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ORIGINAL ARTICLE

Incidence of prescription vitamin B12 use in relation to diagnosis of Alzheimer's disease among community-dwelling persons

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Abstract

Aims To evaluate the incidence of described purchases of vitamin B12 in community-dwelling persons with and without Alzheimer's disease (AD) from 9 years before to 5 years after the diagnosis.

Subject and methods We utilized register-based data from the Finnish nationwide MEDALZ (Medication use and Alzheimer's disease) cohort, including all AD cases who received a diagnosis in 2005–2011 ($N = 70,718$) and their age-, gender-, and region of residence-matched comparison persons without AD. Information on vitamin B12 use during 1995–2012 was collected from the Prescription Register.

Results During the follow-up, 5669 persons (8.2%) with AD and 3408 comparison persons (4.9%) initiated vitamin B12 use. The incidence rate of vitamin B12 use was significantly higher among persons with AD, beginning from one and a half years before the diagnosis and remained higher until 3 years after the diagnosis. The difference between the incidence rates was highest at the time of diagnosis (incidence rate ratio = 4.43, 95% confidence interval 3.82–5.14). The incidence started to increase also in persons without AD approximately 4 years before the diagnosis, remaining higher during the follow-up.

Conclusions The incidence of vitamin B12 use was considerably higher among persons with AD than in persons without AD around the time of AD diagnosis. On the other hand, the incidence of vitamin B12 use increased during the follow-up also in persons without AD. Regular checks of vitamin B12 levels among older people and earlier treatment of deficiency might reduce the disability related to vitamin B12 deficiency.

Keywords Alzheimer's disease · Incidence · Older people · Registries · Vitamin B12

Background

Alzheimer's disease (AD), a progressive, neurodegenerative disorder and the leading cause of dementia, is an increasing public health concern in ageing populations (Alzheimer's Disease International Consortium 2015). Worldwide, 46.8 million people were estimated to have dementia in 2015, and its prevalence is predicted to increase dramatically in the next few decades, which poses challenges and costs to the health-care system. With increasing number of people with AD, understanding the factors which contribute to cognitive function and cognitive decline in older age has gained public health importance.

Vitamin B12 (cobalamin) deficiency is relatively common among the older population, and its prevalence increases with age (Clarke et al. 2004; Loikas et al. 2007; Hunt et al. 2014). In a Finnish study of people aged 65 years or older, the prevalence of vitamin B12 deficiency was 12% (Loikas et al. 2007). Low blood level of this vitamin can cause reversible macrocytosis and anemia, but also several, in some cases irreversible, neurologic and neuropsychiatric symptoms such as neuropathy, myelopathy, and depression (Stabler 2013; Hunt et al. 2014). Vitamin B12 deficiency has also been associated with increased rate of brain atrophy (Hooshmand et al. 2016), higher risk of dementia (Kim et al. 2008; Kivipelto et al. 2009)

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and AD (Refsum and Smith 2003; Kivipelto et al. 2009; Hooshmand et al. 2010). However, the findings have been inconclusive (Basun et al. 1994; Narayan et al. 2011). Possible explanations for these discrepant results are differences in the methods used to assess vitamin B12 status (serum vitamin B12 concentrations, or biomarkers of vitamin B12 such as methylmalonic acid or holotranscobalamin) and small study populations, as well as differences in outcome measures, such as cognitive decline or clinically diagnosed AD and short follow-up times.

Clinical diagnosis of vitamin B12 deficiency is based on clinical symptoms and laboratory findings in Finland. Vitamin B12 treatment has been usually initiated for patients with serum or plasma total vitamin B12 level below the lower end of the laboratory reference range, usually 150 picomole/l (pmol/l) (Loikas et al. 2007; Smith and Refsum 2009). Most vitamin B12 deficient patients are treated with intramuscular vitamin B12 injections (cyanocobalamin tannin complex or hydroxocobalamin) which are prescription drugs, but an over-the-counter drug, oral cyanocobalamin supplementation, is also possible (Devalia et al. 2014; Chan et al. 2016).

The objective of this Finnish nationwide cohort study was to evaluate the incidence of described purchases of vitamin B12 (cyanocobalamin tannin complex or hydroxocobalamin) in community-dwelling persons with and without AD from 9 years before to 5 years after the diagnosis of AD.

Methods

Study population

This study is a part of the Medication use and Alzheimer's disease (MEDALZ) study, which contains all residents of Finland who received a clinically verified diagnosis of AD between 2005 and 2011 and were community dwelling at the time of diagnosis ($N = 70{,}718$) (Tolppanen et al. 2016). For each person with AD, one age-, sex- and region of residence-matched comparison person without AD were selected from a nationwide database including all residents. Data of the MEDALZ cohort has been linked to several nationwide registers including Prescription Register, Special Reimbursement Register, Hospital Discharge Register (Hilmo), and Register of Care at Social Institutions. The detailed description of the MEDALZ cohort and the applied registers was previously published by Tolppanen et al. (2016).

Persons with AD were identified from the Special Reimbursement Register maintained by the Social Insurance Institution (SII) (Tolppanen et al. 2016). The Finnish tax-funded public health care system covers all residents living in Finland for at least 2 years. Finland has unrestricted social security in the sense that all residents are entitled to, for example, reimbursed medication. The Special Reimbursement Register includes data on entitlement to special reimbursement of drugs due to clinically diagnosed chronic diseases such as AD. The Finnish Current Care Guideline on memory disorders recommends that all persons with AD are treated with antidementia drugs unless there is a specific contraindication (Working group set up by the Finnish Medical Society Duodecim, Societas Gerontologica Fennica, the Finnish Neurological Society, Finnish Psychogeriatric Association and the Finnish Association for General Practice 2017). The SII criteria for the AD diagnosis included symptoms consistent with mild to moderate AD, decrease in social capacity, computed tomography or magnetic resonance imaging scan, exclusion of alternative diagnoses, and confirmation of the diagnosis by registered neurologist or geriatrician. The statement on diagnostic findings is sent to the SII for approval, and special reimbursement is granted if the predefined criteria are fulfilled. AD diagnosis is based on the NINCDS–ADRDA and DSM-IV criteria for AD, including laboratory tests for vitamin B12 levels (McKhann et al. 1984; American Psychiatric Association 1994).

Vitamin B12 use

Initiation of vitamin B12 use among persons with and without AD during 1995–2012 was collected from the Prescription Register according to the World Health Organisation (WHO) anatomical therapeutic chemical (ATC) classification codes B03BA02 (cyanocobalamin tannin complex) and B03BA03 (hydroxocobalamin). The Finnish Prescription Register, maintained by the SII, contains information about all reimbursed drug purchases recorded in pharmacies. SII does not cover drug use in hospitals and nursing homes. Non-reimbursed and over-the-counter (OTC) drugs are not included in the register.

The follow-up for the incidence of vitamin B12 use began 9 years before and ended 5 years after the diagnosis of AD or corresponding matching date for comparison persons. Prevalent users ($N = 742$ and 643 among persons with and without AD respectively) were excluded from the analyses using a 1-year washout period starting 10 years before the AD diagnosis or a corresponding matching date for comparison persons. Furthermore, persons hospitalized for over half of the washout period were excluded due to uncertainty of drug use, as drugs used during hospital stays are not recorded in the Prescription Register (73 persons with AD, 74 persons without AD). After these exclusions, the matching was retained and 69,199 persons with AD and 69,199 persons without AD were included in this study. The follow-up for the incidence of vitamin B12 use ended for the following reasons: death, ≥ 90 days hospitalization period, end of study (31 December 2012), or initiation of vitamin B12 use, which ever occurred first.

Statistical analyses

The incidence was defined as having at least one vitamin B12 purchase, and incidence rates (IR) of vitamin B12 use were calculated for 6-month intervals as initiations per 100 person-years. The IRs between persons with AD and their comparison persons were compared with the Poisson regression, and the results were reported as incidence rate ratios (IRR) with 95% confidence intervals (CI). Analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Ethics of the study

No ethics committee approval or informed consents were required by the Finnish legislation as only de-identified data were utilized and persons in the sample were not contacted. In addition, permissions for data use were received from the SII.

Results

The study population included 69,199 persons with AD and 69,199 comparison persons without AD. During the follow-up, altogether 5669 persons with AD (8.2%) and 3408 comparison persons (4.9%) initiated prescription vitamin B12 use. The mean ages of users at the time of initiation of vitamin B12 use were slightly higher for comparison persons without AD than persons with AD [mean age 82.1, standard deviation (SD) 6.4, and 80.9 years, SD 6.4 respectively]. Both users with AD and users without AD were more likely to be women (62.6%) (Table 1). Prevalence of comorbidities, except for asthma/ chronic obstructive pulmonary disease (COPD), were significantly more common among users without AD than users with AD.

The IR of vitamin B12 use was significantly higher among persons with AD, beginning from one and a half years before the diagnosis of AD (IR in persons with AD = 0.71/100 person-years; IR in persons without AD = 0.41/100 person-years; IRR = 1.75, 95% CI 1.42–2.16) and remained higher until 3 years after AD diagnosis (IR in persons with AD = 1.63/100 person-years; IR in persons without AD = 0.97/100 person-years; IRR = 1.64, 95% CI 1.35–1.98) (Fig. 1). The difference between the IRs of vitamin B12 use was highest at the time of diagnosis (IRR = 4.43, 95% CI 3.82–5.14), when the IR in persons with AD was 3.0 initiations/100 person-years and in comparison persons without AD 0.7 initiations/100 person-years. However, the IR of vitamin B12 use started to increase also in persons without AD approximately 4 years before the AD diagnosis or the corresponding matching date for comparison persons, and remained higher during the rest of the follow-up.

Discussion

As far as we know, this is the first study assessing the incidence of described purchases of vitamin B12 among persons with AD in relation to time of diagnosis. In our study, the incidence of purchases of vitamin B12 was significantly higher in persons with AD compared with persons without AD from one and a half years before to 3 years after the diagnosis of AD. The incidence was highest at the time of the AD diagnosis, when it was four-fold compared with persons without AD. This might be due to the guidelines of care for diagnosis of cognitive disorder. According to this guideline, assessment of vitamin B12 status is an obligatory part of diagnostic process (Working group set up by the Finnish Medical Society Duodecim, Societas Gerontologica Fennica, the Finnish Neurological Society, Finnish Psychogeriatric Association and the Finnish Association for General Practice 2017). Diagnostic protocol requires that alternative diagnoses and reasons (such as vitamin B12 deficiency) should be excluded and treated before AD diagnoses can be verified. In addition, it might be that some persons had suffered from cognitive symptoms and vitamin B12 status was tested already a few years before the diagnosis of AD. This may explain why the incidence of vitamin B12 use in persons with AD started to increase already before to the diagnosis of AD. Further, to get a special reimbursement for AD medication, vitamin B12 status must be reported to SII as one of the clinical findings.

The association between vitamin B12 status and cognition is inconclusive. O'Leary et al. (2012) concluded in their systematic review of prospective studies that low serum B12 concentrations were not associated with cognitive decline or dementia. However, it was noticed that in studies using the biomarkers (methylmalonic acid or holotranscobalamin) for measuring vitamin B12 status, the association between low vitamin B12 status and cognitive decline, dementia, and also AD existed. A previous meta-analysis and systematic review of a large number of case–control and cross-sectional studies reported that total vitamin B12 level were lower in AD compared to healthy controls (Van Dam and Van Gool 2009; Lopes da Silva et al. 2014). Further research with larger study populations with longer follow-ups and carefully chosen markers for vitamin B12 status and assessments for cognitive decline, dementia, or AD may clarify the role of vitamin B12 in the process of cognitive decline.

Our study showed that the incidence of vitamin B12 use increased during the follow-up also in persons without AD. This is in line with several studies which have reported that vitamin B12 deficiency is common among the older population, and its prevalence increases with age (Clarke et al. 2004; Loikas et al. 2007). Hence, it seems that also aging itself increases the probability of vitamin B12 deficiency. In older persons, the most frequent cause of vitamin B12 deficiency is malabsorption of the food-bound vitamin B12, which is mainly caused by atrophic gastritis (approximately 30% of people 60 years or older)

Table 1 Characteristics and comorbidities of the incident vitamin B12 users with and without AD

	Users without AD: *n* (%; 95% CI)	Users with AD: *n* (%; 95% CI)	*P* value
Demographic characteristics			
Female	2132 (62.6; 60.9–64.2)	3546 (62.6; 61.3–63.8)	0.994
≥ 80 years of age	2248 (66.0; 64.4–67.5)	3312 (58.4; 57.1–59.7)	< 0.001
Comorbidities			
Asthma/COPD	3170 (9.3; 8.4–10.3)	4700 (8.3; 7.6–9.0)	0.097
Cancer	2320 (6.8; 6.0–7.7)	2950 (5.2; 4.7–5.8)	0.002
Cardiovascular diseases	1904 (55.9; 54.2–57.5)	2673 (47.2; 45.9–48.5)	< 0.001
Diabetes	8210 (24.1; 22.7–25.6)	1168 (20.6; 19.6–21.7)	< 0.001
Hypothyroidism	2660 (7.8; 7.0–8.8)	3320 (5.9; 5.3–6.5)	< 0.001
Rheumatoid arthritis	1750 (5.1; 4.4–5.9)	2180 (3.9; 3.4–4.4)	0.004

Comparison is made at the time of initiation of vitamin B12 use

AD, Alzheimer's disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease

(Hughes et al. 2013). Atrophic gastritis is a chronic inflammation of the stomach leading to atrophy of the mucosa and resulting in reduced gastric acid (hypochlorhydria) and pepsinogen secretion, which lead to the inability to release vitamin B12 from food or its carrier proteins (Carmel 1997). In addition, the decreased acid secretion may lead to bacterial overgrowth in the stomach and small intestine, and reduce the bioavailability of the vitamin B12 (Fried et al. 1994).

Brain changes start to develop years or even decades before AD can be clinically diagnosed (Holtzman et al. 2011; Scheltens et al. 2016). In addition, neurological symptoms associated with vitamin B12 deficiency may be irreversible and occur before or without hematological disorders (Lindenbaum et al. 1988; Devalia et al. 2014). Hence, regular checks in primary care of vitamin B12 levels among older people, and so early supplementation and treatment of deficiency already in an early state, might have an effect on disability related to vitamin B12 deficiency and severe adverse effects such as neuropathy.

Major strengths of this study are nationwide cohort of clinically verified AD cases and long follow-up time for the study population both before and after the diagnosis. In addition, the diagnoses in the Special Reimbursement Register were based on explicit, predefined criteria, providing a valid estimate of persons with AD in Finland. The limitations of this study were related to data based on registers. The Prescription Register did not include oral vitamin B12 supplements, which are over-the-counter drugs in Finland, and thus the results are not representative of overall use of vitamin B12. Further, the data did not cover vitamin B12 use during hospital care or nursing home stays. This may have led to minor underestimation of vitamin B12 use in our study population. However, this study gives an estimate of diagnosed vitamin B12 deficiency in this

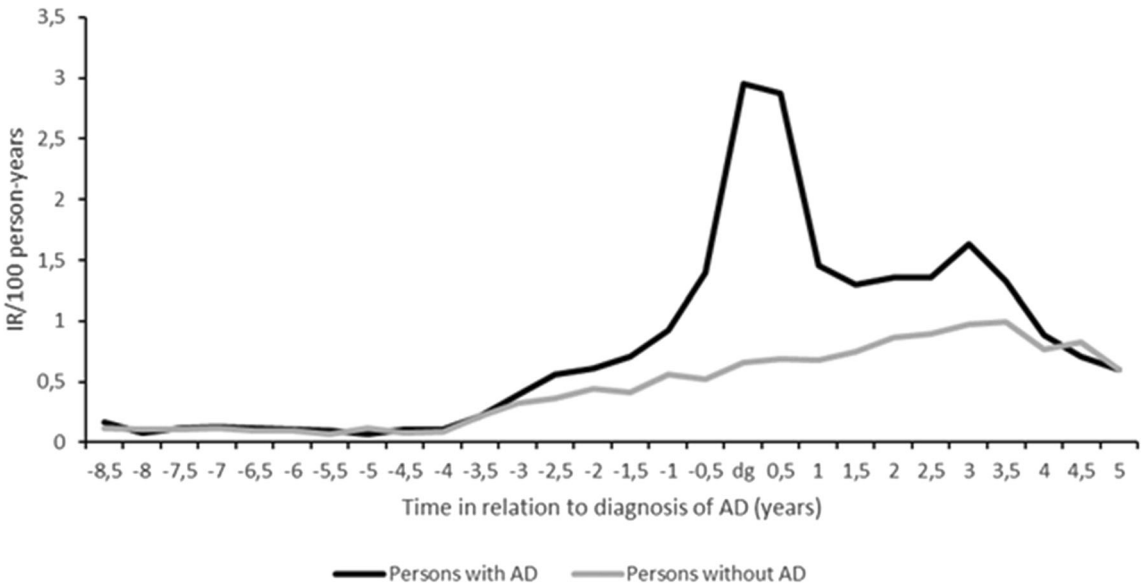

Fig. 1 The incidence of purchases of vitamin B12 in persons with and without AD per 100 person-years related to AD diagnosis. *IR*, incidence rate; *AD*, Alzheimer's disease; *dg*, diagnosis of AD

population. In addition, information on prevalence and severity of vitamin B12 deficiency, severity of AD, or presence of other types of dementia were not available.

The incidence of vitamin B12 use was considerably higher among persons with AD than in persons without AD around the time of AD diagnosis. On the other hand, the incidence of vitamin B12 use increased during the follow-up also in persons without AD. Regular checks of vitamin B12 levels among older people and earlier treatment of deficiency might reduce disability related to vitamin B12 deficiency.

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Author contribution SP analyzed data and wrote the paper. All authors contributed on study design and commented on and edited the article. All authors have approved the final article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study formal consent is not required.

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