic Black	19.95	14.98	10.23	<0.001
Hispanic-Mexican	13.77	7.66	4.97	<0.001
Other Ethnicity	17.33	14.58	13.7	0.024
Smoking status (%)				
Never	52.06	46.64	44.25	0.017
Former	27.29	34.54	42.26	
Current	20.65	18.82	13.5	
BMI (kg/m2)	32.8 ± 0.3	32.9 ± 0.3	32.6 ± 0.4	0.611
TC/HDL-C ratio	2.3 ± 0.1	2.3 ± 0.1	2.5 ± 0.1	0.282
Hypertension (%)	58.72	70.54	77.9	<0.001
Cancer (%)	14.71	21.03	39.45	<0.001
CVD (%)	10.17	15.35	18.71	<0.001
eGFR (mL/min per 1.73m^2)	100.4 ± 0.7	86.6 ± 0.8	67.7 ± 1.0	<0.001
UACR (mg/g)	50.2 ± 6.5	73.4 ± 8.7	284.4 ± 32.2	<0.001
HbA1c (%)	7.6 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	0.007
HbA1c (mmol/mol)	59.1 ± 0.8	57.7 ± 0.8	56.1 ± 0.8	0.007
Duration of diabetes (year)	6.6 ± 0.3	8.5 ± 0.5	11.4 ± 0.5	<0.001
Diabetic complications (%)	24.9	22.68	34.74	0.001
Retinopathy (%)	11.92	12.49	21.27	<0.001
Foot ulcer/sore (%)	2.528	2.534	5.55	0.009
Peripheral neuropathy (%)	14.84	11.79	18.93	0.076
Metformin (%)	40.80	43.30	34.32	0.027
B12 supplements(%)	36.37	38.45	32.56	0.167
B12 intake from foods (μg/d)	5.1 ± 0.4	4.9 ± 0.2	4.3 ± 0.1	0.042
Serum B12 (pg/ml)	671.9 ± 20.4	621.3 ± 18.8	504.7 ± 13.3	<0.001

Data are represented as weighted percentage or mean (SE). P trend was estimated by weighted linear or logistic regression. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, High-density lipoprotein cholesterol; TC, total cholesterol; UACR, urinary albumin-creatinine ratio.

Supplementary Table 5. The associations of all-cause mortality with serum and dietary cobalamin and MMA in diabetic patients

	Events/ Total num	Unadjusted		Model 1		Model 2		Model 3	
		HR(95%CI)	p value	HR(95%CI)	p value	HR(95%CI)	p value	HR(95%CI)	p value
Serum B12									
$\log_2$ B12	865/3,277	0.96(0.83-1.13)	0.641	1.00(0.87-1.15)	0.998	0.92(0.80-1.06)	0.227	0.92(0.80-1.06)	0.268
Tertile 1	321/1093	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	289/1095	0.89(0.73-1.10)		1.01(0.83-1.22)		0.92(0.75-1.14)		0.93(0.75-1.15)	
Tertile 3	255/1089	0.96(0.76-1.21)	*0.894	0.97(0.76-1.23)	*0.749	0.82(0.61-1.09)	*0.120	0.83(0.63-1.10)	*0.191
B12 supplement									
Use vs. Non-use	289/1047 vs. 576/2230	0.99(0.79-1.23)	0.906	0.84(0.69-1.02)	0.077	0.87(0.70-1.07)	0.175	0.86(0.70-1.07)	0.176
B12 intake from foods									
increase per 5 μg/d	865/3277	0.98(0.91-1.05)	0.562	0.99(0.93-1.06)	0.780	1.04(0.96-1.12)	0.343	1.04(0.96-1.12)	0.362
Tertile 1	284/1017	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	270/1013	0.85(0.69-1.04)		0.82(0.68-0.98)		0.76(0.61-0.95)		0.76(0.61-0.95)	
Tertile 3	263/1012	0.95(0.74-1.22)	*0.740	0.90(0.70-1.14)	*0.436	0.89(0.69-1.16)	*0.467	0.89(0.68-1.15)	*0.433
Circulating MMA									
$\log_2$ MMA	865/3277	1.67(1.47-1.88)	<0.001	1.41(1.26-1.58)	<0.001	1.31(1.18-1.45)	<0.001	1.31(1.18-1.46)	<0.001
Tertile 1	166/1101	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	262/1089	2.11(1.69-2.64)		1.55(1.22-1.97)		1.46(1.12-1.91)		1.45(1.11-1.90)	
Tertile 3	437/1087	4.14(3.15-5.46)	*<0.001	2.40(1.85-3.11)	*<0.001	1.71(1.27-2.31)	*0.002	1.72(1.27-2.33)	*0.002

B12, vitamin B12, cobalamin. MMA, methylmalonic acid. *p for trend across the tertiles of B12 or MMA. HR (95% CI) was estimated by weighted Cox regression analyses. Model 1 was adjusted for age, sex, and race/ethnicity. Model 2 was additionally adjusted for smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum cobalamin (continuous, only for MMA model 2), eGFR, HbA1c, metformin, duration of diabetes, UACR, and diabetic complications. Models for cobalamin supplements were further adjusted for cobalamin intake from foods (μg/day, continuous) and vice versa. Model 3 was adjusted for covariates in Model 2 except for metformin use.

Supplementary Table 6. The associations of heart-specific mortality with B12 or MMA in patients with T2DM

	Events/	Unadjusted		Model 1		Model 2		Model 3	
	Total num	HR(95%CI)	p value*	HR(95%CI)	p value	HR(95%CI)	p value	HR(95%CI)	p value
Serum B12									
log_2 B12	200/3277	0.94(0.71-1.25)	0.669	1.00(0.78-1.28)	0.979	0.85(0.65-1.10)	0.212	0.87(0.67-1.13)	0.286
Tertile 1	77/1093	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	58/1095	0.71(0.49-1.03)		0.82(0.57-1.18)		0.85(0.54-1.34)		0.86(0.55-1.35)	
Tertile 3	65/1089	1.14(0.81-1.61)	*0.233	1.19(0.84-1.68)	*0.202	1.04(0.66-1.63)	*0.104	1.08(0.69-1.69)	*0.781
B12 supplement									
Users vs. Nonusers	132/2230 vs. 68/1047	1.11(0.78-1.59)	0.554	0.96(0.68-1.35)	0.810	0.89(0.62-1.28)	0.532	0.90(0.63-1.29)	0.553
B12 intake from foods									
increase per 5μg/d	200/3277	0.88(0.65-1.20)	0.413	0.84(0.57-1.25)	0.382	0.96(0.68-1.34)	0.804	0.95(0.68-1.34)	0.784
Tertile 1	69/1017	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	66/1013	0.75(0.47-1.20)		0.68(0.43-1.06)		0.67(0.38-1.16)		0.67(0.38-1.17)	
Tertile 3	51/1012	0.67(0.41-1.12)	*0.130	0.55(0.34-0.91)	*0.022	0.63(0.36-1.12)	*0.133	0.62(0.35-1.10)	*0.120
Circulating MMA									
log_2 MMA	200/3277	1.78(1.53-2.08)	<0.001	1.57(1.35-1.82)	<0.001	1.38(1.14-1.67)	0.001	1.41(1.16-1.71)	0.001
Tertile 1	36/1101	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	59/1089	2.30(1.33-4.01)		1.68(0.93-3.04)		1.49(0.80-2.81)		1.48(0.78-2.78)	
Tertile 3	105/1087	5.15(3.27-8.12)	*<0.001	2.96(1.81-4.86)	*<0.001	1.85(1.02-3.36)	*0.040	1.88(1.03-3.46)	*0.036

* p for trend across the tertiles of B12 or MMA. HR (95%CI) was estimated by weighted Cox regression analyses. Model 1 was adjusted for age, sex and race/ethnicity. Model 2 was additionally adjusted for smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum B12 (only for MMA model 2), eGFR, HbA1c, metformin, duration of diabetes, UACR, and diabetic complications. Models for B12 supplements were further adjusted for B12 intake from foods, and vice versa. Model 3 was adjusted for covariates in Model 2 except for metformin use.

Supplementary Table 7. The associations of cancer-related mortality with B12 or MMA in patients with T2DM

	Events/ Total num	Unadjusted		Model 1		Model 2		Model 3	
		HR(95%CI)	p value*	HR(95%CI)	p value	HR(95%CI)	p value	HR(95%CI)	p value
Serum B12									
$\log_2$ B12	130/3277	0.73(0.54-0.99)	0.044	0.77(0.59-1.01)	0.061	0.79(0.58-1.07)	0.126	0.80(0.59-1.07)	0.135
Tertile 1	55/1093	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	45/1095	0.88(0.51-1.52)		0.95(0.55-1.66)		1.01(0.54-1.90)		1.02(0.55-1.90)	
Tertile 3	30/1089	0.63(0.34-1.16)	0.134	0.63(0.34-1.16)	0.122	0.69(0.36-1.32)	0.215	0.70(0.36-1.34)	*****0.323
B12 supplement									
Users vs. Nonusers	85/2230 vs.45/1047	0.91(0.52-1.57)	0.723	0.78(0.45-1.34)	0.359	0.87(0.49-1.56)	0.678	0.87(0.49-1.56)	0.646
B12 intake from foods									
increase per 5μg/d	130/3277	0.98(0.89-1.08)	0.637	0.98(0.88-1.09)	0.711	1.00(0.87-1.15)	0.973	0.99(0.87-1.14)	0.943
Tertile 1	42/1017	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	35/1013	0.97(0.51-1.84)		0.92(0.49-1.73)	0.802	0.90(0.47-1.70)		0.90(0.47-1.70)	
Tertile 3	40/1012	1.27(0.75-2.16)	0.339	1.21(0.71-2.08)	0.477	1.15(0.65-2.03)	0.585	1.14(0.64-2.02)	*****0.610
Circulating MMA									
$\log_2$ MMA	130/3277	1.38(1.10-1.74)	0.006	1.14(0.82-1.59)	0.416	1.15(0.84-1.57)	0.390	1.16(0.84-1.60)	0.365
Tertile 1	34/1101	1.00(Reference)		1.00(Reference)		1.00(Reference)		1.00(Reference)	
Tertile 2	43/1089	1.23(0.67-2.23)		0.94(0.52-1.67)		0.96(0.54-1.71)		0.95(0.53-1.70)	
Tertile 3	53/1087	1.82(0.98-3.41)	0.053	1.11(0.56-2.19)	0.66	1.16(0.58-2.32)	0.568	1.16(0.58-2.34)	*****0.547

* p for trend across the tertiles of B12 or MMA. HR (95%CI) was estimated by weighted Cox regression analyses. Model 1 was adjusted for age, sex and race/ethnicity. Model 2 was additionally adjusted for smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum B12 (only for MMA model 2), eGFR, HbA1c, metformin, duration of diabetes, UACR, and diabetic complications. Models for B12 supplements were further adjusted for B12 intake from foods, and vice versa. Model 3 was adjusted for covariates in Model 2 except for metformin use.

Supplementary Table 8. Sensitivity analysis for the associations of all-cause mortality with B12 deficiency compared to normal B12

All-cause mortality	Serum vitamin B12			p trend
	≥339 pg/ml HR (95%CI)	203-339 pg/ml HR (95%CI)	<203 pg/ml HR (95%CI)	
Deaths/Total num	640/2560	165/531	60/186	
Unadjusted	1.00 (Reference)	1.30 (1.01-1.68)	1.77 (1.22-2.58)	0.002
Model 1	1.00 (Reference)	1.15 (0.91-1.46)	1.18 (0.78-1.79)	0.171
Model 2	1.00 (Reference)	1.21 (0.92-1.61)	1.24 (0.82-1.87)	0.094

HR (95%CI) was estimated by weighted Cox regression analyses. Model 1 was adjusted for age, sex and race/ethnicity. Model 2 was additionally adjusted for smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, eGFR, HbA1c, metformin, duration of diabetes, UACR, and diabetic complications.

Supplementary Table 9. Characteristics of diabetic adults in tertile 3 versus tertile 1 before and after matching

	Before matching			After matching*		
	Tertile 1 N=1101	Tertile 3 N=1087	p value	Tertile 1 N=393	Tertile 3 N=393	p value
MMA (nmol/L)	95.0 ± 0.6*	392.0 ± 35.6	--	100.0 ± 0.8	374.9 ± 91.1	--
Age (year)	55.9 ± 0.4	67.9 ± 0.4	<0.001	61.8 ± 0.6	62.6 ± 0.6	0.362
Male (%)	48.6	51.4	0.102	57.5	52.4	0.152
Race/ethnicity (%)			<0.001			0.887
Non-Hispanic White	23.5	48.3		36.4	37.6	
Non-Hispanic Black	30.6	19.7		21.1	22.4	
Hispanic-Mexican	27.9	16.1		22.1	20.1	
Other Ethnicity	18	15.9		20.4	19.9	
Smoking status (%)			<0.001			0.676
Never	51.9	47		46.1	48.6	
Former	28.1	40.7		36.6	36.1	
Current	20	12.3		17.3	15.3	
BMI (kg/m2)	32.0 ± 0.2	31.5 ± 0.2	0.111	31.7 ± 0.4	31.5 ± 0.4	0.653
Hypertension (%)	63.5	78.8	<0.001	71	71.7	0.813
Cancer (%)	9.6	16.2	<0.001	13.5	16.3	0.271
CVD (%)	15.3	40.5	<0.001	23.7	24.7	0.739
TC/HDL-C ratio	2.1 ± 0.1	2.4 ± 0.1	0.077	2.4 ± 0.2	2.4 ± 0.1	0.995
eGFR (mL/min per 1.73m²)	99.2 ± 0.6	64.4 ± 0.8	<0.001	85.9 ± 0.9	83.4 ± 1.03	0.137
UACR (mg/g)	84.2 ± 18.2	394.7 ± 40.8	<0.001	132.0 ± 47.0	162.5 ± 38.1	0.614
HbA1c (%)	7.7 ± 0.1	7.3 ± 0.1	<0.001	7.5 ± 0.1	7.5 ± 0.1	0.925
Metformin (%)	40.2	32.2	<0.001	38.7	36.9	0.607
Duration of diabetes (year)	7.5 ± 0.3	12.4 ± 0.4	<0.001	9.1 ± 0.6	9.6 ± 0.7	0.562
Diabetic complications (%)	26.3	37.1	<0.001	30	32.1	0.538
Serum B12 (pg/ml)	612.4 ± 70.8	386.6 ± 9.0	<0.001	398.6 ± 8.3	410.6 ± 14.1	0.462

Data are represented as percentage or mean (SE). P value was assessed by student t test or chi test. *All estimates were unweighted that were different with the weighted estimates in **supplementary table 5**. #A propensity score–matching approach was used to balance the baseline differences between tertile 1 and tertile 3, including age, sex, race/ethnicity, smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, eGFR, HbA1c, metformin, duration of diabetes, UACR, diabetic complications, and serum B12. Paired participants were selected using the nearest neighbor matching algorithm and non-replacement method with a caliper size of 0.2 standard deviation of the logit of the propensity score.

Supplementary Table 10. The hazard ratio for mortality in tertile 3 versus tertile 1 estimated by adjustment or matching

	Tertile 1 Deaths/ total num	Tertile 3 Deaths/ total num	HR (95%CI)	p value
Mutivariable-adjusted*	166/1101	437/1087	1.91 (1.48-2.45)	<0.001
Propensity score matching#	75/393	110/393	2.09 (1.55-2.80)	<0.001

*HR (95%CI) was estimated by unweighted Cox regression analyses. adjusted for age, sex, race/ethnicity, smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, eGFR, HbA1c, metformin, duration of diabetes, UACR, diabetic complications, and serum B12. # HR (95%CI) was estimated after matching the covariates that multivariable-adjusted model included.

Supplementary Table 11. Sensitivity analysis for the associations of all-cause mortality with dietary and serum cobalamin, MMA, and sensitivity to cobalamin restricted in patients taking anti-diabetic agents

	Deaths/ total num	Metformin use (n= 1242)		Deaths/ total num	Non-use (n= 951)	
		HR(95%CI)	p value		HR(95%CI)	p value
B12 supplements*	70/406 vs. 144/836	0.87 (0.58-1.30)	0.496	136/301 vs. 276/650	0.79 (0.60-1.06)	0.114
B12 intake from foods#	214/1242	0.90 (0.72-1.12)	0.333	412/951	1.10 (0.94-1.29)	0.246
Serum B12 (Log_2 B12)	214/1242	0.79 (0.62-1.02)	0.073	412/951	0.89 (0.73-1.09)	0.261
Circulating MMA (Log_2 MMA)	214/1242	1.16 (0.88-1.62)	0.291	412/951	1.29 (1.11-1.51)	0.002
Combination of MMA and B12						
MMA_{low} $B12_{low}$	68/320	1.00(Reference)	-	54/142	1.00(Reference)	-
MMA_{low} $B12_{high}$	107/761	0.90 (0.58-1.40)	0.629	194/542	0.90 (0.58-1.41)	0.653
MMA_{high} $B12_{low}$	28/115	1.31 (0.74-2.31)	0.352	57/91	1.61 (1.01-2.56)	0.047
MMA_{high} $B12_{high}$	11/46	1.28 (0.36-4.52)	0.702	107/176	1.71 (1.16-2.52)	0.007

* B12 supplements use versus non-use, # B12 intake from foods increase per 5μg/d. HR (95%CI) was estimated by weighted Cox regression analyses after adjustment for age, sex and race/ethnicity, smoking, BMI, hypertension, cancer, CVD, TC/HDL-C ratio, serum B12 (only for MMA model), eGFR, HbA1c, duration of diabetes, UACR, and diabetic complications. Model for B12 supplements was further adjusted for B12 intake from foods, and vice versa.