One-Carbon Metabolism–Related Micronutrients Intake and Risk for Hepatocellular Carcinoma: A Prospective Cohort Study

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Supplementary Table 1. Simultaneous evaluation of total [a] intake of one-carbon metabolism-related micronutrients and hepatocellular carcinoma risk among participants with >3years of follow-up, stratified by sex

	Male (*N*=267,670, cases: 457)			**Female (*N*=185,612, cases: 102)**		
Micronutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Folate						
Q1	61747	123	1.00 (ref)	28929	22	1.00 (ref)
Q2	50624	84	0.94 (0.69-1.27)	40053	18	0.54 (0.28-1.06)
Q3	49223	82	0.99 (0.72-1.37)	41454	27	0.73 (0.38-1.40)
Q4	50870	86	1.05 (0.75-1.49)	39807	21	0.53 (0.26-1.10)
Q5	55206	82	0.95 (0.64-1.40)	35471	14	**0.31 (0.12-0.75)**
P-trend [c]			0.92			**0.04**
P-interaction [d]						0.30
Methionine [e]						
Q1	37,878	57	1.00 (ref)	53,208	30	1.00 (ref)
Q2	46,985	73	1.02 (0.71-1.46)	43,625	20	0.76 (0.41-1.41)
Q3	53,942	88	1.01 (0.70-1.44)	37,125	24	0.95 (0.48-1.87)
Q4	60,372	108	1.01 (0.69-1.47)	30,382	16	0.69 (0.29-1.62)
Q5	68,493	131	0.82 (0.51-1.32)	21,374	12	0.53 (0.16-1.82)
P-trend [c]			0.61			0.49
P-interaction [d]						0.65
Vitamin B2						
Q1	58659	98	1.00 (ref)	32018	20	1.00 (ref)
Q2	54161	98	1.16 (0.84-1.60)	36514	19	1.02 (0.49-2.11)
Q3	55637	90	0.98 (0.63-1.53)	35043	13	1.25 (0.43-3.62)
Q4	49351	81	0.96 (0.53-1.72)	41325	26	2.94 (0.72-11.94)
Q5	49862	90	0.74 (0.37-1.47)	40814	24	1.78 (0.34-9.32)
P-trend [c]			0.65			0.37
P-interaction [d]						0.51
Vitamin B3						
Q1	53151	102	1.00 (ref)	37527	27	1.00 (ref)
Q2	56769	105	0.93 (0.69-1.26)	33903	18	0.73 (0.37-1.41)
Q3	55392	83	**0.53 (0.34-0.81)**	35289	16	**0.44 (0.30-0.94)**
Q4	50118	68	**0.35 (0.19-0.63)**	40557	21	**0.40 (0.38-0.66)**
Q5	52240	99	**0.43 (0.22-0.85)**	38438	20	**0.39 (0.22-0.52)**
P-trend [c]			**0.01**			**0.003**
P-interaction [d]						0.24
Vitamin B6						
Q1	58049	108	1.00 (ref)	32630	17	1.00 (ref)
Q2	54436	92	1.02 (0.73-1.42)	36239	22	1.51 (0.72-3.16)
Q3	55236	84	1.18 (0.73-1.89)	35440	15	1.85 (0.64-5.38)
Q4	49139	83	1.72 (0.89-3.33)	41539	22	3.05 (0.70-13.21)
Q5	50810	90	1.67 (0.75-3.72)	39866	26	**6.21 (1.12-34.45)**
P-trend [c]			0.17			**0.005**
P-interaction [d]						0.13
Vitamin B12						
Q1	56871	96	1.00 (ref)	33805	24	1.00 (ref)
Q2	54814	84	0.92 (0.66-1.27)	35864	18	0.66 (0.33-1.33)
Q3	55347	96	1.20 (0.81-1.78)	35330	13	0.38 (0.13-1.09)
Q4	49841	74	1.25 (0.74-2.10)	40835	18	0.32 (0.09-1.15)
Q5	50797	107	1.76 (0.97-3.18)	39880	29	0.57 (0.14-2.37)
P-trend [c]			0.05			0.83
P-interaction [d]						0.35

Supplementary Table 1. Continued

	Male *N*=295,239 (cases: 530)			Female *N*=199,621 (cases: 117)		
	Total *N*	Cases	HR (95% CI)	Total *N*	Cases	HR (95% CI)
Methyl-donor index [f]						
Q1	50822	85	1.00 (ref) [e]	39855	22	1.00 (ref) [e]
Q2	57408	101	1.05 (0.78-1.42)	33268	17	1.01 (0.52-1.97)
Q3	52893	85	0.95 (0.66-1.35)	37784	18	1.16 (0.52-2.58)
Q4	52389	85	1.00 (0.66-1.52)	38288	25	1.79 (0.73-4.39)
Q5	54158	101	1.13 (0.72-1.76)	36519	20	1.53 (0.58-4.07)
P-trend [c]			0.61			0.29
P-interaction [d]						0.83

Abbreviations: HR, hazard ratio; CI, confidence interval; N/A, not applicable; Q1–Q5, calorie-adjusted quintiles of micronutrients intake

[a] Total intake was computed as diet plus supplement use. Each micronutrient was adjusted for total calories intake by the residual method. Quintiles were created from intake values at baseline and categorized based on distribution in the entire cohort using the 20th, 40th, 60th, and 80th percentile values as cut points.

[b] All models adjusted for age (continuous), race/ethnicity (White, Black, Hispanic, other), diabetes (yes, no), smoking status (never, former, current), alcohol use (<1, 1-3, >3 drinks/day), total calorie intake (continuous), body mass index (<25, 25-29, ≥30 kg/m^2), education level (<high school, high school graduate, some college/post-high school education, college graduate/post-graduate), physical activity (0, <1, 1-2, 3-4, 5+ times per week), multivitamin use (yes, no), red meat intake (0-23, 24-41, 42-63, 64-99, >99 grams/day), and the healthy eating index scores (10-59, 60-66, 67-71, 72-76, >76)

[c] *P*-trend were calculated by treating the quintile variable as a continuous variable

[e] Methionine intake levels were based on dietary intake only because data on supplemental use was not available

[e] A separate model was fitted for the methyl-donor index, adjusting for the factors listed in [b].

Supplementary Table 2. Simultaneous evaluation of total [a] intake of one-carbon metabolism-related micronutrients and risk of hepatocellular carcinoma (N=453,384), stratified by body mass index

	< 25 kg/m² (*N*=157,059, cases: 125)			**≥ 25 kg/m² (*N*=285546, cases: 420)**		
Micronutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Total folate						
Q1	27852	32	1.00 (ref)	60694	110	1.00 (ref)
Q2	29496	12	0.45 (0.23-0.91)	58951	87	0.96 (0.71-1.31)
Q3	31145	31	1.16 (0.65-2.06)	57482	74	0.87 (0.62-1.21)
Q4	32772	30	1.07 (0.58-1.97)	55849	76	0.92 (0.65-1.30)
Q5	35794	20	0.60 (0.30-1.22)	52570	73	0.88 (0.61-1.27)
P-trend [c]			0.80			0.42
P-interaction [d]						0.28
Methionine [e]						
Q1	37,858	26	1.00 (ref)	50,531	59	1.00 (ref)
Q2	34,982	23	0.87 (0.48-1.56)	53,474	68	0.99 (0.69-1.42)
Q3	32,413	24	0.87 (0.46-1.63)	56,649	85	1.06 (0.74-1.53)
Q4	28,878	26	0.91 (0.45-1.81)	60,001	94	0.98 (0.66-1.46)
Q5	22,928	26	0.78 (0.31-1.97)	64,891	114	0.85 (0.51-1.39)
P-trend [c]			0.80			0.67
P-interaction [d]						0.73
Vitamin B2						
Q1	29570	21	1.00 (ref)	58726	95	1.00 (ref)
Q2	28882	28	2.01 (1.05-3.85)	59604	86	0.96 (0.68-1.34)
Q3	31489	24	1.42 (0.55-3.64)	57044	77	0.89 (0.57-1.39)
Q4	33343	25	1.05 (0.33-3.39)	55357	79	1.14 (0.63-2.05)
Q5	33775	27	0.67 (0.18-2.54)	54815	83	0.86 (0.42-1.68)
P-trend [c]			0.71			0.34
P-interaction [d]						0.25
Vitamin B3						
Q1	30211	22	1.00 (ref)	57903	102	1.00 (ref)
Q2	28764	26	1.44 (0.77-2.68)	59811	96	0.80 (0.59-1.09)
Q3	31144	23	1.10 (0.46-2.66)	57344	74	**0.40 (0.26-0.62)**
Q4	33639	27	0.98 (0.32-3.03)	55114	61	**0.23 (0.13-0.43)**
Q5	33301	27	0.78 (0.22-2.82)	55374	87	**0.25 (0.13-0.50)**
P-trend [c]			0.99			**<0.0001**
P-interaction [d]						0.28
Vitamin B6						
Q1	28039	29	1.00 (ref)	60321	92	1.00 (ref)
Q2	29123	18	0.47 (0.24-0.92)	59383	93	**1.39 (0.99-1.95)**
Q3	31769	22	0.52 (0.21-1.28)	56712	77	**1.82 (1.14-2.91)**
Q4	33488	29	0.77 (0.23-2.53)	55189	73	**2.82 (1.46-5.46)**
Q5	34640	27	0.67 (0.16-2.85)	53941	85	**3.58 (1.62-7.91)**
P-trend [c]			0.36			**0.0006**
P-interaction [d]						0.08
Vitamin B12						
Q1	32510	28	1.00 (ref)	55712	88	1.00 (ref)
Q2	28415	20	0.75 (0.40-1.41)	60094	80	0.93 (0.67-1.30)
Q3	31338	19	0.68 (0.30-1.57)	57193	89	1.22 (0.81-1.82)
Q4	33208	22	0.95 (0.36-2.53)	55535	66	1.10 (0.65-1.89)
Q5	31588	36	2.62 (0.95-7.25)	57012	97	1.50 (0.83-2.69)
P-trend [c]			0.08			0.19
P-interaction [d]						0.11

Supplementary Table 2. Continued

	< 25 kg/m^2 (*N*=157,059, cases: 125)			**≥ 25 kg/m^2 (*N*=285546, cases: 420)**		
Micronutrient [a]	Total *N*	Cases	HR (95% CI)	Total *N*	Cases	HR (95% CI)
Methyl-donor index [f]						
Q1	30419	22	1.00 (ref) [e]	57782	82	1.00 (ref) [e]
Q2	28852	20	0.91 (0.49-1.72)	59743	95	1.06 (0.78-1.44)
Q3	31934	25	1.09 (0.54-2.20)	56572	77	0.95 (0.66-1.38)
Q4	33075	33	1.39 (0.63-3.07)	55637	74	0.99 (0.64-1.54)
Q5	32779	25	1.03 (0.43-2.47)	55812	92	1.20 (0.75-1.91)
P-trend [c]			0.81			0.46
P-interaction [d]						0.39

Abbreviations: HR, hazard ratio; CI, confidence interval; N/A, not applicable; Q1–Q5, calorie-adjusted quintiles of micronutrients intake

[a] Total intake was computed as diet plus supplement use. Each micronutrient was adjusted for total calories intake by the residual method. Quintiles were created from intake values at baseline and categorized based on distribution in the entire cohort using the 20th, 40th, 60th, and 80th percentile values as cut points.

[b] All models adjusted for age (continuous), sex, race/ethnicity (White, Black, Hispanic, other), diabetes (yes, no), smoking status (never, former, current), alcohol use (<1, 1-3, >3 drinks/day), total calorie intake (continuous), education level (<high school, high school graduate, some college/post-high school education, college graduate/post-graduate), physical activity (0, <1, 1-2, 3-4, 5+ times per week), multivitamin use (yes, no), red meat intake (0-23, 24-41, 42-63, 64-99, >99 grams/day), and the healthy eating index scores (10-59, 60-66, 67-71, 72-76, >76)

[c] *P*-trend were calculated by treating the quintile variable as a continuous variable

[e] Methionine intake levels were based on dietary intake only because data on supplemental use was not available

[e] A separate model was fitted for the methyl-donor index, adjusting for the factors listed in [b].

Supplementary Table 3. Total [a] intake of one-carbon metabolism-related nutrients and risk of hepatocellular carcinoma among individuals with more than 3 years of follow-up (*N*=453,384), stratified by the number of drinks consumed per day

	Non-drinkers *N*=110,169 (cases: 179)			**< 1drink/day *N*=240,258 (cases: 240)**			**1-3 drinks/day *N*=69,465 (cases: 69)**			**>3 drinks/day *N*=33,492 (cases: 71)**		
Micronutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Folate												
Q1	19827	35	1.00 (ref)	37843	44	1.00 (ref)	14883	17	1.00 (ref)	18123	49	1.00 (ref)
Q2	22139	28	0.74 (0.44-1.26)	48457	56	1.16 (0.76-1.76)	14544	13	1.05 (0.49-2.24)	5537	5	0.37 (0.14-0.95)
Q3	22036	38	1.02 (0.61-1.70)	51390	49	0.96 (0.61-1.50)	13459	13	1.41 (0.63-3.14)	3792	9	0.93 (0.43-2.02)
Q4	22284	43	1.13 (0.67-1.90)	52231	48	0.90 (0.56-1.44)	13116	13	1.70 (0.73-3.93)	3046	3	0.40 (0.12-1.36)
Q5	23883	35	0.78 (0.43-1.36)	50337	43	0.78 (0.47-1.30)	13463	13	1.84 (0.74-4.62)	2994	5	0.72 (0.25-2.03)
P-trend [c]			0.69			0.21			0.13			0.34
P-interaction [d]												0.29
Methionine [e]												
Q1	25742	32	1.00 (ref)	49978	36	1.00 (ref)	10830	9	1.00 (ref)	4536	10	1.00 (ref)
Q2	21797	33	1.09 (0.65-1.83)	49842	38	0.85 (0.53-1.36)	13487	11	1.03 (0.41-2.60)	5484	11	0.91 (0.38-2.17)
Q3	20791	37	1.13 (0.66-1.96)	49094	48	0.88 (0.55-1.43)	14645	13	1.16 (0.44-3.05)	6537	14	1.04 (0.44-2.44)
Q4	20488	39	1.08 (0.58-2.00)	47301	55	0.84 (0.50-1.41)	15415	17	1.40 (0.49-4.01)	7550	13	0.83 (0.33-2.07)
Q5	21351	38	0.77 (0.33-1.78)	44043	63	0.61 (0.30-1.24)	15088	19	1.63 (0.41-6.41)	9385	23	1.09 (0.39-2.99)
P-trend [c]			0.91		36	0.36			0.45			0.98
P-interaction [d]												0.97
Vitamin B2												
Q1	20143	32	1.00 (ref)	42237	39	1.00 (ref)	15796	18	1.00 (ref)	12501	29	1.00 (ref)
Q2	23214	33	0.95 (0.55-1.64)	50154	58	1.39 (0.88-2.20)	12934	13	1.08 (0.48-2.45)	4373	13	1.12 (0.51-2.45)
Q3	21877	34	1.15 (0.57-2.31)	46828	44	1.25 (0.67-2.32)	14038	10	0.89 (0.24-3.27)	7937	15	0.61 (0.20-1.84)
Q4	22091	35	1.37 (0.54-3.47)	51394	49	1.30 (0.58-2.89)	13514	16	1.24 (0.25-6.12)	3677	7	0.73 (0.17-3.07)
Q5	22844	45	0.97 (0.33-2.86)	49645	50	1.01 (0.40-2.57)	13183	12	0.66 (0.10-4.36)	5004	7	0.78 (0.14-4.53)
P-trend [c]			0.83			0.74			0.89			0.53
P-interaction [d]												0.80
Vitamin B3												
Q1	24504	43	1.00 (ref)	43523	48	1.00 (ref)	13008	16	1.00 (ref)	9643	22	1.00 (ref)
Q2	21653	34	0.75 (0.46-1.23)	49613	60	1.00 (0.66-1.52)	14057	15	0.87 (0.40-1.89)	5349	14	0.89 (0.40-1.99)
Q3	21467	29	0.46 (0.23-0.93)	47352	37	0.50 (0.27-0.90)	13856	12	0.48 (0.14-1.66)	8006	21	0.63 (0.22-1.77)
Q4	21077	27	0.33 (0.13-0.85)	50281	40	0.39 (0.17-0.87)	14342	14	0.25 (0.05-1.20)	4975	8	0.25 (0.06-1.05)
Q5	21468	46	0.40 (0.14-1.14)	49489	55	0.53 (0.21-1.32)	14202	12	0.11 (0.02-0.69)	5519	6	0.31 (0.02-1.75)
P-trend [c]			0.09			0.14			0.05			0.12
P-interaction [d]												0.11

Supplementary Table 3. Continued

	Non-drinkers *N*=110,169 (cases: 179)			< 1drink/day *N*=240,258 (cases: 240)			1-3 drinks/day *N*=69,465 (cases: 69)			>3 drinks/day *N*=33,492 (cases: 71)		
Micronutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Vitamin B6												
Q1	21926	35	1.00 (ref)	44836	48	1.00 (ref)	14071	21	1.00 (ref)	9846	21	1.00 (ref)
Q2	22531	35	1.02 (0.60-1.76)	49035	55	1.28 (0.82-2.01)	13708	10	0.47 (0.19-1.13)	5401	14	1.64 (0.72-3.73)
Q3	21922	32	1.24 (0.60-2.57)	47237	39	1.44 (0.76-2.73)	13564	10	0.52 (0.14-1.97)	7953	18	2.20 (0.73-6.64)
Q4	21127	31	1.47 (0.53-4.12)	50062	50	2.45 (0.99-5.94)	14444	13	0.65 (0.11-3.77)	5045	11	**5.46 (1.23-24.23)**
Q5	22663	46	1.72 (0.52-5.73)	49088	48	2.13 (0.73-6.24)	13678	15	1.42 (0.19-10.75)	5247	7	**7.38 (1.02-53.20)**
P-trend [c]			0.26			0.16			0.95			**0.04**
P-interaction [d]												0.68
Vitamin B12												
Q1	22761	35	1.00 (ref)	42564	44	1.00 (ref)	14143	15	1.00 (ref)	11208	26	1.00 (ref)
Q2	22625	33	0.93 (0.54-1.58)	49990	45	0.80 (0.51-1.27)	13112	13	0.97 (0.43-2.18)	4951	11	0.87 (0.40-1.89)
Q3	21619	33	1.01 (0.52-1.96)	47513	48	1.11 (0.65-1.92)	14136	10	0.80 (0.27-2.34)	7409	18	1.16 (0.49-2.77)
Q4	21267	26	0.87 (0.37-2.07)	50481	44	1.26 (0.61-2.58)	14102	13	1.30 (0.35-4.87)	4826	9	0.98 (0.31-3.11)
Q5	21897	52	1.71 (0.68-4.28)	49710	59	1.59 (0.73-3.48)	13972	18	2.61 (0.65-10.47)	5098	7	0.76 (0.19-3.05)
P-trend [c]			0.24			0.30			0.21			0.87
P-interaction [d]												0.28
Methyl-donor index [e]												
Q1	23380	34	1.00 (ref)	45760	39	1.00 (ref)	13055	16	1.00 (ref)	8482	18	1.00 (ref)
Q2	21720	33	0.94 (0.57-1.56)	48555	56	1.26 (0.82-1.94)	13960	10	0.55 (0.24-1.27)	6441	19	1.20 (0.61-2.35)
Q3	21719	32	0.96 (0.54-1.72)	47965	41	1.15 (0.68-1.92)	13830	14	0.80 (0.32-2.00)	7163	16	0.84 (0.38-1.87)
Q4	21241	37	1.19 (0.61-2.34)	49390	48	1.49 (0.82-2.72)	14347	13	0.73 (0.24-2.20)	5699	12	0.72 (0.28-1.82)
Q5	22109	43	1.30 (0.63-2.67)	48588	56	1.72 (0.91-3.26)	14273	16	0.93 (0.29-2.97)	5707	6	0.32 (0.10-1.01)
P-trend [c]			0.38			0.09			0.93			0.05
P-interaction [d]												0.14

Abbreviations: HR, hazard ratio; CI, confidence interval; N/A, not applicable; Q1–Q5, calorie-adjusted quintiles of micronutrients intake

[a] Total intake was computed as diet plus supplement use. Each micronutrient was adjusted for total calories intake by the residual method. Quintiles were created from intake values at baseline and categorized based on distribution in the entire cohort using the 20th, 40th, 60th, and 80th percentile values as cut points.

[b] All models adjusted for age (continuous), sex, race/ethnicity (White, Black, Hispanic, other), diabetes (yes, no), smoking status (never, former, current), total calorie intake (continuous), body mass index (<25, 25-29, ≥30 kg/m^2), education level (<high school, high school graduate, some college/post-high school education, college graduate/post-graduate), physical activity (0, <1, 1-2, 3-4, 5+ times per week), multivitamin use (yes, no), red meat intake (0-23, 24-41, 42-63, 64-99, >99 grams/day), and the healthy eating index scores (10-59, 60-66, 67-71, 72-76, >76)

[c] *P*-trend were calculated by treating the quintile variable as a continuous variable

[e] Methionine intake levels were based on dietary intake only because data on supplemental use was not available

[e] A separate model was fitted for the methyl-donor index, adjusting for the factors listed in [b].

Supplementary Table 4. Total [a] intake of one-carbon metabolism nutrients and risk of hepatocellular carcinoma among individuals with more than 3 years of follow-up (*N*=453,384), stratified by level physical activity per week

	0 ***N*=19,320 (cases: 28)**			**< 1 per week** ***N*=122,095 (cases: 177)**			**1-2 per week** ***N*=97,816 (cases: 126)**			**3-4 per week** ***N*=121,856 (cases: 146)**			**5+ per week** ***N*=87,438 (cases: 74)**		
Micronutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Folate															
Q1	5900	7	1.00 (ref)	31734	59	1.00 (ref)	20014	28	1.00 (ref)	18877	36	1.00 (ref)	13088	13	1.00 (ref)
Q2	4323	7	1.70 (0.55-5.29)	27956	37	0.85 (0.52-1.38)	20501	26	1.17 (0.66-2.08)	22538	21	0.63 (0.35-1.11)	14305	10	0.69 (0.29-1.63)
Q3	3347	4	1.36 (0.35-5.24)	24295	33	0.68 (0.39-1.17)	20368	26	1.30 (0.71-2.36)	25306	23	0.66 (0.36-1.19)	16440	21	1.26 (0.58-2.75)
Q4	2979	2	0.62 (0.11-3.47)	21093	24	0.72 (0.40-1.28)	19559	30	1.64 (0.89-3.03)	27205	31	0.84 (0.47-1.49)	19008	19	0.97 (0.42-2.22)
Q5	2771	8	2.17 (0.56-8.43)	17017	24	0.85 (0.52-1.38)	17374	16	0.95 (0.45-1.98)	27930	35	0.90 (0.49-1.64)	24597	11	0.41 (0.15-1.07)
P-trend [c]			0.81			0.24			0.78			0.94			0.18
P-interaction [d]															0.09
Methionine [e]															
Q1	4966	2	1.00 (ref)	27444	26	1.00 (ref)	18759	23	1.00 (ref)	22822	18	1.00 (ref)	15498	15	1.00 (ref)
Q2	3704	2	1.22 (0.16-9.09)	25224	32	1.17 (0.68-1.99)	19439	16	0.58 (0.30-1.12)	24758	27	1.23 (0.67-2.29)	16621	16	0.86 (0.41-1.80)
Q3	3457	6	3.32 (0.59-18.55)	23970	39	1.30 (0.76-2.24)	19817	27	0.83 (0.44-1.54)	25308	24	0.96 (0.50-1.87)	17718	13	0.54 (0.23-1.23)
Q4	3411	6	2.79 (0.46-17.07)	23049	34	0.99 (0.54-1.81)	20258	31	0.81 (0.40-1.61)	25215	35	1.22 (0.62-2.42)	18057	17	0.58 (0.24-1.40)
Q5	3782	12	4.55 (0.58-35.93)	22408	46	0.92 (0.44-1.92)	19543	29	0.55 (0.21-1.39)	23753	42	1.17 (0.50-2.75)	19544	13	**0.26 (0.07-0.92**)
P-trend [c]			0.10			0.78			0.55			0.68			0.06
P-interaction [d]															0.32
Vitamin B2															
Q1	5225	6	1.00 (ref)	29059	45	1.00 (ref)	19601	22	1.00 (ref)	20790	36	1.00 (ref)	14823	8	1.00 (ref)
Q2	4000	4	1.68 (0.42-6.69)	25573	44	1.16 (0.72-1.89)	20058	27	1.40 (0.73-2.69)	23783	28	0.72 (0.41-1.27)	16172	12	1.96 (0.73-5.29)
Q3	3789	6	6.57 (1.48-29.25)	24561	32	0.75 (0.38-1.48)	20094	22	1.17 (0.48-2.83)	24354	24	0.56 (0.25-1.23)	16951	18	3.61 (1.06-12.28)
Q4	3154	6	**19.34 (2.24-166.7)**	21424	24	0.83 (0.33-2.05)	19088	25	1.17 (0.37-3.65)	26813	33	0.82 (0.29-2.29)	19410	17	2.07 (0.45-9.52)
Q5	3152	6	**30.47 (2.71-342.1)**	21478	32	0.80 (0.28-2.33)	18975	30	0.87 (0.23-3.25)	26116	25	0.46 (0.13-1.56)	20082	19	1.04 (0.18-5.98)
P-trend [c]			**0.005**			0.50			0.80			0.21			0.81
P-interaction [d]															0.12
Vitamin B3															
Q1	5608	10	1.00 (ref)	28539	45	1.00 (ref)	19130	30	1.00 (ref)	20758	32	1.00 (ref)	15212	12	1.00 (ref)
Q2	3958	5	0.93 (0.28-3.08)	26021	47	0.99 (0.63-1.57)	20162	24	0.61 (0.34-1.10)	23760	29	0.78 (0.45-1.36)	15821	15	1.19 (0.51-2.78)
Q3	3617	3	0.93 (0.17-5.04)	24507	33	**0.47 (0.24-0.91)**	20135	20	**0.47 (0.21-0.66)**	24313	31	0.74 (0.36-1.49)	17213	10	0.32 (0.08-1.23)
Q4	3132	5	1.72 (0.15-19.3)	21957	24	**0.35 (0.14-0.87)**	19496	20	**0.51 (0.24-0.76)**	26379	24	0.44 (0.16-1.18)	18935	14	0.21 (0.04-1.06)
Q5	3005	5	2.33 (0.17-32.9)	21071	28	**0.25 (0.12-0.75)**	18893	32	**0.45 (0.14-0.65)**	26646	30	0.55 (0.18-1.65)	20257	23	0.31 (0.05-1.75)
P-trend [c]			0.60			**0.01**			**0.008**			0.27			0.33
P-interaction [d]															0.93

Supplementary Table 4. Continued

	0 *N*=19,320 (cases: 28)			< 1 per week *N*=122,095 (cases: 177)			1-2 per week *N*=97,816 (cases: 126)			3-4 per week *N*=121,856 (cases: 146)			5+ per week *N*=87,438 (cases: 74)		
Nutrient [a]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]	Total *N*	Cases	HR (95% CI) [b]
Vitamin B6															
Q1	5791	12	1.00 (ref)	31398	43	1.00 (ref)	20248	29	1.00 (ref)	19138	28	1.00 (ref)	12937	12	1.00 (ref)
Q2	3788	3	0.19 (0.04-0.82)	25245	43	1.50 (0.91-2.45)	20037	23	0.95 (0.50-1.79)	24224	31	1.40 (0.77-2.55)	16320	11	0.63 (0.25-1.59)
Q3	3792	3	0.13 (0.02-0.87)	24217	39	2.23 (1.12-4.42)	19870	18	1.18 (0.46-3.00)	24507	27	1.63 (0.73-3.62)	17302	11	0.81 (0.24-2.73)
Q4	3108	6	0.24 (0.02-2.81)	21638	24	2.39 (0.88-6.44)	19501	25	2.53 (0.71-8.99)	26893	33	3.34 (1.10-10.13)	18757	15	1.41 (0.27-7.38)
Q5	2841	4	0.07 (0.01-1.36)	19597	28	2.76 (0.79-9.63)	18160	31	3.82 (0.84-17.18)	27094	27	2.54 (0.67-9.62)	22122	25	3.31 (0.51-21.30)
P-trend [c]			0.11			0.04			0.10			0.10			0.36
P-interaction [d]															0.13
Vitamin B12															
Q1	4775	7	1.00 (ref)	25680	43	1.00 (ref)	18521	22	1.00 (ref)	22834	34	1.00 (ref)	17694	13	1.00 (ref)
Q2	4210	6	0.70 (0.20-2.47)	27066	35	0.83 (0.50-1.36)	20378	21	0.84 (0.43-1.61)	22888	30	1.07 (0.61-1.85)	15040	8	0.54 (0.21-1.44)
Q3	3700	3	0.31 (0.06-1.70)	24349	38	1.18 (0.65-2.11)	20078	24	1.25 (0.58-2.72)	24367	28	0.84 (0.40-1.73)	17276	15	1.05 (0.36-3.10)
Q4	3243	7	0.99 (0.16-6.23)	22434	21	1.01 (0.45-2.27)	19447	23	1.52 (0.56-4.09)	26243	22	0.58 (0.22-1.49)	18497	17	1.51 (0.40-5.66)
Q5	3392	5	0.50 (0.06-4.22)	22566	40	1.97 (0.85-4.59)	19392	36	2.16 (0.74-6.32)	25524	32	1.06 (0.38-2.94)	18931	21	1.81 (0.41-7.92)
P-trend [c]			0.66			0.22			0.14			0.96			0.40
P-interaction [d]															0.76
Methyl-donor index [e]															
Q1	5663	8	1.00 (ref)	31264	40	1.00 (ref)	19667	22	1.00 (ref)	19994	27	1.00 (ref)	12729	9	1.00 (ref)
Q2	3814	4	0.56 (0.16-1.95)	25061	47	1.20 (0.77-1.88)	20336	28	1.19 (0.66-2.15)	24018	26	0.77 (0.44-1.34)	16511	11	0.98 (0.39-2.43)
Q3	3843	5	0.91 (0.25-3.28)	24676	35	0.91 (0.52-1.57)	19906	18	0.80 (0.38-1.68)	24490	27	0.91 (0.48-1.70)	16818	17	1.48 (0.56-3.89)
Q4	3091	5	1.59 (0.35-7.31)	21342	25	0.70 (0.36-1.37)	19495	25	1.25 (0.55-2.82)	26558	35	1.30 (0.63-2.68)	19445	17	1.32 (0.42-4.11)
Q5	2909	6	1.61 (0.30-8.59)	19752	30	0.81 (0.41-1.63)	18412	33	1.73 (0.74-4.03)	26796	31	1.08 (0.49-2.41)	21935	20	1.53 (0.46-5.04)
P-trend [c]			0.48			0.36			0.15			0.62			0.49
P-interaction [d]															0.74

Abbreviations: HR, hazard ratio; CI, confidence interval; N/A, not applicable; Q1–Q5, calorie-adjusted quintiles of micronutrients intake

[a] Total intake was computed as diet plus supplement use. Each micronutrient was adjusted for total calories intake by the residual method. Quintiles were created from intake values at baseline and categorized based on distribution in the entire cohort using the 20th, 40th, 60th, and 80th percentile values as cut points.

[b] All models adjusted for age (continuous), sex, race/ethnicity (White, Black, Hispanic, other), diabetes (yes, no), smoking status (never, former, current), alcohol use (<1, 1-3, >3 drinks/day), total calorie intake (continuous), body mass index (<25, 25-29, ≥30 kg/m^2), education level (<high school, high school graduate, some college/post-high school education, college graduate/post-graduate), multivitamin use (yes, no), red meat intake (0-23, 24-41, 42-63, 64-99, >99 grams/day), and the healthy eating index scores (10-59, 60-66, 67-71, 72-76, >76)

[c] *P*-trend were calculated by treating the quintile variable as a continuous variable

[e] Methionine intake levels were based on dietary intake only because data on supplemental use was not available

[e] A separate model was fitted for the methyl-donor index, adjusting for the factors listed in [b].