Pre-diagnostic Circulating Concentrations of Fat-soluble Vitamins and Risk of Glioma in Three Cohort Studies

Authors:
Yiyang Yue,[1] Jordan H. Creed,[2] David J. Cote,[3,4] Meir J. Stampfer,[1,3,5] Molin Wang,[3,5,6] Øivind Midttun,[7] Adrian McCann,[7] Per Magne Ueland,[8,9] Jeremy Furtado,[1] Kathleen M. Egan,*[#10] Stephanie A. Smith-Warner[#1,5]

[#] Equal contribution as last authors
*denotes corresponding author

Affiliations:
[1] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[2] Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center, Tampa, FL, USA
[3]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA,USA
[4]Computational Neuroscience Outcomes Center, Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA
[5]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[6]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[7]Bevital A/S, Bergen, Norway
[8]Department of Clinical Science, University of Bergen, N-5021 Bergen, Norway
[9]Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway
[10]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Correspondence:
Kathleen M. Egan
Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center, Tampa, FL, USA
Kathleen.Egan@moffitt.org

Supplementary Table 1. Characteristics of participants in the fat-soluble vitamins and risk of Glioma analysis by sex in the UK Biobank, Nurses' Health Study, and Health Professionals Follow-up Study.

Characteristics	UKB				NHS and HPFS			
	Women		Men		Women		Men	
	Cases	Cohort	Cases	Cohort	Cases	Controls	Cases	Controls
N	168	182972	276	163813	52	104	32	64
Age, years	59.8 (6.9)	55.6 (8.1)	59.8 (7.0)	55.8 (8.2)	57.8 (6.1)	58.0 (6.1)	63.8 (9.2)	63.9 (9.1)
Follow-up, years	4.1 (2.2)	/	3.9 (2.2)	/	9.4 (4.3)	/	7.3 (4.0)	/
Body mass index, kg/m^2	27.0 (4.7)	27.0 (5.2)	27.6 (4.2)	27.8 (4.3)	24.5 (4.9)	26.6 (5.2)	25.7 (4.8)	25.3 (3.4)
Current multivitamin use, %	/	/	/	/	32.7	31.7	43.8	48.4
Current smoker, %	7.1	8.4	11.6	12.3	13.5	10.6	3.1	1.6
Past smoker, %	36.9	30.5	40.6	37.2	48.1	44.2	56.3	34.4
25(OH)D, nmol/L	48.2 (20.5)	48.5 (20.9)	48.6 (19.0)	48.0 (21.1)	72.5 (22.2)	67.5 (24.0)	70.2 (16.4)	67.5 (16.9)
Retinol, μmol/L	/	/	/	/	2.3 (0.7)	2.2 (0.5)	2.3 (0.4)	2.3 (0.4)
α-tocopherol, μmol/L	/	/	/	/	47.2 (22.3)	46.3 (20.4)	38.7 (11.5)	42.8 (17.5)
γ-tocopherol, μmol/L	/	/	/	/	7.0 (3.9)	6.3 (3.0)	5.1 (2.9)	5.0 (2.9)
Cholesterol, mg/dL	226 (38)	221 (38)	212 (40)	210 (40)	201 (36)	199 (32)	186 (27)	194 (33)
Season of blood draw, %								
Spring	29.8	29.5	25.4	28.4	28.9	32.7	15.6	21.9
Summer	20.8	26.9	22.8	26.1	38.5	30.8	34.4	37.5
Fall	28.0	24.6	28.3	24.0	11.5	14.4	34.4	26.6
Winter	21.4	19.0	23.6	21.5	21.2	22.1	15.6	14.1

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; UKB, United Kingdom Biobank.
/ denotes not applicable or data not available
Continuous variables presented as mean (SD) and categorical variables as percentage (%).

Supplementary Table 2. Associations between circulating 25(OH)D and glioma risk by sex in the UK Biobank, Nurses' Health Study, and Health Professionals Follow-up Study.

	UKB				HPFS and NHS			
	Women		Men		Women		Men	
Study specific tertiles[3]	Number of glioma cases	HR (95% CI)[1]	Number of glioma cases	HR (95% CI)[1]	Number of glioma cases	RR (95% CI)[2]	Number of glioma cases	RR (95% CI)[2]
1	54	1 (ref)	89	1 (ref)	14	1 (ref)	11	1 (ref)
2	55	0.92 (0.63-1.136)	95	0.92 (0.68-1.24)	16	1.17 (0.47-2.91)	12	0.94 (0.33-2.73)
3	59	0.94 (0.64-1.39)	92	0.83 (0.61-1.13)	22	1.42 (0.61-3.32)	9	0.66 (0.20-2.18)
P_{trend}[4]		0.77		0.23		0.41		0.51
IOM guidelines for bone health, nmol/L								
<50(deficiency/insufficiency)	62	0.96 (0.69-1.34)	108	0.91 (0.70-1.18)	8	1.11 (0.40-3.06)	4	0.54 (0.14-2.04)
50-<75(sufficiency)	91	1 (ref)	143	1 (ref)	20	1 (ref)	17	1 (ref)
≥75 (above sufficiency)	15	0.74 (0.42-1.30)	25	0.71 (0.46-1.10)	24	1.24 (0.59-2.60)	11	0.52 (0.17-1.60)
P_{trend}[4]		0.55		0.61		0.70		0.77
Continuous[5 6]	168	0.99 (0.83-1.19)	276	0.93 (0.80-1.07)	52	1.12 (0.76-1.67)	32	1.02 (0.52-2.00)

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IOM, Institute of Medicine; NHS, Nurses' Health Study; RR, risk ratio; UKB, United Kingdom Biobank.

[1]Adjusted for sex (male vs female), age (continuous), race (non-white vs white), month of blood collection (continuous), BMI (continuous), and smoking status (never, current and previous).

[2]In addition to conditioning on matching factors in the NHS and HPFS (age, fasting status, month of blood collection, and race), adjusted for BMI (continuous) and smoking status (never, current and previous).

[3]Median serum 25(OH)D for each tertile in the UKB 26.91, 46.43, 68.67 nmol/L; median plasma 25(OH)D for each tertile in the NHS and HPFS: 47.55, 68.29, and 87.90 nmol/L.

[4]The p-value for linear trend corresponds to the p-value of the ordinal variable constructed by assigning the median value of each category to all participants in that category.

[5]Results for the continuous analyses are given for a 25 nmol/L increment.

[6]P for interaction by sex: 0.62 for UKB; 0.84 for NHS and HPFS.

Supplementary Table 3. Associations between circulating 25(OH)D and glioma risk among non-smokers and after a 4-year lag in the UK Biobank, Nurses' Health Study, and Health Professionals Follow-up Study.

	Non-smokers				After applying a 4-year lag			
	UKB		NHS and HPFS		UKB		NHS and HPFS	
	Number of glioma cases	HR (95%CI)[1]	Number of glioma cases	RR (95%CI)[2]	Number of glioma cases	HR (95%CI)[1]	Number of glioma cases	RR (95%CI)[2]
Study specific tertiles[3]								
1	118	1 (ref)	23	1 (ref)	70	1 (ref)	18	1 (ref)
2	139	0.97 (0.75-1.25)	27	1.07 (0.53-2.16)	76	0.95 (0.68-1.33)	25	1.43 (0.66-3.09)
3	138	0.88 (0.68-1.15)	26	1.01 (0.49-2.07)	75	0.91 (0.65-1.29)	24	1.21 (0.56-2.64)
P_{trend}[4]		0.34		0.99		0.60		0.74
IOM guidelines for bone health, nmol/L								
<50(deficiency/insufficiency)	158	0.92 (0.74-1.14)	11	0.82 (0.36-1.90)	84	0.90 (0.68-1.21)	12	0.77 (0.35-1.68)
50-<75(sufficiency)	202	I (ref)	35	1 (ref)	115	1 (ref)	37	1 (ref)
≥75 (beyond sufficiency)	35	0.68 (0.47-0.98)	30	0.91 (0.49-1.71)	22	0.82 (0.51-1.32)	31	0.79 (0.43-1.46)
P_{trend}[4]		0.38		0.93		1.00		0.87
Continuous[5 6]	395	0.94 (0.84-1.07)	76	1.09 (0.55-2.16)	221	0.97 (0.82-1.14)	67	1.08 (0.73-1.58)

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IOM, Institute of Medicine; NHS, Nurses' Health Study; RR, risk ratio; UKB, United Kingdom Biobank.

[1]Adjusted for sex (male vs female), age (continuous), race (non-white vs white), month of blood collection (continuous), BMI (continuous), and smoking status (never, current and previous).

[2]In addition to conditioning on matching factors in the NHS and HPFS (age, fasting status, month of blood collection, and race), adjusted for BMI (continuous) and smoking status (never, current and previous).

[3]Median serum 25(OH)D for each tertile in the UKB 26.91, 46.43, 68.67 nmol/L; median plasma 25(OH)D for each tertile in the NHS and HPFS: 47.55, 68.29, and 87.90 nmol/L.

[4]The p-value for linear trend corresponds to the p-value of the ordinal variable constructed by assigning the median value of each category to all participants in that category.

[5]Results for the continuous analyses are given for a 25 nmol/L increment.

Supplementary Table 4. Spearman correlation coefficients for fat soluble vitamins and cholesterol in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

	25 (OH)D	Retinol	α-tocopherol	γ-tocopherol	Cholesterol
NHS (Females) *n*=104					
25(OH)D	1	0.22*	0.30*	-0.21*	0.01
Retinol		1	0.55*	0.02	0.42*
α-tocopherol			1	-0.15	0.55*
γ-tocopherol				1	0.24*
Cholesterol					1
HPFS (Males) *n*=64					
25(OH)D	1	0.12	0.11	-0.22	-0.04
Retinol		1	0.32*	0.12	0.39*
α-tocopherol			1	-0.27*	0.41*
γ-tocopherol				1	0.31*
Cholesterol					1.0

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; *p<0.05

Supplementary Table 5. Associations between circulating retinol, α- and γ-tocopherol and glioma risk by sex in the Nurses' Health Study and Health Professionals Follow-up Study.

	Women		Men	
	Number of glioma cases	RR (95%CI)[1]	Number of glioma cases	RR (95%CI)[1]
Retinol				
Tertile[2]				
1	17	1	7	1
2	15	1.23 (0.49-3.06)	15	1.09 (0.33-3.54)
3	20	1.14 (0.47-2.77)	10	1.31 (0.37-4.60)
p_{trend}[3]		0.80		0.66
Continuous[4 5]	52	1.00 (0.70-1.45)	32	0.76 (0.37-1.56)
α-tocopherol				
Tertile[6]				
1	18	1	16	1
2	14	0.48 (0.18-1.27)	11	1.21 (0.44-3.29)
3	20	0.66 (0.23-1.91)	5	0.39 (0.10-1.52)
p_{trend}[3]		0.55		0.24
Continuous[4 7]	52	1.39 (0.99-1.95)	32	1.18 (0.68-2.04)
γ-tocopherol				
Tertile[8]				
1	12	1	17	1
2	19	1.23 (0.48-3.14)	7	0.82 (0.28-2.38)
3	21	1.37 (0.51-3.65)	8	1.28 (0.39-4.17)
p_{trend}[3]		0.54		0.76
Continuous[4 9]	52	1.03 (0.74-1.42)	32	1.50 (0.80-2.81)

Abbreviations: CI, confidence interval; RR, risk ratio.

[1]In addition to conditioning on matching factors in the NHS and HPFS (age, fasting status, month of blood collection, and race), adjusted for BMI (continuous), smoking status (never, current and previous), and cholesterol (continuous).

[2]Median plasma retinol for each tertile in the NHS and HPFS: 1.74, 2.16, and 2.74 μmol/L.

[3]The p-value for linear trend across tertiles was the p-value of the ordinal variable constructed by assigning medians to all participants in the tertiles.

[4]Results for continuous analyses for each standard deviation increment.

[5]P for ineraction by sex: 0.29 for retinol.

[6]Median plasma α-tocopherol for each tertile in the NHS and HPFS: 29.66, 41.32, and 57.50 μmol/L.

[7]P for ineraction by sex: 0.50 for α-tocopherol.

[8]Median plasma γ-tocopherol for each tertile in the NHS and HPFS: 2.94, 5.60, and 8.59 μmol/L.

[9]P for ineraction by sex: 0.62 for γ-tocopherol.

Supplementary Table 6. Associations between circulating retinol, α- and γ-tocopherol and glioma risk among non-smokers and after a 4-year lag in the Nurses' Health Study, and Health Professionals Follow-up Study.

		Non-smokers		After applying a 4-year lag	
		Number of glioma cases	RR (95%CI)	Number of glioma cases	RR (95%CI)
Retinol					
Tertile[2]					
	1	22	1 (ref)	18	1 (ref)
	2	28	1.05 (0.51-2.19)	26	1.24 (0.57-2.71)
	3	26	1.23 (0.56-2.70)	23	1.17 (0.49-2.80)
	p_{trend}[3]		0.59		0.75
Continuous[4]		76	1.15 (0.83-1.60)	67	1.06 (0.77-1.46)
α-tocopherol					
Tertile[5]					
	1	33	1 (ref)	29	1
	2	23	0.68 (0.34-1.37)	21	0.60 (0.28-1.31)
	3	20	0.56 (0.24-1.29)	17	0.46 (0.19-1.12)
	p_{trend}[3]		0.17		0.09
Continuous[4]		76	0.97 (0.66-1.41)	67	0.86 (0.60-1.23)
γ-tocopherol					
Tertile[6]					
	1	28	1 (ref)	22	1 (ref)
	2	24	1.18 (0.58-2.40)	22	1.12 (0.52-2.41)
	3	24	1.20 (0.56, 2.60)	23	1.42 (0.62-3.21)
	p_{trend}[3]		0.65		0.39
Continuous[4]		76	1.32 (0.97-1.79)	67	1.30 (0.96-1.77)

Abbreviations: CI, confidence interval; RR, risk ratio.

[1]In addition to conditioning on matching factors in the NHS and HPFS (age, fasting status, month of blood collection, and race), adjusted for BMI (continuous), smoking status (never, current and previous), and cholesterol (continuous).

[2]Median plasma retinol for each tertile in the NHS and HPFS: 1.74, 2.16, and 2.74 μmol/L.

[3]The p-value for linear trend across tertiles was the p-value of the ordinal variable constructed by assigning medians to all participants in the tertiles.

[4]Results for continuous analyses for each standard deviation increment.

[5]Median plasma α-tocopherol for each tertile in the NHS and HPFS: 29.66, 41.32, and 57.50 μmol/L.

[6]Median plasma γ -tocopherol for each tertile in the NHS and HPFS: 2.94, 5.60, and 8.59 μmol/L.

Supplementary Table 7. Joint associations between plasma α- and γ-tocopherol and glioma risk in the Nurses' Health Study and Health Professionals Follow-up Study.

	Lower[1] γ-tocopherol		Higher[2] γ-tocopherol	
	Gliomas	RR (95%CI) [3]	Gliomas	RR (95%CI) [3]
Lower[1] α-tocopherol	22	1 (ref)	25	1.06 (0.48-2.34)
Higher[2] α-tocopherol	18	0.60 (0.26-1.41)	19	0.84 (0.33-2.14)

Abbreviations: CI, confidence interval; RR, risk ratio.
[1] Below median level.
[2]Above median level.
[3]In addition to conditioning on matching factors in the NHS and HPFS (age, fasting status, month of blood collection, and race), adjusted for BMI (continuous), smoking status (never, current and previous), and cholesterol (continuous).