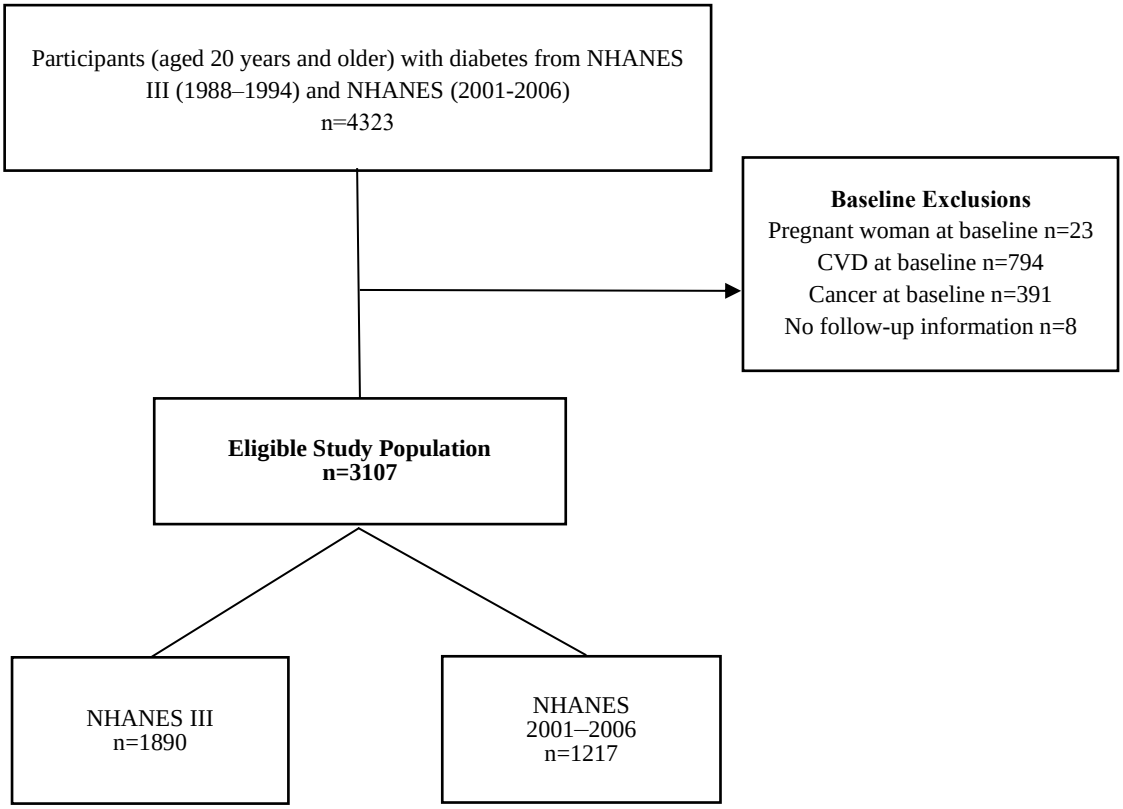
Associations of Serum Carotenoids with Risk of Cardiovascular Mortality among Patients with Type 2 Diabetes

Zixin Qiu,[#], Xue Chen,[#], Tingting Geng, Zhenzhen Wan, Qi Lu, Lin Li, Kai Zhu, Xuena Zhang, Yujie Liu, Xiaoyu Lin, Liangkai Chen, Zhilei Shan, Liegang Liu, An Pan, Gang Liu

#Contributed equally as co-first authors

Online Supplementary Material



Supplementary Figure 1. Flowchart of the study participants

Supplementary Table 1. HRs (95% CIs) of CVD mortality according to quartiles of serum total carotenoids concentrations among patients with type 2 diabetes in NHANES III and NHANES 2001–2006

	Serum total carotenoids (nmol/L)				
	Q1	**Q2**	**Q3**	**Q4**	***P* trend**
Range	<960.0	960.0–1321.0	1321.1–1800.1	>1800.1	
No. deaths/total	91/673	98/666	106/670	107/669	
Model 1	1	1.30 (0.88, 1.92)	1.42 (1.01, 1.92)	1.46 (1.01, 2.10)	0.084
Model 2	1	1.38 (0.91, 2.10)	1.56 (1.14, 2.15)	1.47 (0.96, 2.27)	0.036
Model 3	1	1.34 (0.89, 1.99)	1.42 (1.05, 1.92)	1.48 (0.96, 2.28)	0.140

Model 1: adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, or other).

Model 2: model 1 + BMI (continuous), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (≤1.0, 1.0–3.0, or >3.0), drinking status (nondrinker, low to moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), HEI (in quartiles), total energy intakes (in quartiles), and supplement use (yes, or no).

Model 3: model 2 + diabetes medication use (yes, or no), diabetes duration (<3, 3–10, >10 years), HbA_{1c} (<7%, or ≥7%), self-reported hypertension (yes, or no), serum total cholesterol (in quintiles), and triglycerides (in quintiles).

Supplementary Table 2. HRs (95% CIs) of CVD mortality according to quartiles of serum β-carotene concentrations among type 2 diabetes after excluding participants who died within two years of follow-up in NHANES III and NHANES 2001–2006 (n=2987)

	Serum β-carotene (nmol/L)				
	Q1	**Q2**	**Q3**	**Q4**	***P*** **trend**
	<148.4	**148.4–240.0**	**240.1–429.9**	**>429.9**	
No. deaths/total	67/746	91/746	105/748	137/747	
Model 1	1	1.51 (0.82, 2.77)	1.91 (1.03, 3.53)	2.34 (0.52, 3.60)	<0.001
Model 2	1	1.58 (0.90, 2.79)	1.94 (1.05, 3.59)	2.27 (1.39, 3.71)	0.018
Model 3	1	1.52 (0.86, 2.67)	2.17 (1.21, 3.89)	2.43 (1.58, 3.75)	0.005

Model 1: adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, or other).

Model 2: model 1 + BMI (continuous), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (≤1.0, 1.0–3.0, or >3.0), drinking status (nondrinker, low-to -moderate drinker or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), HEI (in quartiles), total energy intakes (in quartiles), supplement use (yes, or no), and serum α-carotene, β-cryptoxanthin, lutein + zeaxanthin, and lycopene (all natural log-transformed).

Model 3: model 2 + diabetes medication use (yes, or no), diabetes duration (<3, 3–10, >10 years), HbA_{1c} (<7%, or ≥7%), self-reported hypertension (yes, or no), serum total cholesterol (in quintiles), and triglycerides (in quintiles).

Supplementary Table 3. HRs (95% CIs) of CVD mortality according to quartiles of serum β-carotene concentrations among patients with type 2 diabetes with further adjustment of dietary factors and serum nutrient biomarkers in NHANES III and NHANES 2001–2006

	Serum β-carotene (nmol/L)				
	Q1	Q2	Q3	Q4	P_{trend}
	<148.4	148.4–240.0	240.1–424.9	>424.9	
Model 1*	1	1.43 (0.85, 2.42)	2.16 (1.24, 3.75)	2.47 (1.62, 3.76)	0.002
Model 1+dietary β-carotene intake	1	1.36 (0.80, 2.31)	1.92 (1.11, 3.31)	2.20 (1.41, 3.44)	0.004
Model 1+dietary factors †	1	1.34 (0.80, 2.24)	1.97 (1.17, 3.32)	2.19 (1.42, 3.38)	0.006
Model 1+nutrient biomarkers ‡	1	1.42 (0.85, 2.37)	2.16 (1.25, 3.73)	2.32 (1.48, 3.63)	0.010

*Model 1 was adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, or other), BMI (continuous), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (≤1.0, 1.0–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), HEI (in quartiles), total energy intakes (in quartiles), supplement use (yes, or no), serum total cholesterol (in quintiles), triglycerides (in quintiles), diabetes medication use (yes, or no), diabetes duration (<3, 3–10, or >10 years), HbA_{1c} (<7%, or ≥7%), self-reported hypertension (yes, or no), serum α-carotene, β-cryptoxanthin, lutein + zeaxanthin, and lycopene (all natural log-transformed).

† Further adjusted for intakes of vegetables, fruits, total polyunsaturated fatty acids, total monounsaturated fatty acids, total saturated fatty acids, cholesterol, vitamin A, vitamin E, vitamin C and fiber (all in quintiles), There were 127 missing values for all these variables.

‡ Further adjusted for serum vitamin A, vitamin E, vitamin C and 25-hydroxyvitamin D levels (all in quintiles). There were 487 missing values for serum vitamin C levels.

Supplementary Table 4. HRs (95% CIs) of CVD mortality according to quartiles of serum β-carotene concentrations among patients with type 2 diabetes without mutual adjustment of carotenoids in NHANES III and NHANES 2001–2006

	Serum β-carotene (nmol/L)				
	Q1	**Q2**	**Q3**	**Q4**	P_{trend}
	<148.4	**148.4–240.0**	**240.1–424.9**	**>424.9**	
Crude	1	1.43 (0.83, 2.47)	1.83 (1.04, 3.22)	2.23 (1.49, 3.34)	<0.001
Model 1	1	1.35 (0.84, 2.17)	1.52 (0.95, 2.42)	1.69 (1.22, 2.33)	0.023
Model 2	1	1.23 (0.75, 2.02)	1.57 (0.98, 2.51)	1.67 (1.18, 2.37)	0.024

Model 1: adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, or other).

Model 2: model 1 + BMI (continuous), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (≤1.0, 1.0–3.0, or >3.0), drinking status (nondrinker, low-to -moderate drinker or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), HEI (in quartiles), total energy intakes (in quartiles), and supplement use (yes, or no).

Model 3: mode 2+diabetes medication use (yes, or no), diabetes duration (<3, 3–10, >10 years), HbA_{1c} (<7%, or ≥7%), self-reported hypertension (yes, or no), serum total cholesterol (in quintiles), and triglycerides (in quintiles).

Supplementary Table 5. HRs (95% CIs) of CVD mortality according to quartiles of dietary carotenoids intakes among patients with type 2 diabetes in NHANES 2001–2014 (n=3686)

	Quartiles of dietary intake (μg/day)				
	Q1	**Q2**	**Q3**	**Q4**	P_{trend}
α-carotene					
Range	<14.0	14.0–51.0	51.1–274.0	>274.0	
No. deaths/total	31/918	28/932	31/915	22/921	
Crude	1	1.00 (0.49, 2.01)	0.83 (0.41, 1.71)	0.55 (0.28, 1.08)	0.056
Multivariable adjusted*	1	0.80 (0.38, 1.69)	0.62 (0.29, 1.33)	0.40 (0.17, 0.91)	0.030
β-carotene					
Range	<279.0	279.0–753.0	753.1–2249.0	>2249.0	
No. deaths/total	30/923	30/920	26/922	26/921	
Crude	1	1.42 (0.76, 2.63)	1.43 (0.69, 2.98)	1.07 (0.49, 2.34)	0.724
Multivariable adjusted*	1	2.14 (1.05, 4.38)	1.95 (0.79, 4.19)	1.40 (0.47, 4.19)	0.622
β-cryptoxanthin					
Range	<7.0	7.0–28.0	28.1–103.0	>103.0	
No. deaths/total	27/929	25/925	26/908	34/924	
Crude	1	0.95 (0.44, 2.04)	0.97 (0.47, 2.04)	0.96 (0.50, 1.86)	0.966
Multivariable adjusted*	1	0.93 (0.45, 1.92)	0.83 (0.43, 1.62)	0.76 (0.35, 1.64)	0.595
Lycopene					
Range	0.0	1.0–1261.0	1261.1–4902.0	>4902.0	
No. deaths/total	47/1007	20/836	23/922	22/921	
Crude	1	0.45 (0.23, 0.86)	0.56 (0.31, 1.01)	0.64 (0.34, 1.18)	0.673
Multivariable adjusted*	1	0.41 (0.19, 0.87)	0.60 (0.30, 1.20)	0.56 (0.27, 1.13)	0.607
Lutein/zeaxanthin					
Range	<330.0	330.0–663.0	663.1–1333.0	>1333.0	
No. deaths/total	22/920	34/923	28/922	28/921	
Crude	1	1.97 (1.01, 3.84)	1.06 (0.50, 2.23)	1.79 (0.92, 3.46)	0.319
Multivariable adjusted*	1	1.70 (0.85, 3.41)	1.01 (0.45, 2.25)	1.97 (0.66, 5.84)	0.375

*Adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, or other), BMI (continuous), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (≤1.0, 1.0–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), HEI, intakes of total energy, vitamin C, vitamin A, vitamin E, selenium, total cholesterol, total fat, fiber, other dietary carotenoids (all in quartiles), self-reported hypertension (yes, or no) and hypercholesterolemia (yes, or no), diabetes medication use (yes, or no), diabetes duration (<3, 3–10, >10 years), and HbA_{1c} (<7%, or ≥7%).