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Dietary intake of nutrients involved in one-carbon metabolism and risk of urothelial cell carcinoma: a prospective cohort study

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Novelty and Impact: B vitamins and methionine are involved in one-carbon metabolism and may play a role in carcinogenesis through DNA replication, repair and methylation mechanisms. We assessed associations between B vitamins and methionine and urothelial cancer risk, overall, by tumour aggressiveness, and for higher-risk population subgroups whose nutritional status may be compromised. Our study found no evidence that dietary intake of nutrients involved in one-carbon metabolism play a role in urothelial cancer development.

Short title: One-carbon metabolism nutrients and urothelial cancer risk

Keywords: urothelial cell carcinoma, bladder cancer, one-carbon metabolism, B vitamin, folate, methionine, diet

Word count: 3,125; **Tables:** 5; **Supplementary Material**: 1 Table and 2 Figures

ABSTRACT

Nutrients involved in one-carbon metabolism may play a role in carcinogenesis through DNA replication, repair and methylation mechanisms. Most studies on urothelial cell carcinoma (UCC) have focused on folate. We sought to examine the association between B-group vitamins and methionine intake and UCC risk, overall and by subtype, and to test whether these associations are different for population subgroups whose nutritional status may be compromised. We followed participants in the Melbourne Collaborative Cohort Study (N=41,513) for over 20 years, and observed 500 UCC cases (89% originating in the bladder; superficial: 279, invasive: 221). Energy-adjusted dietary intakes of B vitamins (B1, B2, B3, B5, B6, B8, B9, and B12) and methionine were estimated from a 121-item food frequency questionnaire administered at baseline (1990-1994), using the residuals method. We used Cox regression models to compute hazard ratios (HR) of UCC risk per standard deviation of log-transformed nutrient intakes and 95% confidence intervals (CI), adjusted for potential confounders. We investigated associations by tumour subtype, and tested interactions with sex, country of birth, smoking, and alcohol drinking. The risk of UCC appeared not to be associated with intake of B-group vitamins or methionine, and findings were consistent across tumour subtypes and across demographic and lifestyle characteristics of the participants. A potential interaction between vitamin B1 and alcohol drinking was observed (all participants: HR per 1 SD=0.99 (0.91-1.09), never drinkers: HR=0.81 (0.69-0.97), P-interaction=0.02), which needs to be confirmed by other studies. Our findings do not indicate that dietary intake of nutrients involved in one-carbon metabolism are associated with UCC risk.

INTRODUCTION

Urothelial cell carcinoma (UCC) includes tumours of the renal pelvis, the ureter, urinary bladder and proximal urethra, with about 90% of these originating in the urothelium of the bladder. [1] While age, sex, smoking, and occupational exposure to chemicals are established risk factors for the development of UCC, [2] the role of dietary factors remains unclear. [3, 4]

Although it is biologically plausible that dietary factors are involved in the aetiology of UCC due to their opportunity for contact with the urothelium, [5] the World Cancer Research Fund's (WCRF) Second Expert Report in 2007 found that the evidence was too limited to conclude that any food or nutrient was directly associated with the risk of bladder cancer, but limited evidence was identified suggesting that consumption of folate and milk, rich in vitamin B2 and B12, are associated with reduced risk, and drinking water contaminated with arsenic is associated with increased risk of developing bladder cancer. [6] Similar conclusions were reached by the 2015 WCRF Systematic Literature Review Continuous Update Project Report. [7] Folate (vitamin B9), which is one of several B group vitamins that are water-soluble and excreted via the urinary tract, may modify arsenic metabolism. [8]

B-group vitamins such as folate and vitamins B2, B6 and B12 are present in a wide range of foods such as cereals, meat, fruit and vegetables, and are involved in key cellular functions such as the metabolism of energy providing macronutrients. [9, 10] These vitamins also form part of the one-carbon metabolism pathway and, as such, play a key role in DNA synthesis, repair and methylation, and therefore potentially influence carcinogenesis. [11] In a recent study, we found that global DNA methylation was differentially associated with risk of UCC subtypes. [12] While there is mounting evidence of a role for these key nutrients in the development of tumours at other sites, the few studies that have investigated associations between B vitamins and risk of UCC have been heterogeneous in design, measures, analyses and findings. [13-17]

A 2014 meta-analysis reported a potential inverse association between folate intake and bladder cancer risk, although this association was only evident from retrospective studies and not in prospective studies. [18] One large US case-control study included in the meta-analysis which found no association of bladder cancer risk with folate intake, identified a potential inverse association with vitamin B12 intake. [19]

Our principal aim was to investigate prospectively associations between dietary intake of B-group vitamins and methionine and the risk of developing UCC, using a cohort of ethnically

diverse, middle-aged individuals. Our secondary aims were to examine potential differences in risk between superficial and invasive disease, and to assess whether associations were more evident for higher-risk groups such as smokers and alcohol drinkers, as these behaviours may alter nutritional status.

MATERIAL AND METHODS

Study sample

The Melbourne Collaborative Cohort Study (MCCS) is a prospective study of 41,513 participants (17,045 men) recruited between 1990 and 1994, 99.3% of whom were aged between 40 and 69 years at baseline. [20] Study participants were recruited from the metropolitan area of Melbourne in Victoria, Australia. People of Southern European descent (born in Italy or Greece) were oversampled to extend the range of lifestyle exposures, including dietary habits. All study participants provided informed consent in accordance with the Declaration of Helsinki. The study was approved by Cancer Council Victoria's Human Research Ethics Committee.

Case ascertainment

Cases of UCC were identified by record linkage with the Victorian Cancer Registry, which receives mandatory notification of all new cancer cases in Victoria, Australia, and the Australian Cancer Database. Incident UCC cases were identified up to 31 December 2015, using ICD-O-3 morphology codes 8120, 8122, 8130 or 8131. Diagnostic pathology reports were reviewed and classified according to the International Classification of Disease (ICD-O-3 WHO classification). Disease subtypes were defined according to behaviour, with invasive UCC including any tumour that had penetrated or invaded the basement membrane. Superficial UCC included papillary transitional/urothelial cell neoplasm of low malignant potential (PUNLMP) or carcinoma in situ (CIS) that was completely confined within the epithelium. [21] Cases with uncertain behaviour type, including PUNLMP, and with a topography code corresponding to vagina (ICD-4: C52.9) were censored at the time of diagnosis. The remaining cases included topographic codes (ICD-O-3) corresponding to the bladder (C67), the kidney (C64-C65), the ureter (C66), and the urethra (C68).

Exclusion criteria

We excluded from the analysis participants who were diagnosed with UCC before study entry (N=69). To avoid misclassification of dietary habits, we also excluded individuals who reported a personal history of stroke, heart disease, angina, or diabetes at study entry as they may have changed their diet in response to their diagnoses (N =3,793). Participants in the first and 99th percentile of the sex-specific energy intake distributions were also excluded, as they may represent aberrant reporting of food habits (N=725); that is, males with energy intakes of <3,770 or >25,372 kJ/day, and females with energy intakes of <3,142 or >21,380 kJ/day. Finally, we excluded participants with missing dietary data (N=38). Missing data (<1 % in any of the other variables) were imputed with the median (for continuous variables) or mode (for categorical variables) of observed values of the corresponding variable.

Dietary intake estimates

Dietary information was obtained from a food frequency questionnaire (FFQ) specifically developed for the MCCS. [22] This FFQ estimates the intake of 121 food items including meats, fish, fruits, vegetables, cereal-based foods, fats and oils, and both alcoholic and non-alcoholic beverages. Dietary measures for the B vitamins and methionine were derived from the Australian NUTTAB nutritional 2006 database. [23] Mean daily intakes for 9 nutrients (thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, biotin (B8), folate (B9), vitamin B12 and methionine) were estimated by multiplying the daily frequency of each food item by the nutrient composition for an average sex-specific portion size. [24-27] Folate intake was estimated using only that occurring naturally in food, as folate fortification was rare in Australia at the time baseline measures were collected. Intakes of energy and each nutrient were log transformed to obtain distributions closer to Gaussian, as these may provide a better model fit. Nutrient intakes were adjusted for energy using the residuals method. [28] We calculated the Mediterranean diet score (MDS) as a measure of overall diet quality, which we have previously shown to be associated with invasive UCC risk. [4] Using other dietary scores made virtually no difference to the results.

Questionnaire and anthropometric measures

Extensive data were also collected at recruitment on a wide range of exposures such as smoking, anthropometry (height, weight, waist and hip circumferences measured by trained staff using standard methods), alcoholic beverage intake, multivitamin use, country of birth, socioeconomic status (score ranging from 1 to 10 representing deciles of relative

socioeconomic disadvantage of area of residence), [29] highest level of educational attainment and physical activity. [30]

Statistical analysis

Follow-up began at study entry and continued until date of diagnosis of UCC, date of diagnosis of cancer of an unknown primary site, date of an unconfirmed UCC or a tumour with uncertain behaviour, date of death, date last known to be in Australia, or 31 December 2015, whichever came first.

Cox regression models were fitted, with age as the time axis, [31] to estimate hazard ratios (HRs) and 95% confidence intervals for UCC risk associated with each nutrient measure. For each nutrient, the proportional hazards assumption was assessed by test and visual inspection of the Schoenfeld residuals[32]; these showed no violation of the assumption for any nutrient variable (Supplementary Material). For each energy-adjusted nutrient, sex-specific quartiles were obtained using the whole sample, and analysed using the lowest quartile as the reference category. Departure from linearity in the relationship between B-group vitamins and UCC risk (overall, invasive, and superficial) was investigated using likelihood ratio tests to compare models including dietary intake variables as linear versus categorical (using quartiles). If the relationship was found not to be linear, we tested for potentially U-shaped or bell-shaped relationship by adding a quadratic term to the model, which we tested using a likelihood ratio test. Hazard ratios were given per one standard deviation increase of each log-transformed nutrient variable, in order to minimise the influence of very large values on the natural scale. Results for the raw variables of nutrient intakes showed similar results and were presented in Supplementary Material.

Based on directed acyclic graphs (DAG), [33] we fitted two models. Model 1 adjusted for the main potential confounders: sex, country of birth (Australia/New-Zealand, Southern Europe, Northern Europe), educational attainment (completed primary school or lower, some high or technical school, completed high or technical school, completed tertiary degree or diploma), socioeconomic status (decile categories fit as a continuous variable), smoking status (never, former: quit ≤15 years prior, former: quit >15 years prior, current ≤20 cigarettes per day, current >20 cigarettes per day), and alcohol intake (Australian NHMRC recommendations: none, 1-39 g/d [males] and 1-19 g/d [females], 40-59 g/d [males] and 20-39 g/d [females], 60+ g/d [males] and 40+ g/d [females])). Model 2 additionally adjusted for waist

circumference (continuous), physical activity score (continuous), Mediterranean diet score (continuous), red meat intake (continuous), and reported intake of nonsteroidal anti-inflammatory drugs (NSAIDS) (none, aspirin only, other NSAIDs only, aspirin and other NSAIDs).

To test for heterogeneity in the HRs by tumour subtype (invasive vs. superficial) we fitted Cox proportional hazard regression models for competing risk using a data duplication method. [34]

To examine the interaction of intake of each nutrient with alcohol and smoking, both of which may affect the assimilation of vitamins, alcohol intake was categorized as never / low / high (>40 g/d for men and > 20 g/d for women) and smoking as current / former / never.

Finally, we conducted a sensitivity analysis excluding participants who reported using multivitamin tablets, as these may contain B vitamins for which intake could not be assessed.

RESULTS

We included 36,882 participants in the analysis, followed for a median time of 22.2 years. In total, 500 UCC cases were diagnosed (89% originating in the bladder, 7% in the kidney, 3% in the ureter, and 1% in the urethra), including 279 superficial and 221 invasive cases. Cases were more likely to be males from Southern Europe, smokers, alcohol drinkers and have higher BMI (Table 1). Spearman correlations between nutrient intakes are presented in Table 2. Moderate to strong correlations ($\rho \approx 0.5$ to 0.7) were observed for vitamin B12 with vitamin B6 and methionine, for folate with biotin, for thiamine with riboflavin, for vitamin B5 and B6, for vitamin B5 and B12, and for riboflavin and niacin.

We did not observe significant linear associations between intakes of B-group vitamins or methionine (on the log scale) and the risk of UCC, either in the basic or in the more comprehensive model (Table 3). The association appeared to be non-linear for the intake of vitamin B6 (departure from linearity P =0.004), and there was evidence of an inverse U-shaped relationship (quadratic term P=0.01, not shown). Moderate intakes of vitamin B6 appeared to be associated with higher risk (quartile 2 vs. quartile 1: HR=1.41 (95% CI: 1.09-1.82), quartile 3 vs. quartile 1: HR=1.47 (95% CI: 1.13-1.91), quartile 4 vs. quartile 1: HR=1.16 (95% CI: 0.88-1.53). Results from Model 1 and Model 2 were very similar, indicating that confounding was unlikely to play a role in any of the observed associations (Table 3). There was no evidence that intakes of B vitamins or methionine were differentially

associated with risk of invasive or superficial UCC subtype (Table 4, for all nutrients: P heterogeneity>0.1).

In Table 5, we present results for potential effect modification by smoking and alcohol drinking status, as these may affect the metabolism of B vitamins. With the exception of thiamine, for which there was weak evidence of an inverse association with UCC risk for never drinkers (P heterogeneity=0.02), we did not find that smoking or alcohol consumption modified the association between B-group vitamin or methionine intakes and UCC risk. No heterogeneity in the associations was observed by sex or country of birth either (data not shown).

Finally, we conducted the same analyses after excluding 6,184 (17%) participants who reported using multivitamin tablets, and similar findings were obtained (data not shown).

DISCUSSION

We did not find evidence that dietary intake of any B-group vitamin or methionine, as estimated using a 121-item FFQ, was associated with the risk of UCC. The quadratic association we observed for vitamin B6 intake is difficult to interpret because both low and high intakes were associated with a lower risk of UCC (thus intermediary intakes associated with increased risk). There was no consistent evidence of effect heterogeneity across UCC subtypes, or within participant subgroups. That is, there did not appear to be a more protective effect of B vitamin intakes among higher-risk individuals such as smokers or alcohol drinkers as hypothesised. We did observe an interaction between alcohol drinking status and vitamin B1; an inverse association with UCC was observed in never drinkers. This association did not appear to have a clear explanation as we hypothesised that B vitamin intakes would be more beneficial in participants whose absorption of B vitamins may have deteriorated due to smoking or alcohol drinking. [35, 36] Given the number of tests performed in our study, we therefore conclude that the few and inconsistent tests with P<0.05 we observed were likely due to chance and require confirmation by other studies.

The main strength of our study is that it was prospective, thus minimising the possibility of recall and selection biases. We had lengthy and virtually complete follow-up since the identification of incident UCC cases was performed by record linkage to Australian population-based cancer registries that have virtually complete coverage of the cohort participants. Although UCC is not a common cancer, we could include in our analysis a

relatively large number of cases (N=500), with information on tumour behaviour. We also had extensive data on participant characteristics, which we used to produce less confounded estimates of association.

The main limitation of our analysis pertains to the use of a single food frequency questionnaire administered at baseline to examine the risk of UCC over more than two decades: first, measurement error is considered to be large in FFQ-assessed dietary intakes, as we observed in our study, [37] and this generally tends to attenuate measures of association; [38] second, participants may have changed their diets substantially over two decades. These sources of measurement error are likely to have substantially reduced the power of our study. Additionally, we did not formally adjust our results for multiple testing because tests were largely non-independent in our study, but rather interpreted the few and inconsistent tests with $P<0.05$ as potential chance findings. We used food composition data for B vitamins and methionine from 2006 to apply to dietary data collected in the early 1990s. The mandatory fortification of bread flour with folate was not introduced until 2009 and voluntary fortification of flour and cereals was not permitted until June 1995 [39]; however, mandatory fortification of bread flour with thiamine was introduced from January 1st 1991 [40] so levels assumed for FFQs completed early on may be over-estimated. B vitamins have also been added to breakfast cereals in amounts determined by manufacturers and probably did not change systematically between 1990 and 2006. We were also not able to assess possible genetic influences such as variants in the *MTHFR* and *MTR* genes, which play a key role in DNA methylation processes and may substantially affect plasma concentrations of B vitamins. [41] It has been suggested that extra folate will be required by individuals with the CT or TT genotypes of the MTHFR polymorphism, [42] hence dietary intake is likely to be less important to people with the CC genotype and combining the genotypes may hide any association. Other associations between genetic loci and assimilation of B vitamins have been identified, for example polymorphisms in *ALPL* with vitamin B6 and *FUT2, FUT6, TCN1, TCN2, CUBN*, and *MMAA* with vitamin B12. [43, 44] While at present, limited evidence exists that gene-diet interactions contribute to cancer risk, [45] to our knowledge such associations have not been assessed in the case of B vitamins and urothelial cancer.

Another limitation is that we did not have information on environmental and occupational exposures to chemicals associated with increased risk of bladder cancer (e.g., polycyclic aromatic hydrocarbons and aromatic amines), which could have confounded our estimates if exposed industry workers had unhealthier dietary habits than other cohort participants.

Occupational exposure to carcinogens in Australia is estimated to cause 14% of bladder cancer in men and 0.7% in women. [46] Any resulting confounding effect from differential eating habits is, therefore, likely to be very small. We adjusted our results for socioeconomic status and educational level, which provided some indirect control for occupational exposures.

The one-carbon metabolism pathway is complex and little is known about the relationship between the different B-group vitamins, and their biological interactions with other dietary and environmental exposures. [10] Even though our study population appeared to have a high daily intake of B group vitamins (see Table 1), UCC is a disease that typically affects older people, and the bioavailability of these vitamins may be compromised in this demographic by certain drugs such as acid lowering agents (Proton Pump Inhibitors), and diuretics because of the water-soluble nature of this group of vitamins. [47]

To our knowledge, few other studies have assessed associations between B-group vitamins and UCC risk in a systematic manner. A Danish prospective cohort study (N = 322 urothelial cancer cases) concluded that there was no association between intake of folate and risk of UCC, and their findings were also similar to ours for subgroup analyses by smoking status.[16] A Spanish case-control study of 912 bladder cancer patient cases matched with hospital-based controls, reported inverse associations of several B vitamins (B12, B6, B2, and a borderline association for folate) with UCC risk. [14] Using data from another case-control study (the New Hampshire study, N=322 bladder cancer cases), Brinkman et al. [13] reported inverse associations with thiamine and niacin, but as in our study, no association with riboflavin, vitamin B6 and B12 or folate. Case-control studies are more prone to bias, and often result in stronger risk estimates than those obtained from prospective studies. [48] A meta-analysis of the association of folate with bladder cancer risk found an inverse association in cross-sectional but not in prospective studies.[18]

In conclusion, our study corroborates previous research in not detecting associations between dietary intakes of B-group vitamins and the risk of urothelial cell carcinoma. Future studies on B vitamins and UCC should focus on plasma measures, investigate in more detail interactions between B vitamins and methionine regarding UCC risk, and assess interactions of dietary intakes with key genetic polymorphisms involved in the one-carbon metabolism pathway.

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COMPETING INTERESTS

None of the authors have any conflicts of interest to declare.

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Table 1 – Participants' characteristics at baseline (1990-1994), N=36,882

		Cases (N=500)	Non-cases (N=36,382)
Age at baseline	Median [IQR]	61.4 [54.7-65.9]	54.7 [47.1-62.2]
Sex	Male (%)	371 (74%)	14,150 (39%)
Country of birth	Australia, NZ, other	313 (63%)	25,458 (70%)
	Northern Europe	36 (7%)	2,348 (6%)
	Southern Europe	151 (30%)	8,576 (24%)
Education	Primary school	126 (25%)	6,531 (18%)
	Some high / technical school	170 (34%)	13,912 (38%)
	Completed high /technical school	108 (22%)	7,559 (21%)
	Degree / diploma	96 (19%)	8,380 (23%)
SEIFA[a] score	Median [IQR]	6 (3-8)	6 (3-9)
Smoking	Never	171 (34%)	21,487 (59%)
	Former quit > 15 yrs	132 (26%)	5,135 (14%)
	Former quit <= 15 yrs	111 (22%)	5,771 (16%)
	Current <20 cig/day	33 (7%)	1,875 (5%)
	Current >20 cig/day	53 (11%)	2,114 (6%)
Alcohol consumption	0	117 (23%)	11,518 (32%)
	1-39 g/d (M), 1-19 g/d (F)	287 (57%)	20,050 (55%)
	40-59 g/d (M), 20-39 g/d (F)	54 (11%)	3,243 (9%)
	60+ g/d (M), 40+ g/d (F)	42 (8%)	1,571 (4%)
Physical activity score	Median [IQR]	4 [1.5-5.5]	4 [1.5-5.5]
BMI	Median [IQR]	26.9 [23.7-29.1]	26.2 [24.6-29.7]
Waist circumference	Median [IQR]	92.0 [84.4-99.1]	84.3 [75.0-93.5]
Mediterranean Diet Score	Median [IQR]	5 [4-6]	5 [4-6]
Thiamine (B1) (in mg/d) RDI[b]: 1.2 mg/day (M); 1.1 mg/day (F)	Median [IQR]	2.1 [1.7-2.4]	2.1 [1.7-2.4]
Riboflavin (B2) (in mg/d) RDI: 1.3 mg/day (M); 1.1 mg/day (F)	Median [IQR]	2.2 [1.9-2.7]	2.4 [2.0-2.9]
Niacin (B3) (in mg/d) RDI: 16 mg/day (M); 14 mg/day (F)	Median [IQR]	30.3 [25.3-36.1]	30.3 [24.9-36.3]
Pantothenic acid (B5) (in mg/d) AI[c]: 6 mg/day (M); 4 mg/day (F)	Median [IQR]	4.2 [3.7-5.0]	4.2 [3.7-5.0]
Vitamin B6 (in mg/d) RDI: 1.3 to 1.7 mg/day (M); 1.3 to 1.5 mg/day (F)	Median [IQR]	2.0 [1.7-2.5]	1.9 [1.6-2.5]
Biotin (B8) (in µg/d) AI: 30 µg/d (M); 25 µg/d (F)	Median [IQR]	44.8 [39.3-51.9]	45.7 [39.6-52.8]
Folate (B9) (in µg/d) RDI: 400 µg/d (M); 400 µg/d (F)	Median [IQR]	297 [241-363]	314 [257-377]
Vitamin B12 (in µg/d) RDI: 2.4 µg/d (M); 2.4 µg/d (F)	Median [IQR]	3.3 (2.5-4.2)	3.0 [2.3-4.1]
Methionine (in mg/d)	Median [IQR]	1,664 [1,418-1,912]	1,612 [1,384-1,879]
Tumour subtype	Invasive	221 (44%)	
	Superficial	279 (56%)	
Tumour site (ICD-O-3 code)	Bladder (C67)	443 (89%)	
	Kidney (C64-C65)	37 (7%)	
	Ureter (C66)	14 (3%)	
	Urethra (C68)	6 (1%)	
Age at diagnosis	Median [IQR]	74.4 [67.5-79.4]	

[a] SEIFA= Socio-Economic Indexes for Area, index ranging from 1 to 10 representing relative socioeconomic disadvantage of area of residence (Pink, 2013)
[b] RDI: Recommended dietary intake, M: males, F: females
[c] AI: Adequate intake, M: males, F: females

Table 2 – Spearman correlations between log-transformed intakes of B group vitamins and methionine

	Riboflavin (B2)	Niacin (B3)	Pantothenic acid (B5)	Vitamin B6	Biotin (B8)	Folate (B9)	Vitamin B12	Methionine
Thiamine (B1)	0.51	0.26	0.07	0.02	0.47	0.52	-0.11	0.11
Riboflavin (B2)		0.62	0.28	0.01	0.50	0.40	-0.15	0.13
Niacin (B3)			0.44	0.17	0.20	0.11	0.15	0.28
Pantothenic acid (B5)				0.73	0.27	0.19	0.50	0.17
Vitamin B6					0.14	0.15	0.55	0.13
Biotin (B8)						0.56	-0.27	-0.02
Folate (B9)							-0.14	0.07
Vitamin B12								0.53

Table 3. Associations between log-transformed intakes of B group vitamins and methionine intake with the risk of UCC (N=500)

		Model 1[a]			Model 2[b]			
		HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**Linearity P [c] (Model 2)**
Thiamine (B1) quartiles (in mg/d)	Q1 [0.5 – 1.7[		Ref			Ref		
	Q2 [1.7 – 2.1[	0.94	0.73-1.21	0.64	0.95	0.74-1.22	0.68	
	Q3 [2.1 – 2.4[	1.05	0.82-1.35	0.67	1.06	0.83-1.36	0.64	
	Q4 [2.4 – 10.4]	0.98	0.76-1.27	0.88	0.98	0.76-1.27	0.90	
	Test for trend[d]		*P=0.89*			*P=0.88*		
Linear model	per 1 SD	0.99	0.91-1.09	0.87	0.99	0.91-1.09	0.89	0.64
Riboflavin (B2) quartiles (in mg/d)	Q1 [0.6 – 2.0[		Ref			Ref		
	Q2 [2.0 – 2.4[	1.14	0.90-1.46	0.27	1.16	0.91-1.48	0.22	
	Q3 [2.4 – 2.9[	0.89	0.68-1.17	0.40	0.90	0.69-1.18	0.46	
	Q4 [2.9 – 14.9]	1.00	0.76-1.31	0.98	1.00	0.76-1.31	0.99	
	Test for trend		*P=0.58*			*P=0.59*		
Linear model	per 1 SD	1.01	0.91-1.11	0.91	1.01	0.92-1.11	0.86	0.64
Niacin (B3) quartiles (in mg/d)	Q1 [7.2 – 24.9[		Ref			Ref		
	Q2 [24.9 – 30.3[	0.91	0.71-1.17	0.46	0.92	0.72-1.18	0.51	
	Q3 [30.3 – 36.3[	0.98	0.76-1.24	0.84	0.99	0.77-1.27	0.94	
	Q4 [36.3 – 116.5]	0.93	0.72-1.19	0.55	0.94	0.73-1.21	0.63	
	Test for trend		*P=0.69*			*P=0.77*		
Linear model	per 1 SD	0.99	0.90-1.09	0.88	1.00	0.91-1.10	0.98	0.72
Pantothenic acid (B5) quartiles (in mg/d)	Q1 [1.3 – 3.7[		Ref			Ref		
	Q2 [3.7 – 4.2[	1.27	0.99-1.61	0.06	1.28	1.01-1.64	0.04	
	Q3 [4.2 – 5.0[	1.05	0.81-1.36	0.69	1.07	0.82-1.38	0.62	
	Q4 [5.0 – 31.2]	1.12	0.87-1.44	0.37	1.12	0.87-1.44	0.39	
	Test for trend		*P=0.68*			*P=0.71*		
Linear model	per 1 SD	1.01	0.93-1.09	0.90	1.00	0.92-1.09	0.97	0.11
Vitamin B6 quartiles (in mg/d)	Q1 [0.6 – 1.6[		Ref			Ref		
	Q2 [1.6 – 1.9[	1.39	1.08-1.79	0.01	1.41	1.09-1.82	0.01	
	Q3 [1.9 – 2.5[	1.43	1.11-1.85	0.01	1.47	1.13-1.91	0.00	
	Q4 [2.5 – 30.0]	1.15	0.88-1.51	0.31	1.16	0.88-1.53	0.28	
	Test for trend		*P=0.30*			*P=0.30*		

Linear model	per 1 SD	1.01	0.93-1.09	0.88	1.00	0.92-1.09	0.95	0.004
Biotin (B8) quartiles	Q1 [10.8 – 39.6[		Ref			Ref		
(in µg/d)	Q2 [39.6 – 45.7[	1.10	0.85-1.41	0.47	1.10	0.85-1.42	0.48	
	Q3 [45.7 – 52.8[	1.15	0.89-1.50	0.29	1.16	0.88-1.51	0.29	
	Q4 [52.8 – 164.3]	1.19	0.90-1.55	0.22	1.19	0.90-1.59	0.22	
	Test for trend		*P=0.21*			*P=0.21*		
Linear model	per 1 SD	1.03	0.94-1.13	0.47	1.03	0.94-1.14	0.50	0.49
Folate (B9) quartiles	Q1 [50 – 256[		Ref			Ref		
(in µg/d)	Q2 [256 – 313[	1.01	0.79-1.29	0.94	1.02	0.79-1.32	0.87	
	Q3 [313 – 377[	0.97	0.75-1.26	0.83	0.98	0.75-1.28	0.89	
	Q4 [377 – 1191]	0.99	0.77-1.28	0.95	1.00	0.76-1.32	1.00	
	Test for trend		*P=0.88*			*P=0.93*		
Linear model	per 1 SD	1.00	0.91-1.09	0.95	1.00	0.91-1.10	1.00	0.89
Vitamin B12 quartiles	Q1 [0.3 – 2.3[		Ref			Ref		
(in µg/d)	Q2 [2.3 – 3.0[	1.03	0.80-1.33	0.80	1.05	0.81-1.35	0.72	
	Q3 [3.0 – 4.1[	1.18	0.92-1.52	0.19	1.20	0.93-1.56	0.15	
	Q4 [4.1 – 31.9]	0.97	0.75-1.27	0.85	1.00	0.75-1.33	1.00	
	Test for trend		*P=0.87*			*P=0.73*		
Linear model	per 1 SD	1.00	0.91-1.09	0.94	1.00	0.91-1.11	0.95	0.22
Methionine quartiles	Q1 [352 – 1,384[		Ref			Ref		
(in mg/d)	Q2 [1,384 – 1,613[	0.97	0.74-1.26	0.81	0.99	0.76-1.29	0.92	
	Q3 [1,613 – 1,880[	1.19	0.92-1.52	0.18	1.23	0.95-1.59	0.11	
	Q4 [1,880 – 5,633]	1.05	0.81-1.36	0.70	1.12	0.85-1.49	0.42	
	Test for trend		*P=0.40*			*P=0.20*		
Linear model	per 1 SD	1.02	0.94-1.12	0.62	1.05	0.95-1.17	0.30	0.24

[a] Model 1: Adjusting for age, sex, country of birth, educational attainment, socioeconomic status, smoking status and alcohol intake. Hazard ratios (HR) for the linear model are given per 1 SD of the log-transformed nutrient intakes.
[b] Model 2: Adjusting for Model 1 variables + waist circumference, physical activity, Mediterranean diet score, red meat intake, and use of NSAIDs. Hazard ratios (HR) for the linear model are given per 1 SD of the log-transformed nutrient intakes.
[c] Linearity P: departure from linearity in the relationship between B-group vitamins and UCC risk was investigated in Model 2, using likelihood ratio tests to compare models including dietary intake variables as a categorical (using quartiles) versus linear variable.
[d] To estimate the trend in quartiles, each nutrient variable was fitted as pseudo-continuous, using the median raw value in each nutrient quartile.

Table 4. Associations between log-transformed intakes of B group vitamins and methionine with risk of UCC by subtypes (invasive: N=221, superficial: N=279)

	Invasive cases (N=221)			Linearity P[b]	Superficial cases (N=279)			Linearity P[b]	Heterogeneity test[c]
	HR[a]	95% CI	p		HR[a]	95% CI	p		p
Thiamine (B1)	1.02	0.89-1.17	0.74	0.56	0.97	0.86-1.10	0.63	0.93	0.57
Riboflavin (B2)	1.08	0.94-1.25	0.26	0.11	0.95	0.84-1.08	0.44	0.11	0.18
Niacin (B3)	1.05	0.91-1.21	0.48	0.78	0.96	0.84-1.09	0.51	0.75	0.33
Pantothenic acid (B5)	1.05	0.93-1.18	0.45	0.05	0.97	0.86-1.08	0.53	0.64	0.52[d]
Vitamin B6	1.05	0.93-1.19	0.43	0.02	0.97	0.86-1.08	0.56	0.10	0.47[d]
Biotin (B8)	1.13	0.98-1.30	0.10	0.50	0.96	0.84-1.10	0.56	0.83	0.11
Folate (B9)	1.01	0.87-1.18	0.85	0.22	0.99	0.87-1.13	0.87	0.46	0.80
Vitamin B12	1.01	0.87-1.16	0.93	0.61	1.00	0.88-1.14	0.98	0.33	0.96
Methionine	1.00	0.86-1.16	0.98	0.48	1.10	0.96-1.26	0.15	0.32	0.33

[a] Model 2: Adjusting for age, sex, country of birth, educational attainment, socioeconomic status, smoking status, alcohol intake, waist circumference, physical activity, Mediterranean diet score, red meat intake, and use of NSAIDs. Hazard ratios (HR) are given per 1 SD of the log-transformed nutrient intakes.

[b] Linearity P: departure from linearity in the relationship between B-group vitamins and UCC risk was investigated in Model 2, using likelihood ratio tests to compare models using dietary intake variables as linear versus categorical (using quartiles).

[c] To test for heterogeneity in the HRs by tumour subtype (invasive vs. superficial) we fitted Cox proportional hazard regression models for competing risk using the data duplication method of Lunn and McNeil.[34]

[d] Heterogeneity was tested using the B vitamin variable divided into quartile, because the association with risk of invasive UCC departed from linearity (P=0.05 and P=0.02 for vitamin B5 and vitamin B6, respectively)

Table 5. Associations between log-transformed intakes of B group vitamins and methionine with risk of UCC by smoking and alcohol drinking status (Model 2)

	Interaction with smoking					Interaction with alcohol drinking				
		HR[a]	95% CI	P	P heterogeneity		HR[a]	95% CI	P	P heterogeneity
Thiamine (B1)	**Never** (N=171)	1.05	0.90-1.23	0.86		**Never** (N=117)	0.81	0.69-0.97	0.02	
	Current (N=86)	1.10	0.90-1.34	0.57	0.21	**Low** (N=287)	1.05	0.93-1.19	0.44	0.02
	Former (N=243)	0.92	0.81-1.04	0.08		**High** (N=96)	1.12	0.92-1.36	0.27	
Riboflavin (B2)	**Never** (N=171)	0.99	0.85-1.16	0.89		**Never** (N=117)	0.95	0.79-1.13	0.54	
	Current (N=86)	1.06	0.86-1.30	0.58	0.88	**Low** (N=287)	1.00	0.88-1.13	0.98	0.45
	Former (N=243)	1.00	0.89-1.14	0.78		**High** (N=96)	1.12	0.92-1.35	0.25	
Niacin (B3)	**Never** (N=171)	1.02	0.87-1.19	0.59		**Never** (N=117)	0.96	0.80-1.14	0.63	
	Current (N=86)	1.03	0.84-1.28	0.99	0.87	**Low** (N=287)	1.03	0.91-1.17	0.67	0.77
	Former (N=243)	0.97	0.85-1.12	0.27		**High** (N=96)	0.97	0.77-1.22	0.81	
Pantothenic acid (B5)	**Never** (N=171)	0.98	0.84-1.13	0.74		**Never** (N=117)	1.09	0.93-1.27	0.29	
	Current (N=86)	1.08	0.92-1.27	0.1	0.60	**Low** (N=287)	0.95	0.84-1.06	0.33	0.30
	Former (N=243)	0.98	0.87-1.10	0.99		**High** (N=96)	1.05	0.88-1.25	0.57	
Vitamin B6	**Never** (N=171)	0.98	0.85-1.14	0.81		**Never** (N=117)	1.08	0.93-1.26	0.33	
	Current (N=86)	1.03	0.86-1.22	0.33	0.94	**Low** (N=287)	0.99	0.89-1.11	0.85	0.48
	Former (N=243)	1.00	0.89-1.13	0.82		**High** (N=96)	0.93	0.75-1.15	0.48	
Biotin (B8)	**Never** (N=171)	1.09	0.93-1.27	0.89		**Never** (N=117)	1.05	0.88-1.25	0.6	
	Current (N=86)	1.00	0.81-1.22	0.76	0.72	**Low** (N=287)	0.97	0.86-1.10	0.63	0.16
	Former (N=243)	1.01	0.89-1.15	0.85		**High** (N=96)	1.20	0.99-1.45	0.07	
Folate (B9)	**Never** (N=171)	1.03	0.88-1.21	0.86		**Never** (N=117)	0.91	0.76-1.08	0.29	
	Current (N=86)	1.00	0.81-1.23	0.97	0.85	**Low** (N=287)	0.99	0.87-1.12	0.87	0.14
	Former (N=243)	0.98	0.85-1.12	0.46		**High** (N=96)	1.18	0.96-1.44	0.11	
Vitamin B12	**Never** (N=171)	0.95	0.81-1.12	0.99		**Never** (N=117)	0.97	0.81-1.16	0.74	
	Current (N=86)	1.13	0.93-1.38	0.11	0.41	**Low** (N=287)	1.02	0.90-1.15	0.75	0.88
	Former (N=243)	0.99	0.87-1.13	0.89		**High** (N=96)	1.00	0.82-1.23	1.00	
Methionine	**Never** (N=171)	0.94	0.80-1.10	0.64		**Never** (N=117)	0.96	0.81-1.14	0.62	
	Current (N=86)	1.04	0.86-1.28	0.76	0.14	**Low** (N=287)	1.11	0.97-1.26	0.13	0.41
	Former (N=243)	1.15	1.00-1.31	0.09		**High** (N=96)	1.07	0.87-1.31	0.52	

[a] Model 2: Adjusting for age, sex, country of birth, educational attainment, socioeconomic status, smoking status, alcohol intake, waist circumference, physical activity, Mediterranean diet score, red meat intake, and use of NSAIDs. Hazard ratios (HR) are given per 1 SD of the log-transformed nutrient intakes.