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High-dose B-vitamin supplements and risk for age-related cataract: a population-based prospective study of men and women

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Abstract

Previous studies that have investigated the association between B-vitamin supplement use and risk for cataract yield conflicting results. The aim of this study was to examine the association between use of high-dose B-vitamin supplements (approximately 10 times recommended daily intake) and risk for age-related cataract in a population-based prospective study of 13 757 women from the Swedish Mammography Cohort and 22 823 men from the Cohort of Swedish Men. Dietary supplement use and potential confounders were assessed using a questionnaire at baseline. Information on cataract diagnosis and extraction was obtained through linkage to registers. During the follow-up period between January 1998 and December 2011, we identified 8395 cataract cases (3851 for women and 4544 for men). The use of B vitamins plus other supplements and B vitamins only was associated with 9% (95% CI 2, 17) and 27% (95% CI 12, 43) increased risk for cataract, respectively. The hazard ratios for use of B vitamins only and risk for cataract stratified by different age groups were as follows: <60 years: 1·88 (95% CI 1·47, 2·39); 60–69 years: 1·21 (95% CI 0·96, 1·53); and ≥70 years: 1·09 (95% CI 0·91, 1·31) ($P_{interaction} = 0·002$). Our results suggest that the use of high-dose B-vitamin supplements was associated with an increased risk for cataract. This association might be confined to younger participants.

Key words: **B-vitamin supplements: Cataracts: Prospective cohort studies: Nutritional epidemiology**

The aetiology of age-related cataract includes oxidative damage of the lens[1]. Although antioxidants can protect against oxidative stress, the use of several high-dose antioxidant supplements, such as β-carotene, vitamin C and vitamin E, have not shown a protective effect against age-related cataract development in large, randomised clinical trials (RCT)[2]. Of note, we have previously observed in cohort studies of women[3] and men[4] that the use of single, high-dose vitamin C and vitamin E supplements was associated with increased risk for cataract.

Low plasma B-vitamin levels, especially of vitamin B_6, have been associated with higher oxidative stress and inflammation, as well as with an increased risk for many diseases such as CVD[5–8]. However, RCT examining the effect of B-vitamin supplements on cancer[9], CVD[10] and Alzheimer disease[11] have not shown any protective effects. B vitamins at high concentrations have also been shown to be toxic and may exert pro-oxidative properties[12,13]. B vitamins are found in a variety of foods including eggs, dairy products, meat, cereals and legumes.

Few studies have examined the association between B-vitamin supplement use and risk for cataract and have shown inconsistent results. One RCT reported in a population with micronutrient deficiencies at baseline that those who received B vitamins (doses approximately twice the recommended daily intake (RDI)) had a decreased risk for nuclear cataract but an increased risk for posterior subcapsular cataract[14]. One cross-sectional study also observed a lower prevalence of nuclear and cortical cataracts, but a higher prevalence of posterior subcapsular cataract among users of high-dose B vitamins[15]. On the other hand, two prospective cohort studies observed no association between the use of B vitamins and risk for cataract[16,17]. However, the studied doses were unknown in those two prospective cohorts. With a longer follow-up time and more cataract cases, this study was an extension of our previous studies on other high-dose supplements (vitamin C, E) and low-dose multivitamins and risk for cataract[3,4]. The aim was to examine the associations of high-dose B-vitamin supplements with the risk for age-related cataract in women and men. We also examined whether the associations varied by age and oxidative stress-related factors.

Abbreviations: HR, hazard ratio; RCT, randomised clinical trial; RDI, recommended daily intake.

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Methods

Study population

The study population consisted of women and men from two population-based cohorts: the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM). The SMC was established during 1987–1990 and invited all women born between 1914 and 1948 and residing in Uppsala and Västmanland Counties in central Sweden to complete a mailed questionnaire regarding diet and lifestyle factors (response rate 74 %). In the late fall of 1997, a second follow-up questionnaire was sent to the women aged 48–83 years, and 70 % responded. The COSM was established in the late fall of 1997 and invited all men, aged 45–79 years, living in Örebro and Västmanlands Counties in central Sweden to complete a questionnaire regarding diet and lifestyle factors, similar to the one used in the SMC (response rate 49 %). The study participants are representative of the Swedish population of middle-aged and elderly women and men with regard to factors such as age distribution, BMI and smoking habits during the study period[18].

For the analysis, we excluded those who returned a blank questionnaire (n 448), had a missing or erroneous personal identity number (n 92), who died before 1 January 1998 (n 97), had a previous cancer diagnosis other than non-melanoma skin cancer (n 4309; identified from the Swedish National Cancer Register), had a cataract diagnosis and/or cataract extraction before baseline (n 1719), those with missing information on supplement use (n 7409) or those who only used other supplements than B vitamins (n 31 168) – in order to avoid potential confounding by other supplements – and those with missing information on variables included in the final model (smoking status, n 564; corticosteroid use, n 7195; and education, n 175), leaving a total of 36 580 participants (13 757 women and 22 823 men). The analytical cohort included non-supplement users and users of B vitamins plus other supplements or users of B vitamins only.

This study was approved by the Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden). Completion and return of the self-administered questionnaire was considered to imply informed consent to participate in this study.

Assessment of B-vitamin supplements

Dietary supplement use was assessed by a self-administered questionnaire at baseline that included a general question 'Do you use vitamin, mineral, or other supplements?' with the prespecified responses of no, regular use and occasional use, followed by questions on specific supplements including vitamin-B complex, vitamin B_6 and folic acid. On the basis of the B-vitamin supplements available on the Swedish market, the dose of the different B vitamins included in vitamin-B complex was estimated to be approximately 10 times RDI and, as a single supplement, approximately 25 times RDI during the studied period[19].

Assessment of confounders

The self-administered questionnaire completed by the participants at baseline contained information on potential confounders including age, smoking status (never, past or current smokers), use of corticosteroids (yes or no), use of aspirin (yes or no), abdominal obesity (defined as waist circumference ≥80 cm in women and ≥94 cm in men), educational level (<9, 9–12 or >12 years), alcohol intake (g/d) and fruit and vegetable intake (g/d). Participants with a history of hypertension or CVD were identified through linkage to the National Inpatient and Outpatient Registers at the National Board of Health and Welfare and hypertension was also identified through self-reported data from the questionnaire. Diabetes history was obtained through the National Outpatient Register, National Diabetes Register and self-reports.

Case ascertainment and follow-up

We obtained information on cataract diagnosis and cataract extraction through linkage to the National Outpatient and Inpatient Registers at the National Board of Health and Welfare (*International Classification of Diseases (ICD)*-10, code H25 and operation codes CJC, CJD, CJE, CJG). We also linked with local cataract extraction registers from both public and private clinics and with the Swedish National Cataract Register (coverage: approximately 97 % of all cataract extractions in Sweden)[20]. Cataracts were not included if they were considered to be congenital or secondary to ocular trauma, intraocular inflammation or previous intraocular surgery (*ICD*-10, code H26).

During the follow-up period between 1 January 1998 and 31 December 2011, we identified 8395 incident cases of age-related cataract (3851 cases in women and 4544 cases in men), defined as women and men with cataract diagnosis and/or cataract extraction. Among those, 2156 participants had only cataract diagnosis and not extraction; and 6239 participants had cataract extraction. Date of death was identified through linkage to the Swedish Death Register.

Statistical analysis

B-vitamin supplement users were categorised into users of B vitamins (including vitamin-B complex, folic acid and/or vitamin B_6) plus other supplements or users of B vitamins only. The reference group was non-supplement users. The cumulative cataract incidence rate over time of follow-up among users of B vitamins and non-users was derived from Kaplan–Meier curves. Cox proportional hazards models were used to calculate multivariable-adjusted hazard ratios (HR) and 95 % CI in the cohort. Stratified analyses by age groups (<60, 60–69 and ≥70 years) and sex were also performed. Follow-up ended at the date of cataract diagnosis, date of cataract extraction, date of death or at the end of the follow-up period (31 December 2011), whichever came first. The main multivariable model was adjusted for age (5-years age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74 and ≥75), sex, smoking status (never, past and current smokers), corticosteroid use (yes or no), educational level (<9, 9–12 or >12 years) and history of CVD and/or diabetes (yes or no). In addition, we adjusted for abdominal obesity (waist circumference ≥80 cm in women and ≥94 cm in men), history of hypertension (yes or no), use of aspirin (yes or no), alcohol intake (g/d) and fruit and vegetable intake (g/d). Complete subject analyses

(by only including participants with values available for all covariates) were performed. Similar results were obtained if we used age as the underlying timescale in the Cox models. For the main analyses, we estimated HR both in the whole study cohort and after exclusions of those with a history of CVD and/or diabetes (to evaluate potential influence from diet and lifestyle-related changes due to the diagnoses, as both diseases are associated with an increased risk for cataract). The proportional hazard assumption between the exposed and non-exposed was tested by including the product of B-vitamin supplements and the natural logarithm of time in the models and we found no departure from this assumption. In sensitivity analyses, we excluded the first 4 years of follow-up to evaluate the potential risk for reverse causality, as well as used shorter follow-up period (between 1998 and 2006), to check for potential exposure misclassification due to long follow-up.

The difference in time to event (cataract diagnosis and/or cataract extraction) between users of B-vitamin supplements and non-users was estimated by applying Laplace regression[21–23]. We modelled the 10th percentile of survival in both groups, which is the point in time when 10 % of the group has had an event. The survival time for the 10th percentile was adjusted for the same covariates as in the proportional hazard multivariable model.

Further, we examined whether the risk between B vitamins and cataract differed by oxidative stress-related factors, including smoking, corticosteroid use, history of CVD and/or diabetes and alcohol intake. The likelihood ratio test was used to test for interaction between these factors and use of B-vitamin supplements.

All P values shown are two-sided and $P < 0{\cdot}05$ were considered statistically significant. The statistical analyses were performed using SAS (version 9.3; SAS Inc.) and Stata (version 12; StataCorp LP).

Results

During an average of 11·6 years of follow-up (424 862 person-years), we identified 8395 cases of age-related cataract (3851 cases in women and 4544 cases in men). In this study, 8·9 % of the participants used B vitamins plus other supplements and 2·4 % used B-vitamin supplements only. Baseline characteristics of the participants by B-vitamin supplement use are presented in Table 1.

The cumulative cataract incidence rate over time of follow-up and stratified by B-vitamin supplement use is shown in Fig. 1. The incidence rates of cataract and the HR and 95 % CI for users of B-vitamin supplements in the study cohort and in the CVD and diabetes-free cohort (by excluding those with a history of CVD and/or diabetes) are presented in Table 2. In the study cohort, users of B vitamins plus other supplements and users of B vitamins only had a statistically significantly increased risk of 9 % (95 % CI 2, 17) and 27 % (95 % CI 12, 43) for cataract (diagnosis and/or extraction), respectively, compared with non-supplement users. We observed similar associations in the CVD and diabetes-free cohort. The results also remained similar after additional adjustments for abdominal obesity, history of hypertension, aspirin use and dietary factors, including alcohol intake and fruit and vegetable intake (HR for B vitamins plus other supplements and B vitamins only were 1·08 (95 % CI 1·01, 1·16) and 1·27 (95 % CI 1·12, 1·43), respectively), as well as for separate analyses of cataract extractions and cataract diagnosis.

The use of B vitamins stratified by different age groups (<60, 60–69 and ≥70 years) are shown in Table 3. There was no significant interaction between use of B vitamins plus other supplements and age in relation to cataract risk ($P_{interaction} = 0{\cdot}26$). However, the use of B vitamins only was associated with a statistically significantly increased risk of 88 % (95 % CI 47, 139) for cataract in the youngest age group (<60 years), but not in the older age groups ($P_{interaction} = 0{\cdot}002$). Moreover, similar

Table 1. Age-standardised baseline characteristics by B-vitamin supplement use in women and men, 1998 (Mean values and standard deviations)

	B-vitamin supplement use											
	Women (*n* 13 757)						Men (*n* 22 823)					
	No supplement use		B vitamins* plus other supplements†		B vitamins* only		No supplement use		B vitamins* plus other supplements†		B vitamins* only	
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No. of participants	11 271		2007		479		21 329		1160		334	
Age (years)	61·0	8·9	60·8	9·1	62·6	9·6	59·2	9·4	61·3	9·8	62·9	10·0
Current smoking (%)	24·9		23·9		25·8		26·2		27·8		34·1	
Corticosteroid use (%)	11·9		18·4		11·9		10·3		13·7		16·0	
Abdominal obesity (%)‡	55·2		48·7		49·0		48·8		44·7		45·5	
Education >12 years (%)	16·3		24·2		14·8		14·9		20·3		13·5	
History of hypertension (%)	22·5		21·0		19·1		24·5		26·6		29·2	
History of CVD (%)	8·0		7·3		6·8		10·8		9·8		12·5	
History of diabetes (%)	5·4		3·7		4·7		9·0		10·0		10·5	
Alcohol intake (g/d)	5·4	10·2	6·6	10·7	6·7	11·0	14·1	20·3	16·0	26·0	18·8	28·1
Diet intake (g/d)												
Fruit and vegetables	448·7	261·2	537·9	308·5	474·4	270·9	375·9	238·8	473·6	341·5	405·6	260·5
B vitamins	18·8	3·1	19·0	3·3	18·6	3·5	27·8	4·4	28·3	4·8	27·6	4·5

* Including high-dose vitamin-B complex, folic acid and vitamin-B_6 supplements.
† Other supplements including multivitamins/minerals, vitamin C, vitamin E, β-carotene, folic acid, fish oil, Ca, Se, Zn and/or Mg.
‡ Defined as waist circumference ≥80 cm (for women) and ≥94 cm (for men).

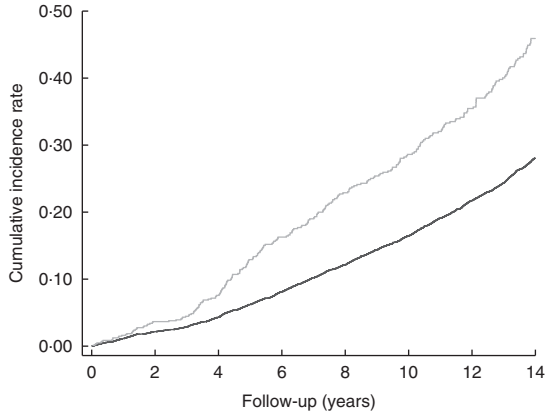

Fig. 1. Cumulative cataract incidence rate over time of follow-up (between 1998 and 2011) stratified by non-supplement users (——) and users of B-vitamin supplements only (——) in 36 580 participants.

associations were observed in women and men separately for the use of B vitamins plus other supplements ($P_{interaction}$ = 0·11) and B vitamins only ($P_{interaction}$ = 0·15).

In the sensitivity analysis, we excluded the first 4 years of follow-up to check for potential reversed causality (e.g. changes in B-vitamin supplement use related to early cataract symptoms). The results remained similar: the HR and 95% CI for cataract risk among users of B vitamins plus other supplements and users of B vitamins only were 1·08 (95% CI 1·00, 1·17) and 1·26 (95% CI 1·09, 1·45), respectively, compared with non-users. Similar results were also observed when using a shorter follow-up period (between 1998 and 2006), to check for potential exposure misclassification (B vitamins plus other supplements: HR = 1·13; 95% CI 1·03, 1·24; and B vitamins only: HR = 1·30; 95% CI 1·11, 1·52).

We used Laplace regression to estimate the difference in time to event (cataract diagnosis and/or cataract extraction) between B-vitamin users and non-users. Among non-users, 10% of the participants had the event by an overall 10 years of study entry, whereas among users of B vitamins only the same proportion (10%) had the event 1·5 years (95% CI 0·59, 2·43) earlier, after adjusting for the same covariates as in the proportional hazard multivariable model.

We also investigated whether the association between use of B-vitamin supplements and risk for cataract was modified by factors related to increased oxidative stress, including smoking, corticosteroid use, history of CVD and/or diabetes and alcohol intake. There were no statistically significant interactions between B-vitamin supplement use only and the factors examined (data not shown; all $P_{interactions}$ >0·14).

Discussion

In this large, population-based prospective cohort study, we observed that the use of high-dose B-vitamin supplements was associated with an increased risk for age-related cataract. The positive association with the use of B-vitamin supplements only seemed to be confined to younger participants. By comparing the same proportion (10%) of participants who got diagnosed with cataract and/or had cataract extraction, users of only B-vitamin supplements had the event 1·5 years earlier than non-users.

Table 2. Risk for age-related cataract by B-vitamin supplement use, 1998–2011 (Hazard ratios (HR) and 95% confidence intervals)

			Study cohort (*n* 36 580)					CVD and diabetes-free cohort (*n* 30 941)				
B-vitamin supplements* use	No. of participants/ no. of cases	Incidence rate/1000 person-years	HR†	95% CI	HR‡	95% CI	No. of participants/ no. of cases	Incidence rate/1000 person-years	HR†	95% CI	HR‡	95% CI
Total cataract (including cataract diagnosis and/or extraction)												
No supplement use	32 600/7272	19	1	Ref.	1	Ref.	27 531/5519	17	1	Ref.	1	Ref.
B vitamins plus other supplements§	3161/858	24	1·09	1·02, 1·17	1·09	1·02, 1·17	2739/688	21	1·11	1·03, 1·20	1·11	1·02, 1·20
B vitamins only	813/265	31	1·28	1·13, 1·45	1·27	1·12, 1·43	671/207	28	1·34	1·16, 1·54	1·33	1·16, 1·53
Cataract extractions												
No supplement use	32 600/5387	14	1	Ref.	1	Ref.	27 531/4059	12	1	Ref.	1	Ref.
B vitamins plus other supplements§	3161/645	17	1·08	1·00, 1·18	1·09	1·00, 1·18	2739/525	16	1·13	1·03, 1·24	1·13	1·03, 1·24
B vitamins only	813/207	24	1·31	1·14, 1·50	1·30	1·13, 1·49	671/160	21	1·36	1·16, 1·59	1·35	1·15, 1·58
Cataract diagnosis only												
No supplement use	32 600/1885	4·8	1	Ref.	1	Ref.	27 531/1 460	4·3	1	Ref.	1	Ref.
B vitamins plus other supplements§	3161/213	5·7	1·08	0·94, 1·25	1·09	0·94, 1·25	2739/163	4·9	1·03	0·87, 1·21	1·02	0·86, 1·20
B vitamins only	813/58	6·4	1·15	0·89, 1·50	1·14	0·87, 1·48	671/47	6·0	1·23	0·92, 1·64	1·22	0·91, 1·63

Ref. referent values.
* Including high-dose vitamin-B complex, folic acid and vitamin-B_6 supplements.
† Adjusted for age (5-year age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74 and >75) and sex.
‡ Same as above and additionally adjusted for smoking status (never, past and current), corticosteroid use (yes or no), educational level (<9, 9–12 or >12 years) and history of CVD and/or diabetes (yes or no).
§ Other supplements including multivitamins/minerals, vitamin C, vitamin E, β-carotene, folic acid, fish oil, Ca, Se, Zn and/or Mg.

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Table 3. Risk for age-related cataract by B-vitamin supplement use and stratified by age groups, 1998–2011 (Hazard ratios (HR) and 95 % confidence intervals)

B-vitamin supplement* use	Study cohort (*n* 36 580)				CVD and diabetes-free cohort (*n* 30 941)			
	No. of participants	Incidence rate/1000 person-years	HR†	95 % CI	No. of participants	Incidence rate/1000 person-years	HR†	95 % CI
Age groups								
<60 years								
No supplement use	17 526	7·6	1	Ref.	16 308	7·0	1	Ref.
B vitamins plus other supplements‡	1602	9·4	1·10	0·94, 1·28	1498	8·6	1·07	0·91, 1·27
B vitamins only	352	15·3	1·88	1·47, 2·39	334	14·4	1·84	1·42, 2·38
60–69 years								
No supplement use	8808	28·3	1	Ref.	6999	26·5	1	Ref.
B vitamins plus other supplements‡	853	32·4	1·07	0·95, 1·21	719	30·0	1·03	0·91, 1·18
B vitamins only	206	35·2	1·21	0·96, 1·53	167	37·1	1·39	1·09, 1·78
≥70 years								
No supplement use	6266	53·5	1	Ref.	4224	50·7	1	Ref.
B vitamins plus other supplements‡	712	62·4	1·11	0·99, 1·24	522	63·7	1·21	1·06, 1·37
B Vitamins Only	255	62·1	1·09	0·91, 1·31	170	57·7	1·07	0·86, 1·34

Ref., referent values.
* Including high-dose vitamin-B complex, folic acid and vitamin-B_6 supplements.
† Adjusted for age (5-year age groups: <50, 50–54, 55–59, 60–64, 65–69, 70–74, >75), sex, smoking status (never, past and current), corticosteroid use (yes or no), educational level (<9, 9–12 or >12 years) and history of CVD and/or diabetes (yes or no).
‡ Other supplements including multivitamins/minerals, vitamin C, vitamin E, *β*-carotene, folic acid, fish oil, Ca, Se, Zn and/or Mg.

Of note, we have previously observed in the same cohorts that high-dose vitamin C and vitamin E supplements, but not low-dose multivitamins, were associated with increased risk for age-related cataract[3,4]. Our results are partly in line with those from an RCT (the Linxian Cataract Studies) that reported in participants aged 65–74 years who received riboflavin (3 mg) and niacin (40 mg) supplements a statistically significantly increased risk for posterior subcapsular cataract, but a decreased risk for nuclear cataract[14]. However, the study population in that trial had chronic deficiencies of several micronutrients at baseline, which makes the comparability to our study limited. Moreover, one cross-sectional study (the Blue Mountains Eye Study) also reported a higher prevalence of posterior subcapsular cataract among users of high-dose thiamine and pyridoxine (vitamin B_6) supplements; however, the use of other B-vitamin supplements was associated with a reduced prevalence of nuclear and cortical cataracts[15]. Two prospective cohort studies observed no association between B vitamins and cataract[16,17]. In the Beaver Dam Eye Study, the use of B-vitamin supplements (unknown dose and duration) was not associated with any type of cataract[16]. In the Nurses' Health Study, dietary intake of riboflavin (from foods and supplements) was not associated with cataract extraction[17].

The biological mechanisms behind our findings are unclear. Some studies (mostly experimental) have shown that B vitamins may have antioxidant properties[24–27] such as inhibiting advanced glycation end product formation[28] and protein oxidation in diabetic lens cells[29]. However, B vitamins at higher concentrations may also have pro-oxidative properties[12], such as stimulating lipid peroxidation, which have been shown *in vitro* for vitamin B_1 (2·5 mM) and vitamin B_6 (2·5 mM)[13]. It has been observed that individuals with cataract had higher blood levels of vitamin B_6[30]. The estimated plasma concentration of pyridoxal 5'-phosphate (active form of vitamin B_6) was 78 nM among users of vitamin-B_6 supplements (aged >65 years) and 36 nM among non-users[31]. Vitamin B_6 at high doses (>200 mg/d) has also been shown to be toxic in humans[12]. Our results showed that the increased risk for cataract among users of B vitamins only was statistically significant only in younger participants. The mechanism behind this may be the decreased gastric absorption of B vitamins secondary to atrophic gastritis, which is more common among the elderly[32,33].

The strengths of this study include the large, population-based, prospective cohort design. This study also has a large number of incident cases of cataract diagnosis and cataract extraction. Further, we had detailed information regarding diet and lifestyle factors, such as alcohol intake and smoking status, which allowed us to perform comprehensive adjustment of confounders as well as stratified analyses.

This study also has some limitations. Cataract diagnosis is a complex outcome, because lens opacities can occur without any symptoms. However, we also included cataract extraction as outcome, which may be of more clinical relevance and reflective of visual impairment severe enough to affect activities of daily life. Because of a lack of standardised eye examinations in the cohorts and incomplete documentation of cataract subtypes in medical records, we could not investigate whether the associations with B vitamins differed by specific subtypes. The longer follow-up time and the greater number of cataracts in this study may lead to exposure misclassification due to potential changes in the consumption of B-vitamin supplements. However, we performed sensitivity analysis using a shorter follow-up period and the results were similar. It is possible that women and men who are more

health conscious may also be more likely to seek medical care for visual complaints earlier and also be more likely to use B-vitamin supplements. On the other hand, it is also possible that those using B-vitamin supplements may have a poorer overall health, as, for example, vitamin B_6 may be prescribed to patients with suboptimal or limited nutritional intake or to those with alcohol dependency or taking certain drugs. These factors may lead to potential outcome misclassification and confounding, affecting the risk estimates in either direction. However, we have adjusted for many potential confounders and performed stratified analyses; the risk estimates were similar after adjusting for several covariates. Moreover, the Swedish healthcare system allows all inhabitants to have the same affordable access to cataract extractions (patient charge <$50/surgery). Because of the observational design of our study, we cannot exclude the possibility that our results may be influenced by unmeasured or residual confounding. However, we have explored the risk for reverse causality by excluding the first 4 years of follow-up. The risk estimates remained similar, making it unlikely that reverse causality explains our results. Further, we did not have information on the exact doses of B-vitamin supplements used by the participants. However, we were able to estimate the doses using information available for B-vitamin supplements on the Swedish market during the study period.

In conclusion, our results suggest that the use of high-dose B-vitamin supplements may be associated with an increased risk for age-related cataract. The association seemed to be confined to younger participants. This potentially important association requires confirmation by other studies and in other populations.

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

References

1. Shichi H (2004) Cataract formation and prevention. *Expert Opin Investig Drugs* **13**, 691–701.
2. Mathew MC, Ervin AM, Tao J, *et al.* (2012) Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. *The Cochrane Database of Systematic Reviews 2012*, issue 6, CD004567.
3. Rautiainen S, Lindblad BE, Morgenstern R, *et al.* (2010) Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women. *Am J Clin Nutr* **91**, 487–493.
4. Zheng Selin J, Rautiainen S, Lindblad BE, *et al.* (2013) High-dose supplements of vitamins C and E, low-dose multivitamins, and the risk of age-related cataract: a population-based prospective cohort study of men. *Am J Epidemiol* **177**, 548–555.
5. Ulvik A, Midttun O, Pedersen ER, *et al.* (2012) Association of plasma B-6 vitamers with systemic markers of inflammation before and after pyridoxine treatment in patients with stable angina pectoris. *Am J Clin Nutr* **95**, 1072–1078.
6. Shen J, Lai CQ, Mattei J, *et al.* (2010) Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study. *Am J Clin Nutr* **91**, 337–342.
7. Lotto V, Choi SW & Friso S (2011) Vitamin B_6: a challenging link between nutrition and inflammation in CVD. *Br J Nutr* **106**, 183–195.
8. Selhub J, Troen A & Rosenberg IH (2010) B vitamins and the aging brain. *Nutr Rev* **68**, Suppl. 2, S112–S118.
9. Andreeva VA, Touvier M, Kesse-Guyot E, *et al.* (2012) B vitamin and/or omega-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B_6 and B_{12}, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. *Arch Intern Med* **172**, 540–547.
10. Albert CM, Cook NR, Gaziano JM, *et al.* (2008) Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA* **299**, 2027–2036.
11. Aisen PS, Schneider LS, Sano M, *et al.* (2008) High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA* **300**, 1774–1783.
12. Driskell JA (1994) Vitamin B-6 requirements of humans. *Nutr Res* **14**, 292–324.
13. Hu ML, Chen YK & Lin YF (1995) The antioxidant and prooxidant activity of some B vitamins and vitamin-like compounds. *Chem Biol Interact* **97**, 63–73.
14. Sperduto RD, Hu TS, Milton RC, *et al.* (1993) The Linxian cataract studies. Two nutrition intervention trials. *Arch Ophthalmol* **111**, 1246–1253.
15. Kuzniarz M, Mitchell P, Cumming RG, *et al.* (2001) Use of vitamin supplements and cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* **132**, 19–26.
16. Klein BE, Knudtson MD, Lee KE, *et al.* (2008) Supplements and age-related eye conditions the beaver dam eye study. *Ophthalmology* **115**, 1203–1208.
17. Hankinson SE, Stampfer MJ, Seddon JM, *et al.* (1992) Nutrient intake and cataract-extraction in women – a Prospective Study. *BMJ* **305**, 335–339.
18. Statistics Sweden (2013) Undersökningarna av levnadsförhållanden. http://www.statistikdatabasen.scb.se (accessed February 2017).
19. Farmaceutiska Specialiteter i Sverige (2009) FASS Produktfakta. http://www.fass.se/LIF/produktfakta/substance_products.jsp?substanceId=IDE4POBWU933EVERT1 (accessed February 2017).
20. Lundstrom M, Stenevi U, Montan P, *et al.* Annual report 2011 based on data from National Cataract Register. Nationella Kataraktregistret EyeNet Sweden (in Swedish). http://kataraktreg.se/nationella-kataraktregistret/publikationer/arsrapporter-3 (accessed February 2017).
21. Bottai M & Zhang J (2010) Laplace regression with censored data. *Biom J* **52**, 487–503.
22. Orsini N, Wolk A & Bottai M (2012) Evaluating percentiles of survival. *Epidemiology* **23**, 770–771.
23. Bottai M & Orsini N (2013) A command for Laplace regression. *Stata J* **13**, 302–314.

24. Macedo DS, de Oliveira GV, Gomes PXL, *et al.* (2011) B vitamins attenuate haloperidol-induced orofacial dyskinesia in rats: possible involvement of antioxidant mechanisms. *Behav Pharmacol* **22**, 674–680.
25. Ashoori M & Saedisomeolia A (2014) Riboflavin (vitamin B_2) and oxidative stress: a review. *Br J Nutr* **111**, 1985–1991.
26. Endo N, Nishiyama K, Otsuka A, *et al.* (2006) Antioxidant activity of vitamin B_6 delays homocysteine-induced atherosclerosis in rats. *Br J Nutr* **95**, 1088–1093.
27. Lappas M & Permezel M (2011) The anti-inflammatory and antioxidative effects of nicotinamide, a vitamin B(3) derivative, are elicited by FoxO3 in human gestational tissues: implications for preterm birth. *J Nutr Biochem* **22**, 1195–1201.
28. Padival S & Nagaraj RH (2006) Pyridoxamine inhibits Maillard reactions in diabetic rat lenses. *Ophthalmic Res* **38**, 294–302.
29. Jain AK, Lim G, Langford M, *et al.* (2002) Effect of high-glucose levels on protein oxidation in cultured lens cells, and in crystalline and albumin solution and its inhibition by vitamin B_6 and N-acetylcysteine: its possible relevance to cataract formation in diabetes. *Free Radic Biol Med* **33**, 1615–1621.
30. Jacques PF, Hartz SC, Chylack LT Jr, *et al.* (1988) Nutritional status in persons with and without senile cataract: blood vitamin and mineral levels. *Am J Clin Nutr* **48**, 152–158.
31. Morris MS, Picciano MF, Jacques PF, *et al.* (2008) Plasma pyridoxal 5'-phosphate in the US population: the National Health and Nutrition Examination Survey, 2003–2004. *Am J Clin Nutr* **87**, 1446–1454.
32. Shils ME & Shike M (2006) *Modern Nutrition in Health and Disease*, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins.
33. Russell RM (2001) Factors in aging that effect the bioavailability of nutrients. *J Nutr* **131**, 1359S–1361S.

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