Research Article

Cancer Epidemiology, Biomarkers & Prevention

Elevated Vitamin B12 Levels and Cancer Risk in UK Primary Care: A THIN Database Cohort Study

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Abstract

Background: Elevated vitamin B12 levels (B12) are associated with increased short-term cancer risk. However, the implications for early cancer detection in primary care have not been assessed.

Methods: Individuals with plasma B12 measurements were sampled from The Health Improvement Network primary care database, UK. Persons with low B12 levels were excluded together with persons with cancer or B12 treatment before date of B12 measurement. Incident cancer was the outcome of interest and was identified through Read codes. Individuals were disaggregated according to plasma B12 levels (unit: pmol/L): 150–600 (reference range values), 601–800, 801–1,000, and >1,000.

Results: Among the 757,185 persons who met the inclusion criteria, we identified 33,367 incident cancers during 2,874,059 years of follow-up. We found a higher 1-year cancer risk among the 25,783 (3.4%) persons with elevated B12 levels compared with those with normal B12 levels. After multivariable adjustment for lifestyle factors and social deprivation, persons with B12 >1,000 pmol/L had a 1-year incidence rate ratio of 4.72 (95% confidence interval: 3.99–5.58). The association showed a nonlinear dose–response pattern, and it remained robust in stratified analyses, including when reducing the risk of confounding by indication in subanalyses. The risks were particularly elevated for liver cancer, pancreas cancer, and myeloid malignancies among persons with elevated B12 levels.

Conclusions: Elevated plasma B12 levels were associated with a higher 1-year cancer risk than normal B12 levels among persons seen in UK primary care, suggesting that some cancers may affect B12 metabolism.

Impact: Elevated B12 may mark occult cancer.

Introduction

It is common practice to measure plasma levels of vitamin B12 (B12, cobalamin) in persons suspected of B12 deficiency based on prevalent symptoms and/or risk factors for this condition (1). Cardinal symptoms of B12 deficiency are anemia, neuropsychological complaints, such as fatigue, cognitive dysfunction and paresthesia, and diarrhea and glossitis. Persons at risk of developing B12 deficiency include vegetarians/vegans and those with malabsorption due to pernicious anemia, inflammatory bowel disease, or atrophic gastritis (1).

Among persons with measured B12 levels, elevated levels above the upper reference limit are prevalent. The prevalence ranges from 1.2% to 18%, depending on study population and cutoff values for defining high B12 levels (2–7). These persons have gained attention in recent years, because an association between elevated B12 levels and cancer has been reported in several studies. Four cross-sectional studies reported a higher prevalence of cancer among hospital patients with high B12 levels compared with patients with normal B12 levels (2, 4–6). In addition, two cohort studies showed that patients with elevated plasma B12 levels had 6 to 15 times higher short-term risk of cancer compared with the general population in Denmark (3, 7). This association was found mainly for hematological cancers and smoking- and alcohol-related cancers (3). These findings indicate that elevated B12 levels may be a prodromal sign of undiagnosed cancer.

The cohort studies, conducted in Denmark, had several shortcomings (3, 7). They were unable to include data on whether patients were seen in hospital versus primary care settings. Likewise, data on lifestyle factors were unavailable, such as smoking and alcohol use, which are strong risk factors for cancer. It is not clear whether smoking affects plasma B12 levels (8, 9), but high alcohol use is associated with high B12 levels (2, 10). It is thus unresolved whether these factors influence the association between elevated B12 levels and cancer. In addition, the studies did not address whether risk estimates were confounded by the underlying indication for measuring plasma B12 levels.

In the current study, we assessed cancer risk among persons seen in the United Kingdom (UK) primary care system with elevated plasma B12 levels and included data on lifestyle factors. We also examined the potential confounding effect of the indication for requesting a plasma B12 measurement by examining a cohort of first-time statin users for whom the indication was unlikely related to any suspicion of cancer.

Materials and Methods

Data source

The Health Improvement Network (THIN) primary care database contains pseudonymized data on more than 12 million

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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persons from nearly 600 different practices in the UK (https://www.cegedim.com/). Data collected from electronic GP records on symptoms, diagnoses, and referrals are coded using the hierarchical Read code system (11). Data on drug prescriptions, smoking and alcohol habits, measures of height and weight, and laboratory tests are also recorded. Information on social deprivation is recorded in quintiles of the Townsend score (12), which is based on owner-occupation, car ownership, overcrowding, and unemployment levels, as derived from UK census data and linked to the individual's postal code. More than 98% of members of the UK population are registered with a GP. THIN covers approximately 6% of these individuals and is considered representative of the UK population (13). We used THIN data from 2000 through 2015.

The study was approved by the IMS Health Scientific Review Committee (reference number: 16THIN096). The scheme of providing anonymized person data for research purposes, used by the THIN database administration, was approved by the National Health Service South-East Multi-Centre Research Ethics Committee.

Study population

Our study population included all individuals between 18 and 99 years of age with a first-time plasma B12 measurement performed between 1 January 2000 and 30 June 2015. Data were included only if the period for data collection in the individual practice met the criteria of acceptable computer usage and mortality reporting, as previously described (14, 15). We excluded individuals with any of the following conditions recorded before the date of plasma B12 measurement: (i) diagnosis, treatment, care for, or history of cancer; (ii) cancer diagnosis recorded within 6 months of the person's registration at the GP, which may reflect prevalent cancer (16); (iii) B12 measurement within 6 months of the person's registration at the GP to avoid immortal time; (iv) diagnosis and/or treatment for B12 deficiency, the single most common cause of high B12 measurements (2); or (v) plasma B12 levels below 150 pmol/L and/or below the lower reference limit. Individuals were followed from the date of first plasma B12 measurement until the date of cancer diagnosis, death, transfer to a different GP, end of data contribution by the GP, or December 31, 2015, whichever came first.

Plasma vitamin B12 levels

We defined the following groups based on plasma B12 levels: reference range values of 150–600 pmol/L and three groups with high plasma B12 levels: 601–800 pmol/L, 801–1,000 pmol/L, and >1,000 pmol/L (in pg/mL: 203–813, 814–1,084, 1085–1,355, and >1,355). We chose the cutoff for reference range values based on the distribution of reference range cutoffs in the study population.

Cancer

We developed lists of Read codes for cancer diagnoses using the method described by Dave and Petersen (17). Cancer events were identified as a first-time cancer diagnosis in the persons' records or a record of death due to cancer. The cancer incidence in THIN is similar to the incidence in the UK Quality Outcomes Framework data (13), and to the UK Office for National Statistics' Cancer Registration Statistics (18, 19). Previous studies have assessed the positive predictive values (PPV) of specific cancer diagnosis codes in THIN and found a PPV of 94% for bladder cancer (20) and a PPV of 89% for colorectal cancer (21).

Covariates

Covariates included sex, age, Townsend quintile score, body mass index (WHO definition: body mass index [BMI]: <18.5, 18.5–24.9, 25–29.9, and $\geq$30 kg/m^2), smoking status (never, former, and current), and alcohol use (non-drinker, former drinker, moderate drinker [within UK guidelines, alcohol units per week: male: $\leq$21/female: $\leq$14], and heavy drinker [consuming more than UK guidelines; alcohol units per week: male: 22–49/female: 15–35], and very heavy drinker [alcohol units per week: male: $\geq$50/female: >35]). The value of each covariate recorded closest to the date of plasma B12 measurement was used. Records of smoking and alcohol habits in THIN are considered valid (22, 23).

First-time statin users

Previous cohort studies on the association between high plasma B12 levels and cancer risk did not assess the confounding effect of the indication for measuring plasma B12 (3, 7), and the indication may be related to a clinical suspicion of cancer. To overcome this limitation, we identified a cohort of first-time statin users in the main study population, assuming that these individuals: (i) are unlikely to be suspected of cancer; (ii) have blood samples taken regularly as a part of the routine statin check-up recommended for new statin users by the National Institute for Health and Care Excellence (https://www.nice.org.uk/guidance/cg181/; accessed December 7, 2018); and (iii) are likely to have their plasma B12 levels measured without an indication of any suspected severe disease. Previous reports indeed indicate that B12 is often measured without any indications related to symptoms and/or risk factors for B12 deficiency (24, 25). The inclusion criteria for this cohort were a first-time statin prescription, and a plasma B12 measurement within 6 months after the date of the first statin prescription. Exclusion criteria were the same as for the main study population, as described above.

Statistical analysis

We computed incidence ratios (IRs) and cumulative incidence proportions (CIPs) as measures of the absolute risk of cancer, treating death due to other causes than cancer as a competing risk for computing CIPs (26). We stratified according to the 4 groups of B12 levels with corresponding 95% confidence intervals (CIs).

In addition, we used multivariable Poisson regression analysis to compute adjusted incidence rate ratios (IRR) with corresponding 95% CIs to assess relative cancer risk with higher plasma B12 levels, using persons with plasma B12 levels of 150 to 600 pmol/L as reference. We adjusted for sex, age, Townsend quintile score, BMI, smoking status, and alcohol use. We used stratified analyses to assess if any of the covariates modified the association between B12 and cancer incidence. All risk estimates were stratified according to the following covariates: years of follow-up (<1, $\geq$1–$\leq$2, >2–$\leq$4, and $\geq$5), sex, age (18–39, 40–59, 60–79, and 80–99), Townsend quintile score (1 as the least deprived and 5 as the most deprived), BMI (<18.5, 18.5–24.9, 25–29.9, and $\geq$30 kg/m^2), smoking status (never, former, and current), alcohol use (non-drinker, former drinker, moderate drinker, heavy drinker, and very heavy drinker). We included person-time for all participants in the relevant follow-up time periods. We also stratified risk estimates according to specific cancer types, taking into account the sex-specific types (e.g., excluding females from analyses of prostate cancer). For the regression analyses, we excluded 219,249 people with missing values, including people with no records of Townsend quintile ($n = 30{,}590$), BMI ($n = 59{,}426$), smoking ($n = 26{,}399$), and alcohol use ($n = 170{,}810$). Their characteristics are shown in Supplementary Table S1. We evaluated whether data were clustered by practice using a random effect model, but did not observe any clustering. We conducted restricted cubic spline regression to assess any nonlinear associations between plasma B12 as a continuous variable and risk of cancer (27). We used 5 knots at 150, 400, 600, 800, and 1,000 pmol/L, with plasma B12 of 400 pmol/L (542 pg/mL) as reference and chose a graphical presentation of the smoothed IRRs (overall and after 1 year of follow-up) as a function of a 1 pmol/L (1.36 pg/mL) increase in plasma B12 levels.

We computed CIPs, IRs, and IRRs for the cohort of first-time statin users using the same approach as for the main study population, with follow-up starting at the date of plasma B12 measurement.

All analyses were performed with Stata IC Version 14.2.

Results

The study included 757,185 (64% female) with a first-time plasma B12 measurement (median age = 55.8 years; median follow-up time = 2.8 years [interquartile range: 1.3–5.3 years]). A total of 28,897 (3.5%) had elevated plasma B12 levels (>600 pmol/L). The proportions of heavy drinkers and people from the most deprived areas were higher among people with high plasma B12 levels, whereas the proportions of current smokers and overweight/obese individuals were lower among people with high plasma B12 levels (Table 1).

During 2,874,059 years of follow-up, 33,367 people (4.4%) were diagnosed with cancer. The risk of cancer was higher in people with elevated plasma B12 levels, most pronounced within the first year of follow-up (Table 2). Incidence rates and CIPs in the part of the population with complete data on covariates were very similar to estimates based on the entire population (Supplementary Table S2). Comparing persons with a normal plasma B12 level to those with B12 >1,000 pmol/L and adjusting for covariates, this corresponded to an overall IRR of 2.42 (95% CI, 2.11–2.77) and an IRR within the first year of follow-up of 4.72 (95% CI, 3.99–5.58). The association showed a nonlinear dose–response pattern, as depicted in Fig. 1.

Absolute cancer risk was higher for males than for females and increased with increasing age, but IRRs were almost similar, both overall and within the first year of follow-up. Smokers had higher one-year CIPs risk than nonsmokers (CIP for persons with plasma B12 >1,000 pmol/L, smoker vs. nonsmoker: 6.79 [4.90–9.08] vs. 5.54 [4.55–6.67]). For individuals with normal alcohol use compared with very heavy drinkers, we found paradoxically higher 1-year CIPs with increasing B12 levels (CIP for persons with plasma B12 >1,000 pmol/L, moderate vs. very heavy drinkers: 7.48 [6.07–9.07] vs. 4.05 [2.15–6.89]). Likewise, we found higher 1-year CIPs in those who were from

Table 1. Characteristics of 757,185 individuals in the UK with a first-time plasma B12 measurement, January 1, 2000, to June 30, 2015

	Plasma B12 level groups (pmol/L)			
	150–600	**601–800**	**801–1,000**	**>1,000**
No.	731,402	17,963	4,410	3,410
Sex (female), %	466,980 (64)	12,265 (68)	3,023 (69)	2,302 (68)
Age in years, median (range)	56.3 (18–99)	56.5 (18–99)	58.0 (18–99)	61.5 (18–99)
Year of B12 measurement, *n* (%)[a]				
2000–2004	53,940 (7)	1,581 (9)	495 (11)	376 (11)
2005–2008	137,502 (19)	3,478 (19)	891 (20)	706 (21)
2009–2011	236,058 (32)	5,557 (31)	1,241 (28)	950 (28)
2012–mid-2015	303,902 (42)	7,347 (41)	1,783 (40)	1,378 (40)
Smoking, *n* (%)[a]				
Never smoker	381,992 (52)	10,272 (57)	2,540 (58)	1,866 (55)
Former smoker	185,187 (25)	3,918 (22)	868 (20)	759 (22)
Smoker	139,110 (19)	2,959 (16)	732 (17)	583 (17)
Missing	25,113 (3)	814 (5)	270 (6)	202 (6)
Alcohol use, *n* (%)[a]				
Non-drinker	136,753 (19)	4,359 (24)	1,095 (25)	777 (23)
Former drinker	24,478 (3)	690 (4)	163 (4)	140 (4)
Moderate drinker (within guidelines)	343,248 (47)	7,233 (40)	1,634 (37)	1,229 (36)
Heavy drinker	38,868 (5)	674 (4)	148 (3)	147 (4)
Very heavy drinker	23,283 (3)	873 (5)	299 (7)	284 (8)
Missing	164,772 (23)	4,134 (23)	1,071 (24)	833 (24)
BMI in categories, *n* (%)[a]				
<18.5 kg/m^2	22,984 (3)	1,014 (6)	218 (6)	207 (6)
18.5–24.9 kg/m^2	258,348 (35)	7,411 (41)	1,765 (40)	1,318 (39)
25–29.9 kg/m^2	222,338 (30)	4,884 (27)	1,199 (27)	930 (27)
≥30 kg/m^2	170,635 (23)	3,121 (17)	740 (17)	584 (17)
Missing	57,097 (8)	1,533 (9)	425 (10)	317 (11)
Townsend quintile, *n* (%)[a]				
1	170,732 (23)	3,753 (21)	906 (21)	693 (20)
2	153,188 (21)	3,564 (20)	802 (18)	658 (19)
3	151,111 (21)	3,615 (20)	911 (21)	722 (21)
4	134,076 (18)	3,385 (19)	845 (19)	672 (20)
5	93,080 (13)	2,655 (15)	710 (16)	517 (15)
Missing	29,215 (4)	991 (6)	236 (5)	148 (4)

[a]Numbers do not add up to 100 due to rounding.

Table 2. Cumulative incidence proportions, person-years, number of cancer events, incidence rates, and adjusted IRRs (all with corresponding 95% CIs) for the risk of cancer in the main study population

	Plasma B12 level groups (pmol/L)			
Main study population	**150–600**	**601–800**	**801–1,000**	**>1,000**
CIP in % (95% CI)				
End of follow-up	13.09 (12.70–13.49)	13.96 (11.82–16.28)	17.71 (11.47–25.05)	17.75 (14.14–21.70)
1 year of follow-up	1.61 (1.58–1.64)	2.30 (2.08–2.53)	3.45 (2.93–4.03)	6.62 (5.80–7.50)
2 years of follow-up	2.49 (2.46–2.53)	3.24 (2.97–3.52)	4.32 (3.72–4.98)	7.95 (7.03–8.93)
5 years of follow-up	5.08 (5.01–5.14)	5.58 (5.17–6.02)	6.91 (6.02–7.88)	10.24 (9.10–11.47)
Person-years				
Overall	2,783,636	64,749	15,148	10,527
<1 year	673,276	15,964	3,763	2,714
≥1–≤2 years	533,060	12,424	2,871	1,989
>2–≤4 years	965,797	22,114	5,041	3,447
≥5 years	611,503	14,247	3,473	2,377
Cancer events				
Overall	31,894	877	275	321
<1 year	11,257	397	146	217
≥1–≤2 years	4,982	129	29	34
>2–≤4 years	9,248	204	55	38
≥5 years	6,407	147	45	32
IR/1,000 PYs (95% CI)				
Overall	11.46 (11.33–11.58)	13.55 (12.68–14.47)	18.16 (16.13–20.43)	30.49 (27.33–34.02)
<1 year	16.72 (16.41–17.03)	24.87 (22.54–27.44)	38.79 (32.99–45.63)	79.95 (69.99–91.33)
≥1–≤2 years	9.35 (9.09–9.61)	10.38 (8.74–12.34)	10.10 (7.02–14.54)	17.09 (12.21–23.92)
>2–≤4 years	9.58 (9.38–9.77)	9.23 (8.04–10.58)	10.91 (8.38–14.21)	11.02 (8.02–15.15)
≥5 years	10.48 (10.22–10.74)	10.32 (8.78–12.13)	12.96 (9.68–17.36)	13.46 (9.52–19.04)
Adj. IRR[a] (95% CI)				
Overall	Ref.	1.31 (1.21–1.41)	1.88 (1.64–2.15)	2.42 (2.11–2.77)
<1 year	Ref.	1.74 (1.54–1.96)	2.90 (2.39–3.51)	4.72 (3.99–5.58)
≥1–≤2 years	Ref.	1.39 (1.15–1.69)	1.39 (0.93–2.07)	1.58 (1.04–2.41)
>2–≤4 years	Ref.	0.99 (0.84–1.17)	1.37 (1.03–1.83)	1.23 (0.87–1.75)
≥5 years	Ref.	1.10 (0.91–1.32)	1.54 (1.11–2.12)	1.19 (0.79–1.82)

[a]IRRs were based on the 537,936 persons with complete data on all covariates. Estimates were computed using persons with a plasma B12 level of 150–600 pmol/L as reference and adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. The analyses were stratified according to plasma B12 levels and length of follow-up.

Abbreviation: PYs: person-years.

the least-deprived areas (Townsend quintile 1) compared with persons who were from the most deprived areas (Townsend quintile 5). However, the IRRs were very comparable in the stratified analyses and provided no evidence of an effect modification of the associations between B12 and cancer by alcohol consumption or social deprivation (see Supplementary Table S3 for results from stratified analyses). In both the overall analysis and the analysis stratified according to levels of covariates, the association between elevated B12 levels and cancer attenuated after the first year of follow-up. No overall association was found after 2 years of follow-up (Table 2).

The IRRs for specific cancers are shown in Table 3. We found the strongest association between high plasma B12 and risk of cancers of the upper gastrointestinal tract, the liver, the pancreas, the lung, and myeloid malignancies. The association remained robust, as it was strongest within the first year of follow-up, but the association persisted through more than 5 years of follow-up for liver cancer and myeloid malignancies. In contrast, colorectal, prostate and kidney cancer, as well as lymphatic leukemia and multiple myeloma were not associated with high plasma B12. However, for some cancers, there were very few events. No or only weak associations were found between high B12 levels and several other common cancers, including breast cancer and malignant melanoma (Supplementary Table S4).

There were 10,775 first-time statin users with a plasma B12 measurement. Their characteristics are shown in Supplementary Table S5. Compared with the main study population, first-time statin users were older, more often male and ex-smokers, had higher BMI, but with similar alcohol habits and Townsend quintile distributions. The association between elevated plasma B12 and cancer was robust in the statin-using cohort, with the highest risk of cancer within 1 year of follow-up, both for CIPs, IRs, and IRRs (Table 4). Due to a small sample size with few events, the estimates had wide 95% CIs.

Discussion

In this large cohort study using UK primary care data, we found that having elevated plasma B12 levels was associated with a higher short-term cancer risk compared with having normal B12 levels, and the association showed a nonlinear dose–response pattern. The association persisted when we controlled for several covariates, such as sex, age, smoking, and alcohol use. We also found the association in a cohort of first-time statin users, for whom cancer suspicion is unlikely to be related to the indication for measuring plasma B12 levels.

In the current study, we were able to confirm and elaborate on what we (3) and others (7) have found in the Danish patient population. Our results showed that high B12 levels are a marker of occult, not yet diagnosed cancer, also in the UK population and in the primary care setting. Unlike previous studies on high B12 levels and cancer risk, we were able to include information on smoking and alcohol habits (3, 7). It is interesting that several of the cancer types associated with high

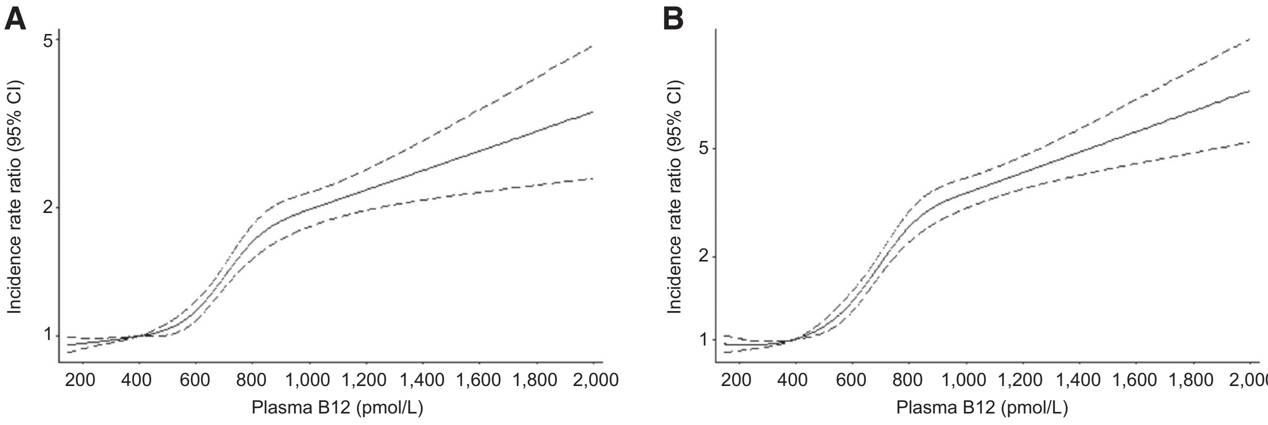

Figure 1.

Smoothed adjusted IRR plot using a five-knot cubic spline transformation at 150, 400, 600, 800, and 1,000 pmol/L. Plasma B12 level of 400 pmol/L was used as a reference. Models were adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. Dashed lines depict 95% CIs. **A,** Overall IRR. **B,** IRR after 1 year of follow-up.

plasma B12 are also associated with these 2 lifestyle factors, but our results remained robust, both when adjusting and stratifying according to smoking status and alcohol intake. However, it is important to note that only a minority of persons with plasma B12 >1,000 pmol/L were diagnosed with cancer within the first year following plasma B12 measurement. This potentially makes high B12 levels a marker of occult cancer, and further study will have to address the implications of including high B12 in clinical guidelines for early cancer detection in general practice.

Table 3. Adjusted IRRs (all with corresponding 95% CIs) for the risk of specific cancer types in the main study population

	Plasma B12 level groups (pmol/L)			
Cancer type	**150–600**	**601–800**	**801–1,000**	**>1,000**
Gastric/esophageal, *n*	1,764	53	11	23
Overall	Ref.	1.58 (1.16–2.15)	1.17 (0.55–2.45)	3.15 (1.92–5.17)
<1 year	Ref.	2.32 (1.54–3.50)	2.67 (1.19–5.97)	5.14 (2.75–9.62)
Colorectal, *n*	4,342	89	33	25
Overall	Ref.	0.91 (0.71–1.18)	1.68 (1.13–2.49)	1.31 (0.80–2.14)
<1 year	Ref.	1.18 (0.84–1.65)	2.44 (1.49–3.99)	1.65 (0.85–3.17)
Liver, *n*	337	30	16	17
Overall	Ref.	4.07 (2.61–6.36)	11.37 (6.62–19.53)	12.64 (7.22–22.13)
<1 year	Ref.	6.77 (3.24–14.12)	29.55 (14.08–62.01)	34.66 (16.50–72.81)
Pancreas, *n*	767	40	10	27
Overall	Ref.	2.40 (1.64–3.51)	2.28 (1.02–5.11)	7.42 (4.51–12.21)
<1 year	Ref.	5.92 (3.75–9.34)	6.27 (2.57–15.30)	19.60 (11.11–34.57)
Lung, *n*	3,820	101	19	26
Overall	Ref.	1.35 (1.08–1.70)	1.12 (0.66–1.89)	2.01 (1.32–3.05)
<1 year	Ref.	1.60 (1.11–2.32)	1.07 (0.40–2.86)	3.54 (2.00–6.26)
Kidney, *n*	590	16	6	≤5
Overall	Ref.	0.97 (0.50–1.88)	2.36 (0.98–5.71)	. (–.)[a]
<1 year	Ref.	0.60 (0.15–2.41)	. (–.)[a]	. (–.)[a]
Prostate, *n*	3,900	68	15	19
Overall	Ref.	0.91 (0.70–1.19)	0.95 (0.55–1.63)	1.07 (0.61–1.89)
<1 year	Ref.	1.34 (0.92–1.97)	1.32 (0.59–2.95)	2.09 (1.04–4.19)
Myeloid malignancies, *n*	2,190	128	63	84
Overall	Ref.	3.11 (2.53–3.81)	6.94 (5.23–9.20)	8.50 (6.41–11.27)
<1 year	Ref.	4.26 (3.21–5.64)	10.33 (7.11–15.02)	17.37 (12.60–23.96)
Lymphatic leukemia, *n*	442	13	≤5	≤5
Overall	Ref.	1.50 (0.80–2.81)	. (–.)[a]	. (–.)[a]
<1 year	Ref.	1.51 (0.56–4.08)	. (–.)[a]	. (–.)[a]
Multiple myeloma, *n*	695	6	7	8
Overall	Ref.	0.38 (0.14–1.01)	0.84 (0.21–3.37)	2.11 (0.79–5.66)
<1 year	Ref.	. (–.)[a]	. (–.)[a]	. (–.)[a]

NOTE: IRRs were based on the 537,936 persons with complete data on all covariates. Estimates were computed using persons with plasma levels B12 of 150–600 pmol/L as reference and adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. The analyses were stratified according to plasma B12 levels and length of follow-up (overall and <1 year).

[a]Too few events to compute estimates.

Table 4. Cumulative incidence proportions, person-years, number of cancer events, incidence rates, and adjusted IRRs (all with corresponding 95% CIs) for the risk of cancer in the subcohort of first-time statin users

First-time statin users	Plasma B12 level groups (pmol/L)			
CIP (95% CI)	150–600	601–800	801–1,000	>1,000
End of follow-up	15.94 (13.78–18.25)	11.27 (5.89–18.60)	12.68 (3.68–27.48)	26.43 (12.42–42.79)
1 year of follow-up	2.06 (1.80–2.36)	2.14 (0.81–4.65)	1.90 (0.16–8.82)	12.06 (4.90–22.70)
2 years of follow-up	3.33 (2.98–3.71)	3.74 (1.75–6.94)	1.90 (0.16–8.82)	16.54 (7.72–28.25)
5 years of follow-up	7.07 (6.49–7.68)	6.33 (3.40–10.51)	8.35 (1.94–20.94)	16.54 (7.72–28.25)
Person-years				
Overall	44,965	860	222	184
<1 year	9,679	213	49	41
≥1–≤2 years	8,066	171	40	35
>2–≤4 years	16,083	303	73	66
≥5 years	11,138	174	59	42
Cancer events				
Overall	715	15	≤5	10
<1 year	207	≤5	≤5	6
≥1–≤2 years	109	≤5	≤5	≤5
>2–≤4 years	230	≤5	≤5	≤5
≥5 years	169	≤5	≤5	≤5
IR/1,000 PYs (95% CI)				
Overall	15.90 (14.78–17.11)	17.44 (10.51–28.92)	18.06 (6.78–48.11)	54.36 (29.25–101.04)
<1 year	21.39 (18.66–24.51)	23.51 (9.78–56.47)	20.30 (2.86–144.14)	146.17 (65.67–325.36)
≥1–≤2 years	13.51 (11.20–16.30)	17.59 (5.67–54.53)	. (.–.)[a]	57.95 (14.49–231.71)
>2–≤4 years	14.30 (12.57–16.27)	13.18 (4.95–35.12)	27.48 (6.87–109.87)	. (.–.)[a]
≥5 years	15.17 (13.05–17.64)	17.29 (5.58–53.60)	16.84 (2.37–119.58)	47.60 (11.90–190.32)
Adj. IRR[b] (95% CI)				
Overall	Ref.	1.24 (0.70–2.21)	1.56 (0.58–4.18)	4.71 (2.34–9.48)
<1 year	Ref.	1.10 (0.35–3.47)	1.23 (0.17–8.92)	8.92 (3.28–24.25)
≥1–≤2 years	Ref.	. (.–.)[a]	. (.–.)[a]	. (.–.)[a]
>2–≤4 years	Ref.	. (.–.)[a]	. (.–.)[a]	. (.–.)[a]
≥5 years	Ref.	. (.–.)[a]	. (.–.)[a]	. (.–.)[a]

[a]Too few events to compute estimates.

[b]IRRs were based on the 8,363 persons with complete data on all covariates. Estimates were computed using persons with a plasma B12 level of 150–600 pmol/L as reference and adjusted for sex, age, Townsend quintile, smoking, alcohol use, and BMI. The analyses were stratified according to plasma B12 levels and length of follow-up.

Abbreviation: PYs: person-years.

Previous studies suggest that in up to two thirds of individuals with a plasma B12 measurement, there was no specific indication for requesting the measurement, such as symptoms and/or risk factors for B12 deficiency (24, 25). The higher IR within the first year of follow-up even for patients with B12 within the reference range may be due to the effect being in diagnostic process (i.e., the reason plasma B12 was measured). Further, the drop in IRs after the first year of follow-up is likely a compensatory deficit—that many cancers are diagnosed shortly after B12 measurement so the incidence drops thereafter. Ultimately, we cannot assess the indication for measuring plasma B12 for the individual person, but our results in the cohort of first-time statin users were robust. These results, together with the robustness of the stratified analyses, suggest that a potential confounding effect of the indication for measuring plasma B12 cannot fully explain the association between cancer and elevated plasma B12.

Some potential study limitations warrant attention. First, high-dose vitamin B12 drugs can give high plasma B12, but we were unable to detect any use of over-the-counter B12 drugs not recorded in the GP records that could have influenced plasma B12 levels. Hence, we might have included persons with high plasma B12 levels due to use of over-the-counter high-dose B12 drugs in the high B12 groups. Because these drugs do not increase cancer risk (28), we might have included some individuals at low risk of cancer in the high B12 groups, resulting in a potential underestimation of the association between high plasma B12 and cancer. Moreover, we cannot preclude that some individuals might have bought high-dose B12 vitamins to self-treat symptoms such as fatigue—a symptom also related to occult cancer. However, it is more likely that such drugs were prescribed by a GP to treat fatigue, and if so, these individuals would have been excluded. In addition, we may have underestimated the association due to random measurement error, leading to misclassification of B12 levels and potential regression dilution bias (29). There is also a risk that high plasma B12 or other concurrent abnormal lab tests could have increased the general practitioner's awareness of cancer, leading to more intense diagnostic efforts in these people. However, high plasma B12 is not currently included in the clinical guideline for early cancer detection (https://www.nice.org.uk/guidance/ng12/; accessed December 7, 2018), so we consider the risk of diagnostic bias to be minimal in our study. Last, we were not able to assess whether first-time statin users were indeed first-time users or prevalent users who newly registered with a GP practice providing data for the THIN database.

It is not entirely understood how the underlying cancer can cause high plasma B12 levels. Circulating B12 is exclusively bound to either haptocorrin or transcobalamin. The cancer may affect B12 metabolism by affecting the levels of these B12-binding proteins that in turn give rise to elevated plasma B12 levels (1). These protein alterations may involve inflammation cells that can produce either haptocorrin (30) or transcobalamin (31), and the potential underlying inflammation may also explain why high plasma B12 is associated with higher mortality risk and risk of venous thromboembolism among cancer patients (32, 33). These results are in concurrence with our previous finding that haptocorrin is elevated in cancer patients with high plasma B12 (2), and earlier reports showing that malignant proliferating leukocytes in patients with chronic myeloid leukemia (10). We were unable to include data on tumor size, lymph node involvement, or distant metastasis. These factors may also be important in the assessment of why and how elevated B12 is associated with cancer. Ultimately, it remains unresolved why high plasma B12 is associated with only some types of cancers and whether different protein alterations can be found in specific cancer types or stages of cancer.

In summary, in this study based on UK primary care data, we found a nonlinear dose–response association between elevated plasma B12 and 1-year cancer risk, suggesting that high B12 levels can mark occult cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The sponsors of this study had no role in the initiation, planning, design, or conduct of the study, data acquisition, management and analyses, interpretation of results, writing and approval of the manuscript, or the decision to submit the manuscript for publication. The researchers involved in this study declare their independence from the sponsors and have no conflicts of interests to report.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.F.H. Arendt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.F.H. Arendt, L.J. Horsfall, I. Petersen
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