Supplemental Table S1- Multivariable-adjusted HRs (95% CIs) of incident diabetes by quintiles of B vitamin intake levels stratified by supplement use, the CARDIA study, 1985-2015[*, †]

Sensitivity analysis 1	Quintiles of nutrient intake					P_{trend}
	Q1	Q2	Q3	Q4	Q5	
Folate						
Supplement nonusers (*n* = 1,975)						
Range (μg/day)	<223.2	223.2-305.9	305.9-402.2	402.2-538.3	≥538.3	--
Median level (μg/day)	173.1	263.7	350.3	454.2	666.1	--
HR (95% CI)	0 (Ref.)	1.07 (0.72, 1.59)	0.75 (0.49, 1.15)	0.88 (0.54, 1.44)	0.86 (0.50, 1.46)	0.48
Supplement users (*n* = 2,728)						
Range (μg/day)	<351.6	351.6-470.0	470.0-594.3	594.3-783.2	≥783.2	--
Median level (μg/day)	281.0	412.8	522.8	677.5	989.2	--
HR (95% CI)	0 (Ref.)	1.13 (0.83, 1.54)	0.93 (0.67, 1.29)	0.89 (0.62, 1.27)	0.87 (0.59, 1.29)	0.17
B6						
Supplement nonusers (*n* = 2,099)						
Range (mg/day)	<1.4	1.4-1.9	1.9-2.3	2.3-3.0	≥3.0	--
Median level (mg/day)	1.1	1.7	2.1	2.6	3.7	--
HR (95% CI)	0 (Ref.)	1.12 (0.80, 1.56)	0.82 (0.56, 1.19)	1.14 (0.76, 1.70)	1.31 (0.81, 2.11)	0.72
Supplement users (*n* = 1,795)						
Range (mg/day)	<2.7	2.7-3.5	3.5-4.5	4.5-7.0	≥7.0	--

Median level (mg/day)	2.2	3.1	4.0	5.3	10.9	--
HR (95% CI)	0 (Ref.)	1.17 (0.77, 1.77)	0.95 (0.61, 1.46)	1.19 (0.77, 1.85)	0.97 (0.60, 1.55)	0.38
B12						
Supplement nonusers (*n* = 2,092)						
Range (μg/day)	<3.2	3.2-4.5	4.5-6.0	6.0-8.6	≥8.6	--
Median level (μg/day)	2.5	3.9	5.2	7.0	11.2	--
HR (95% CI)	0 (Ref.)	1.98 (1.38, 2.86)	1.32 (0.89, 1.95)	1.77 (1.16, 2.69)	2.06 (1.31, 3.24)	<0.01
Supplement users (*n* = 1,802)						
Range (μg/day)	<6.8	6.8-9.3	9.3-13.0	13.0-20.7	≥20.7	--
Median level (μg/day)	5.3	7.9	10.7	15.5	30.1	--
HR (95% CI)	0 (Ref.)	1.14 (0.75, 1.73)	0.96 (0.62, 1.49)	1.14 (0.73, 1.78)	1.09 (0.69, 1.71)	0.99

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; HR, hazard ratio; Q, quintile; Ref., reference; --, not applicable. [*]Cox proportional hazard regression models were used. Linear trend was examined by using the continuous variables that excluded the values above the 99th percentile. [†]Models in sensitivity analysis 1 were adjusted for age, sex, race, study center, total energy intake, education levels, smoking status, alcohol consumption, physical activity levels, BMI, glucose levels at baseline, HDL/LDL-cholesterol ratio, triglycerides, and family history of diabetes.

Supplemental Table S2-Results of sensitivity analyses 2-4, the CARDIA study, 1985-2015[*, †, ‡, §]

| | Quintiles of nutrient intake | | | | | P_{trend} |
	Q1	Q2	Q3	Q4	Q5	
Sensitivity analysis 2						
Folate (*n* = 4,703)						
Range (µg/kcal)	<111.7	111.7-148.0	148.0-192.2	192.2-269.3	≥269.3	--
Median (µg/kcal)	92.5	129.3	168.2	224.3	353.0	--
No. of cases/participants	139/940	146/941	161/941	102/941	107/940	--
HR (95% CI)	1 (Ref.)	0.80 (0.63, 1.01)	0.90 (0.71, 1.14)	0.65 (0.49, 0.87)	0.75 (0.56, 1.01)	0.014
B6 (*n* = 3,894)						
Range (mg/kcal)	<0.8	0.8-0.9	0.9-1.2	1.2-1.8	≥1.8	--
Median (mg/kcal)	0.7	0.8	1.0	1.4	2.8	--
No. of cases/participants	140/778	135/779	120/779	91/779	101/779	--
HR (95% CI)	1 (Ref.)	1.22 (0.96, 1.56)	1.16 (0.89, 1.51)	1.13 (0.81, 1.59)	1.19 (0.83, 1.72)	0.67
B12 (*n* = 3,894)						
Range (µg/kcal)	<1.8	1.8-2.4	2.4-3.4	3.4-5.4	≥5.4	--
Median (µg/kcal)	1.4	2.1	2.8	4.1	8.2	--
No. of cases/participants	122/778	125/779	121/779	111/779	108/779	--
HR (95% CI)	1 (Ref.)	1.11 (0.86, 1.43)	1.13 (0.86, 1.48)	1.30 (0.97, 1.75)	1.29 (0.93, 1.79)	0.95
Sensitivity analysis 3						

HR (95% CI) for folate	1 (Ref.)	0.84 (0.66, 1.07)	0.77 (0.58, 1.01)	0.80 (0.60, 1.08)	0.68 (0.48, 0.96)	0.02
HR (95% CI) for B6	1 (Ref.)	0.89 (0.68, 1.16)	1.07 (0.80, 1.43)	1.06 (0.76, 1.49)	1.05 (0.71, 1.54)	0.40
HR (95% CI) for B12	1 (Ref.)	1.04 (0.80, 1.35)	1.08 (0.81, 1.44)	1.14 (0.83, 1.57)	1.30 (0.91, 1.84)	0.053
Sensitivity analysis 4						
HR (95% CI) for cumulative average intake of folate	1 (Ref.)	0.71 (0.54, 0.94)	0.81 (0.61, 1.08)	0.68 (0.50, 0.92)	0.61 (0.45, 0.84)	<0.01
HR (95% CI) for folate intake at year 20 and following diabetes incidence	1 (Ref.)	1.22 (0.88, 1.69)	1.23 (0.88, 1.72)	1.38 (0.97, 1.97)	1.27 (0.87, 1.85)	0.36

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; HR, hazard ratio; Q, quintile; Ref., reference; --, not applicable. [*]Cox proportional hazard regression models were used. Linear trend was examined by using the continuous variables that excluded the values above the 99th percentile. [†]Models in sensitivity analysis 2 were adjusted for age, sex, race, study center, education levels, smoking status, alcohol consumption, physical activity levels, BMI, glucose levels at baseline, HDL/LDL-cholesterol ratio, triglycerides, family history of diabetes, and supplement use of B vitamin of interest. [‡]Sensitivity analysis 3 was model 3 in Table 2 with additional adjustment for the overall dietary quality using the A Priori Diet Quality Score. [§]In sensitivity analysis 4, we calculated the cumulative average of folate by using the following method: if the survival time ends before exam year 20 (2005), the cumulative folate is the average of baseline (1985) and year 7 (1992) measurements depending on the actual survival time; if the survival time ends after year 20, the cumulative folate is the measurement at year 20. We also examined the association between folate intake at year 20 and following diabetes incidence by excluding those who had incident diabetes or who were censored before year 20.

Supplemental Table S3-Multivariable-adjusted mean differences (95% CI) in other markers of insulin resistance and inflammation according to quintiles of folate intake levels: the CARDIA study, 1985-2015[*, †, ‡]

	Quintiles of folate intake					P_{trend}
	Q1	Q2	Q3	Q4	Q5	
Glucose (mmol/L, $n = 4,813$)						
Range (µg/day)	<259.9	259.9-366.5	366.5-485.5	485.5-664.4	≥664.4	--
Median level (µg/day)	199.2	316.3	424.3	561.6	841.4	--
Mean difference (95% CI)	0 (Ref.)	0.02 (-0.05, 0.09)	-0.01 (-0.09, 0.07)	0.00 (-0.08, 0.08)	0.04 (-0.05, 0.13)	<0.01
HOMA-IR ($n = 4,365$)						
Range (µg/day)	<263.8	263.8-370.4	370.4-488.9	488.9-669.1	≥669.1	--
Median level (µg/day)	203.1	319.4	428.1	565.8	845.5	--
Mean difference (95% CI)	0 (Ref.)	-0.01 (-0.20, 0.18)	-0.08 (-0.27, 0.12)	-0.19 (-0.39, 0.00)	-0.19 (-0.43, 0.05)	0.81
HOMA-β (%, $n = 4,365$)						
Range (µg/day)	<264.1	264.1-370.5	370.5-488.9	488.9-669.1	≥669.1	--
Median level (µg/day)	203.3	319.4	428.1	565.8	845.4	--
Mean difference (95% CI)	0 (Ref.)	-10.77 (-22.40, 0.87)	-19.15 (-32.69, -5.61)	-18.33 (-29.65, -7.01)	-25.36 (-38.13, -12.60)	<0.01
Fibrinogen (g/L, $n = 4,242$)						
Range (µg/day)	<241.5	241.5-348.9	348.9-471.4	471.4-658.5	≥658.5	--
Median level (µg/day)	178.7	296.6	406.2	553.0	818.4	--
Mean difference (95% CI)	0 (Ref.)	-0.04 (-0.09, 0.01)	-0.02 (-0.07, 0.04)	-0.003 (-0.06, 0.05)	-0.02 (-0.07, 0.04)	<0.01

IL-6 (pg/mL, *n* = 3,291)

Range (µg/day)	<315.4	315.4-426.8	426.8-542.2	542.2-722.8	≥722.8	--
Median level (µg/day)	250.1	369.5	476.7	619.3	895.4	--
Mean difference (95% CI)	0 (Ref.)	-0.35 (-0.70, -0.0001)	-0.16 (-0.54, 0.23)	-0.46 (-0.85, -0.07)	-0.47 (-0.86, -0.09)	0.13

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; IL-6, Interleukin-6; Q, quintile; Ref., reference; --, not applicable. [*]Models of glucose, HOMA-IR, HOMA-β, and fibrinogen were constructed using generalized linear regression model with identity linkage under exchangeable correlation structure assumption. IL-6 was assayed only once at year 20, thus the ordinary linear regression model was used. P_{trend} was examined by using the continuous folate intake variable that excluded the values above the 99th percentile. [†]Models were adjusted for age, sex, race, study center, total energy intake, education levels, smoking status, alcohol consumption, physical activity levels, BMI, HDL/LDL-cholesterol ratio, triglycerides, and family history of diabetes, and supplement use of folic acid. [‡]The median (inter-quartile range, mmol/L) of glucose is 4.6 (4.3-4.8) at year 0, 5.0 (4.7-5.3) at years 7 and 10, 5.0 (4.7-5.4) at year 15, 5.3 (5.0-5.7) at year 20, 5.2 (4.8-5.7) at year 25, and 5.3 (4.9-5.8) at year 30. The median (inter-quartile range) of HOMA-IR is 2.0 (1.6-2.7) at year 0, 2.5 (1.9-3.6) at year 7, 2.5 (1.9-3.7) at year 10, 2.7 (1.9-4.1) at year 15, 3.2 (2.2-4.9) at year 20, 2.1 (1.2-3.6) at year 25, and 2.5 (1.5-4.2) at year 30. The median (inter-quartile range, %) of HOMA-β is 205.7 (151.6-291.4) at year 0, 154.2 (122.9-207.1) at year 7, 158.4 (121.1-214.0) at year 10, 156.9 (112.0-218.2) at year 15, 153.8 (113.9-211.6) at year 20, 100.0 (64.4-152.1) at year 25, and 109.4 (73.2-165.6) at year 30. The median (inter-quartile range, g/L) of fibrinogen is 2.6 (2.2-3.0) at year 5 and 3.9 (3.4-4.6) at year 20. The median (inter-quartile range, pg/mL) of IL-6 at year 20 is 1.7 (1.0-3.0).