

Intake of multivitamin supplements and incident asthma in Norwegian adults: the HUNT study

Lin Jiang¹

Ben Brumpton^{1,2}

Arnulf Langhammer¹

Yue Chen³

Xiao-Mei Mai^{1*}

¹Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

²Liason Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology, Trondheim, Norway.

³School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada.

*Corresponding author: Xiao-Mei Mai, Department of Public Health and General Practice, Norwegian University of Science and Technology (NTNU), Postbox 8905, MTF5, NO-7491 Trondheim, Norway.

E-mail: xiao-mei.mai@ntnu.no; office phone: +47 73590598

Key words: adult, asthma, cod liver oil, multivitamin, supplements

Word count: 3030

Summary of the “take home” message of this paper

Intake of multivitamin supplements was associated with an increased odds ratio for incident asthma in Norwegian adults.

Running Head

Multivitamin supplements and incident asthma

Abstract (Word count: 192)

Background: Although intake of multivitamin supplements is becoming increasingly popular, the relationship between intake of multivitamin supplements and incident asthma remains unclear. Prospective studies in adults with long-term follow-up are especially scarce.

Objective: To investigate the association between intake of multivitamin supplements and asthma development in Norwegian adults.

Methods: We followed 16,952 adult subjects from the second survey of the Nord-Trøndelag Health Study (1995-1997) up to 2006-2008, who at baseline were free of asthma and provided information on intake of multivitamin supplements and cod liver oil. Regular intake of multivitamin supplements or cod liver oil was defined as daily intake for ≥ 3 months during the year prior to baseline. Incident asthma was reported new-onset asthma after the 11-year follow-up.

Results: Intake of multivitamin supplements only was associated with an increased odds ratio for incident asthma (OR: 1.55, 95% CI: 1.12-2.13) after adjustment for a number of common confounding factors (Model I). Similar OR was found for intake of cod liver oil only and for intake of both supplements (1.59 and 1.73, respectively).

Conclusions: Regular intake of multivitamin supplements was associated with an increased odds ratio for incident asthma in Norwegian adults.

Introduction

Intake of vitamin supplements to improve health is becoming increasingly popular [1].

Multivitamin supplements are the most commonly used forms of vitamin supplements [1].

The majority of studies, both observational studies and randomized trials, show no overall benefit of multivitamin supplements on cancer and cardiovascular diseases [1, 2]. However, some studies show an increased risk for breast and prostate cancers in relation to multivitamin supplements use [3, 4]. These surprising and unintuitive results have led to ongoing debates.

The relationship between multivitamin supplements use and asthma risk has been previously studied in children with inconsistent results [5, 6]. So far, there have been no prospective studies with a long follow-up time in adults.

In the Norwegian market, brands of multivitamin supplements are limited and the vitamin components are stable chemical synthetic substances in either water-miscible or solid forms (containing mainly vitamin A, B, C, D and E) [7, 8]. Components in the multivitamin supplements are kept within the normal ranges according to the Norwegian daily recommendation [8]. In contrast, cod liver oil, also a commonly used type of vitamin supplements in Norway [7] contained a high concentration of naturally oil-based vitamin A (1,000 µg per 5 ml) before 1999 [9]. The high concentration of vitamin A in this former formula of cod liver oil was hypothesized to be the main reason for an increased risk of asthma associated with cod liver oil intake among Norwegian adults observed in our previous study [10]. In the current analysis, we further evaluated the risk of incident asthma among adults who regularly used 1) cod liver oil only, 2) multivitamin supplements only or 3) both, compared to those who did not regularly use any of these supplements.

Methods

Study design

The Nord-Trøndelag Health Study (HUNT), is one of the largest prospective population-based studies in Norway. It consists of three surveys which were carried out in 1984-1986 (HUNT1), 1995-1997(HUNT2) and 2006-2008(HUNT3) separately [11]. All adults, 19 years or older living in the county of Nord Trøndelag were invited to participate at each cycle [12]. Nord-Trøndelag is considered to be fairly representative of the Norwegian population regarding geography, economy, sources of income, age distribution, morbidity and mortality [11]. The population of HUNT study is reasonably homogenous with more than 97 % Caucasian inhabitants. The response rate was 69.5% (n=65,237) for HUNT2 and about 37,059 adults took part in both HUNT2 and HUNT3 [12](Figure 1). Among the 37,059 participants, we selected those who were less than 65 years of age in HUNT3 (n=25,616) to establish our study cohort to keep a low possibility of misclassification of asthma with chronic obstructive pulmonary disease (COPD).

Incident asthma

The same question regarding asthma 'Do you have or have you had asthma?' was asked in both HUNT2 and HUNT3. We excluded 2,050 subjects because they either reported having asthma in HUNT2 or did not answer the question on asthma in HUNT2 or HUNT3. This left 23, 566 subjects defined as free from asthma at baseline. Cases of incident asthma over an average 11-year follow-up were defined as participants who reported asthma for the first time in HUNT3. Furthermore, we used a stricter definition of asthma for sensitivity analyses; the participants were free from wheeze and asthma at baseline and reported asthma at follow-up in combination with use of asthma medications (eg, inhaled corticosteroids and/or β 2-agonists). Participants who were free from wheeze and asthma both at baseline and at follow-

up served as the reference group. Wheeze referred to attacks of wheezing or breathlessness during the last 12 months. In Norway asthma medications are prescribed to patients after a doctor has confirmed the diagnosis.

Cod liver oil use and multivitamin supplements at baseline

Total months of daily use of cod liver oil and multivitamin supplements during the past 12 months prior to HUNT2 were asked in questionnaires. We defined daily intake of either cod liver oil or multivitamin supplements for at least 3 months as regular intake. There were 16,952 subjects with complete data on use of cod liver oil and multivitamin supplements at baseline, and 6,614 with missing information on the exposure of either cod liver oil or multivitamin supplements or both. The regular intake of supplements was categorized as 1) use of cod liver oil only, 2) use of multivitamin supplements only and 3) use of both. Non-users or daily intake of cod liver oil or multivitamin supplements <3 months served as the reference group.

Other baseline variables

All baseline variables were collected in a clinical examination or by questionnaires in HUNT2. These variables included age, sex, smoking status, average hours of light physical activity per week, years of education, social benefit recipient, economic difficulties, family history of asthma, body mass index (BMI), alcohol consumption, symptoms of anxiety and depression, and any chronic diseases. Current smokers responded “yes” to “Do you smoke cigarettes daily?”. Former smokers respond “no” to “Do you smoke cigarettes daily?” and “no” to “Never smoked daily”. Never smokers respond “no” to “Do you smoke cigarettes daily?” and “yes” to “Never smoked daily”. Social benefit recipients were those who reported receiving any public welfare benefits. Economic difficulties referred to those who had difficulties to meet the costs of food, transportation or housing. Weight and height were

measured by health professionals. Body mass index was grouped into three categories (<25.0 , $25.0-29.9$ and ≥ 30.0 kg/m^2) according to the recommendations of the World Health Organization (WHO) [13]. Alcohol consumption was assessed by the participant's response to the question "How many times a month do you normally drink alcohol?". Symptoms of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) [14]. It included two sets of questions about the participant's feeling in the past week, seven for symptoms of anxiety and seven for symptoms of depression with four-point ordinal scale of symptom severity (0-3) for each question. The total score for anxiety or depression therefore ranges from 0 to 21 [15]. Any chronic diseases at baseline was defined as any long-term (at least 1 year) illness or injury of a physical or psychological nature that impaired functioning in the everyday life.

Statistical analysis

Descriptive statistics for baseline characteristics of the cohort were presented in Table 2. The cumulative incidence of asthma over the approximate 11-year follow-up was compared among four groups using non-users or daily intake of cod liver oil or multivitamin supplements <3 months as the reference group in logistic regression models, which yielded odds ratios (OR) and 95% confidence intervals (CI). Model I included age (19–29, 30–39, 40–49 and 50–55 years), sex (men/women), smoking (current, former, never and unknown), light physical activity (<1 , $1-2$, ≥ 3 hours per week and unknown), education (<10 , $10-12$, ≥ 13 years and unknown), social benefit (yes, no and unknown), economic difficulties (yes, no and unknown), family history of asthma (yes, no and unknown), and BMI categories (<25.0 , $25.0-29.9$, ≥ 30.0 kg/m^2 and unknown) at baseline as covariates. Model II was adjusted for alcohol consumption in addition to the covariates in Model I. Model III was adjusted for symptoms of anxiety and depression and chronic disease at baseline in addition to covariates in Model I. Sensitivity analysis was performed in 14,939 subjects by using the stricter

definition of asthma to test the robustness of our results. All statistical analyses were performed with STATA, release V.12.0.19.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics. All participants signed informed written consent before participating in HUNT.

Results

Subjects who had complete information on use of cod liver oil and multivitamin supplements were included in the study analysis (n=16,952) and they seemed to have a healthier lifestyle and a better socio-economic status than those who had missing data on use of cod liver oil or multivitamins (n=6,614) (**Table 1**). In addition, subjects who were included had a higher proportion of family history of asthma than the excluded subjects.

Among the included subjects, 7% used cod liver oil only, 6% used multivitamin supplements only and 6% used both supplements (**Table 2**). The distribution of age, BMI, education, family history of asthma or alcohol consumption did not show major group differences.

Subjects who used both supplements or used multivitamin supplements only were more likely to be females, report receiving social benefits, having chronic disease and higher HAD scores of anxiety and depression at baseline than those who used cod liver oil only or were in the reference group.

In comparison with subjects in the reference group, those who used cod liver oil only showed a significantly increased OR for incident asthma (OR 1.59, 95% CI 1.16-2.19) after adjustment for potential confounding factors including age, sex, smoking, light physical activity, socio-economic status, family history of asthma and BMI (**Table 3**, Model I).

Subjects who used multivitamin supplements only also had a significantly increased OR for asthma after the 11-year follow-up compared to reference group (OR 1.55, 95% CI 1.12-2.13). The OR for incident asthma in association with use of both supplements was similar to the ORs associated with cod liver oil only or multivitamin supplements only (OR 1.73, 95% CI 1.26-2.37). The pattern of associations remained after stratification by sex, age, smoking, obesity or family history of asthma (data not presented). Additional adjustment for alcohol consumption (Model II), symptoms of anxiety and depression and chronic disease (Model III)

showed similar results. Further adjustment of physician visits during the past year and hospitalization during the past 5 years before baseline after Model III did not show major change in the finding (OR 1.57, 95% CI 1.11-2.21).

In sensitivity analysis when asthma was defined by a stricter definition, the associations remained similar (**Table 4**). The ORs for cod liver oil only, multivitamin supplements only, and both, were 1.72, 1.50 and 1.90, respectively after adjustment for covariates included in Model I. The mean or median duration of intake of multivitamin supplements was about 8 months among the users. There seemed to be a dose-response relationship between the duration of multivitamin supplements use and risk of incident asthma: above the 3-month cut-point each additional month of intake of multivitamin supplements was associated with an OR of 1.03 (95% CI 1.00-1.06) for incident asthma after adjustment for covariates in Model I and additional adjustment for cod liver oil intake ≥ 3 months.

After exclusion of subjects who reported ever COPD, chronic bronchitis or emphysema in HUNT3, similar ORs were obtained for use of cod liver oil only, multivitamin supplements only or both after adjustment of covariates in Model I (1.55, 1.62 and 1.61, respectively, **supplementary table 1**). A comparable pattern was also shown in a younger group (age <40 years at baseline, **supplementary table 2**), and the results were consistent when participants with chronic disease at baseline were excluded (**supplementary table 3**).

Discussion

In this cohort of 16,952 participants, we found that users of multivitamin supplements only had an increased OR for incident asthma after the 11-year follow-up; use of cod liver oil only or use of both supplements demonstrated similar OR to that of the multivitamin supplements only users after adjustment for a complete panel of possible confounding factors.

Our observation on use of cod liver oil only in the current study confirmed our previous finding of a significantly increased risk of asthma in those who used a former formula of cod liver oil containing a high dose of vitamin A [10]. Two previous studies have investigated the association of multivitamin supplements use with asthma among children [5, 6]. No association was found in a Swedish cross-sectional study [5]. While in a prospective study from the USA, use of multivitamin supplements during the first 6 months of life was associated with an increased risk of asthma after 3 years follow-up [6]. Our study is novel and extends previous findings by investigating an adult population with a longer follow-up time (11 years).

High concentration of vitamin A in the former formula of cod liver oil was suggested as the main reason for the increased risk of asthma among Norwegian adults using cod liver oil in our previous study [10]. The mechanisms for an increased OR of incident asthma by use of multivitamin supplements are unclear. However, the similar OR for use of both supplements as the use of individual supplement suggests a common pathway. Otherwise, the OR for use of both supplements would have at least been additive. High concentration of vitamin A in the lung may produce an acute, localized form of intoxication which is recognized as “asthma” [16]. Unlike the former formula cod liver oil which contained a high dose of vitamin A in an oil-based form, multivitamin supplements contained water-miscible or solid form of vitamin A in the normal range according to the Norwegian daily recommended need [8]. However,

studies suggest that water-miscible or solid form of vitamin A preparation is about ten times as toxic as oil-based vitamin A preparation [17]. It has also been reported that the adult Norwegian population has a relatively high intake of vitamin A from the diet [9, 18]. Together with a diet already rich in vitamin A, the vitamin A in the multivitamin supplements may have contributed to the increased risk of adult asthma in our study.

Apart from vitamin A, vitamin D and E are also common components in both cod liver oil and multivitamin supplements. However, current large population studies showed either no association [19, 20] or a protective association of higher serum 25(OH)D levels with incident asthma [21-23]. With respect to the effect of vitamin E on incident asthma, the majority of scientific evidences do not show any detrimental effect [24-26]. Therefore, both vitamin D and E are less likely the explanations for our findings. In addition to the hypothesis on vitamin A, both cod liver oil and multivitamin supplements are combinational formula of different vitamins; it is possible that the interactions of vitamins have played a role in asthma risk.

Scientific evidence regarding the beneficial or harmful effect of multivitamin supplements in relation to asthma is scarce. To our knowledge, the current study is one of the few prospective study evaluating the association of multivitamin supplements intake with onset of asthma in adults over a long follow-up period. Moreover, the study population is considerably large and relatively homogeneous. In this study, we also had possibility to adjust for many potential confounders such as lifestyle factors and chronic diseases.

However, our study may have several potential limitations. First, selection bias might exist since the included population seemed to be different from the population with missing data on cod liver oil or multivitamin supplements use with regard to social economic status and lifestyle factors. However, these factors are more likely to be confounding factors than

consequences of the supplements use and asthma outcome and therefore more appropriate to adjust for. Selection bias, if any, would have resulted in conservative estimate for our findings since the included people seemed to have a higher social economic status but multivitamin supplements use was associated with a lower social economic status.

Furthermore, some confounders such as unhealthy lifestyles, comorbidities and diet might also contribute to our findings. Unfortunately we do not have data on diet, but not a single diet has been confirmed to be associated with asthma risk. In addition, social economic status can be a proxy measure for diet as it is closely related to diet [27]. When we adjusted for various unhealthy lifestyle factors and chronic diseases there were no substantial changes in the results. Restricting the analysis in subjects with no chronic disease or age <40 years (a healthier group) we observed similar results. However, it is worth to note that people who used multivitamin supplements were more likely to report having chronic diseases than the non-users, and therefore asthma may be more likely to be diagnosed in the multivitamin supplements users due to frequent consultations of a physician for other diseases. This may partially explain the positive association between multivitamin use and incident asthma we observed, but further adjustment of physician visits during the past year and hospitalization during the past 5 years before baseline after Model III cannot change our conclusion .

Information bias might also influence our results. Intake of cod liver oil or multivitamin supplements was assessed by self-administered questionnaire which might lead to some attenuation of the association due to non-differential misclassification. We were also unable to carefully investigate the dose-response relationship due to lack of information on the dosage of vitamins. However, there seemed to be a dose-response association between months of multivitamin use and asthma risk. Additionally, in the original HUNT2 questionnaire, the words “vitamin supplements” rather than “multivitamin supplements” were used. Although most of the people were assumed to take multivitamin supplements, single use of vitamin B,

C and D could not be excluded. Vitamin B and C are not contained in the cod liver oil product and therefore less likely to explain the common pathway for multivitamin and cod liver oil supplements. Vitamin D has been discussed in the previous section to have either a protective or no association with asthma risk [19-23]. Finally, there is no established cut-point to define regular intake of multivitamin supplements. We used ≥ 3 months' use of multivitamin supplements during the previous year to reflect a regular intake. Despite being a somewhat arbitrary choice of cut-point, we found similar results as using either ≥ 1 month or ≥ 8 months as the cut-point (data not presented). The 8-month cut-point was the mean duration of intake among users but showed reduced power in subgroup analysis.

There was also a possible misclassification of asthma caused by self-reporting. Many studies however, have reported that the validity and reliability of self-reported asthma are acceptable [28, 29]. In the present study, we did a sensitivity analysis by using a stricter asthma definition (confirmation of asthma medicine usage combined with self-reported asthma) and further excluded subjects who reported ever COPD, chronic bronchitis or emphysema in the data analysis. We did not find any notable differences in results.

Overall, we found that intake of multivitamin supplements was associated with an increased OR for incidence of asthma in Norwegian adults after an 11-year follow-up. Confirmation of this observation and possible mechanisms driving this association deserve further investigation.

Acknowledgments: The Nord-Trøndelag Health Study (The HUNT Study) is collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council and the Norwegian Institute of Public Health.

Funding: This study was supported by fund from the Research Council of Norway (project no. 201895/V50). The Lung Study in HUNT 2 and HUNT 3 received funding from AstraZeneca Norway. Dr Brumpton received a post-doctoral fellowship grant from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology. None of the funding sources was involved in any aspect of the study design, conduct, analysis, interpretation of data, or writing the report.

Competing interests: None.

References

1. Comerford KB. Recent developments in multivitamin/mineral research. *Adv Nutr* 2013; 4(6): 644-656.
2. Kamangar F, Emadi A. Vitamin and mineral supplements: do we really need them? *Int J Prev Med* 2012; 3(3): 221.
3. Larsson SC, Åkesson A, Bergkvist L, Wolk A. Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women. *Am J Clin Nutr* 2010; 91(5): 1268-1272.
4. Zhang Y, Coogan P, Palmer JR, Strom BL, Rosenberg L. Vitamin and mineral use and risk of prostate cancer: the case-control surveillance study. *Cancer causes & control : CCC* 2009; 20(5): 691-698.
5. Marmstö K, Rosenlund H, Kull I, Håkansson N, Wickman M, Pershagen G, Bergström A. Use of multivitamin supplements in relation to allergic disease in 8-y-old children. *Am J Clin Nutr* 2009; 90(6): 1693-1698.
6. Milner JD, Stein DM, McCarter R, Moon RY. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. *Pediatrics* 2004; 114(1): 27-32.
7. Danielsen S, Ekrol PS. Food supplements in the nordic countries-Results from surveys among consumers in the Nordic countries. Oslo: Mattilsynet; 2009.
8. Blomhoff R B-SU, Brot C, Solvoll K, Steingrimsdottir L, Carlsen MH. Health risks related to high intake of preformed retinol (vitamin A) in the Nordic countries. Copenhagen: Nordic Council of Ministers; 2003.
9. Forsmo S, Fjeldbo SK, Langhammer A. Childhood Cod Liver Oil Consumption and Bone Mineral Density in a Population-based Cohort of Peri-and Postmenopausal Women The Nord-Trøndelag Health Study. *Am J Epidemiol* 2008; 167(4): 406-411.
10. Mai X-M, Langhammer A, Chen Y, Camargo CA. Cod liver oil intake and incidence of asthma in Norwegian adults—the HUNT study. *Thorax* 2012; thoraxjnl-2012-202061.
11. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten L, Lund-Larsen PG. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. *Norsk epidemiologi* 2003; 13(1): 19-32.
12. Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013; 42(4): 968-977.
13. Organization WH. preventing and managing the global epidemic [report of a WHO Consultation on Obesity]. Geneva: World Health Organization; 2004.
14. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes* 2003; 1(29): 29.
15. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res* 2002; 52(2): 69-77.
16. Mawson A. Could bronchial asthma be an endogenous, pulmonary expression of retinoid intoxication? *Front Biosci* 2001; 6: D973-985.
17. Myhre AM, Carlsen MH, Bohn SK, Wold HL, Laake P, Blomhoff R. Water-miscible, emulsified, and solid forms of retinol supplements are more toxic than oil-based preparations. *Am J Clin Nutr* 2003; 78(6): 1152-1159.
18. Johansen AMW, Lie RT, Wilcox AJ, Andersen LF, Drevon CA. Maternal dietary intake of vitamin A and risk of orofacial clefts: a population-based case-control study in Norway. *Am J Epidemiol* 2008; 167(10): 1164-1170.
19. Confino-Cohen R, Brufman I, Goldberg A, Feldman BS. Vitamin D, asthma prevalence and asthma exacerbations: a large adult population-based study. *Allergy* 2014; 69(12): 1673-1680.

20. Cheng HM, Kim S, Park GH, Chang SE, Bang S, Won CH, Lee MW, Choi JH, Moon KC. Low vitamin D levels are associated with atopic dermatitis, but not allergic rhinitis, asthma, or IgE sensitization, in the adult Korean population. *The Journal of allergy and clinical immunology* 2014; 133(4): 1048-1055.
21. Mai X-M, Langhammer A, Camargo CA, Chen Y. Serum 25-Hydroxyvitamin D Levels and Incident Asthma in Adults The HUNT Study. *Am J Epidemiol* 2012: 235.
22. Frieri M, Valluri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. *Allergy and asthma proceedings : the official journal of regional and state allergy societies* 2011; 32(6): 438-444.
23. Bozzetto S, Carraro S, Giordano G, Boner A, Baraldi E. Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy* 2012; 67(1): 10-17.
24. Allen S, Britton J, Leonardi-Bee J. Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis. *Thorax* 2009; 64(7): 610-619.
25. Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B, Speizer FE. A prospective study of diet and adult-onset asthma. *Am J Respir Crit Care Med* 1995; 151(5): 1401-1408.
26. Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, Helms PJ, Seaton A. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *American journal of respiratory and critical care medicine* 2006; 174(5): 499-507.
27. Darmon N, Drewnowski A. Does social class predict diet quality? *The American journal of clinical nutrition* 2008; 87(5): 1107-1117.
28. De Marco R, Cerveri I, Bugiani M, Ferrari M, Verlato G. An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma. *The European respiratory journal* 1998; 11(3): 599-605.
29. Brisman J. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *CHEST Journal* 1993; 104(2): 600-608.

Table 1. Subjects missing on information of use of cod liver oil or multivitamin supplements in comparison with subjects with complete data who were included in the analysis, the HUNT Study

	Subjects with complete data		Subjects with missing data	
	mean	SD	mean	SD
	N=16,952		N=6,614	
	mean	SD	mean	SD
Age at baseline (yrs)	39.4	8.8	40.9	8.8
Body mass index (kg/m ²)	25.6	3.7	26.0	4.0
	n	%	n	%
Female sex	9,421	55.6	3,648	55.2
Current smoking	4,640	28.9	2,124	33.8
Physical activity <1	3,702	24.2	1,632	27.8
Education <10 yrs	3,082	18.3	1,611	24.7
Social benefit recipient	3,069	19.3	1,005	32.0
Having economic difficulty	5,310	31.7	1,164	34.8
Family history of asthma	2,824	17.7	614	11.5

Abbreviations: HUNT, Nord-Trøndelag Health Study; SD, standard deviation.

Table 2. Use of cod liver oil and multivitamin supplements by baseline characteristics, the HUNT Study, 1995-97 to 2006-08 (n=16,952)

	Reference group [§]		Cod liver oil only		Multivitamin supplements only		Use of both	
	mean	SD	mean	SD	mean	SD	mean	SD
	N=13,742		N=1,163 (7%)		N=997 (6%)		N=1,050 (6%)	
Age at baseline (yrs)	38.8	8.8	41.6	8.1	40.4	8.9	41.9	8.6
Body mass index (kg/m ²)	25.7	3.8	25.5	3.5	25.4	3.9	25.4	3.7
HADS-Anxiety	4.0	3.1	4.2	3.2	4.7	3.5	4.7	3.5
HADS-Depression	2.9	2.7	2.9	2.7	3.3	2.8	3.1	2.9
	n	%	n	%	n	%	n	%
Female sex	7,229	52.6	657	56.5	794	79.6	741	70.6
Current smoking	3,827	27.9	239	20.6	310	31.1	264	25.1
Physical activity <1	3,140	22.9	202	17.4	181	18.2	179	17.1
Education <10 yrs	2,511	18.3	218	18.7	181	18.2	172	16.4
Social benefit recipient	2,371	17.3	189	16.3	241	24.2	268	25.5
Having economic difficulty	4,384	31.9	274	23.6	357	35.8	295	28.1
Family history of asthma	2,254	16.4	192	16.5	188	18.9	190	18.1
Alcohol consumption ≥5 times/month	1,865	13.6	182	15.7	126	12.6	152	14.5
Any chronic disease at baseline	1,590	11.6	194	16.7	202	20.3	249	23.7

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HUNT, Nord-Trøndelag Health Study; SD, standard deviation.

[§]Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Table 3. The association of use of cod liver oil and multivitamin supplements with cumulative incidence of asthma over 11-year follow-up period, the HUNT Study, 1995-97 to 2006-08 (n=16,952)

Regular use of cod liver oil and multivitamin supplements the previous year	No.	Cases	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I*	Adjusted OR (95% CI) Model II [†]	Adjusted OR (95% CI) Model III [#]
Reference group [§]	13,742	389	2.8	1.00	1.00	1.00	1.00
Cod liver oil only	1,163	46	4.0	1.41 (1.04-1.93)	1.59 (1.16-2.19)	1.59 (1.16-2.18)	1.53 (1.11-2.11)
Multivitamin supplements only	997	46	4.6	1.66 (1.21-2.27)	1.55 (1.12-2.13)	1.54 (1.12-2.13)	1.48 (1.07-2.05)
Use of both	1,050	48	4.6	1.64 (1.21-2.23)	1.73 (1.26-2.37)	1.73 (1.26-2.36)	1.65 (1.20-2.26)

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; OR, odds ratio.

*Model I adjusted for age, sex, smoking (current, former, never and unknown), light physical activity, education, social benefit, economic difficulties, family history of asthma, and body mass index.

[†]Model II adjusted for alcohol consumption in addition to the covariates in Model I.

[#]Model III adjusted for HADS of anxiety and HADS of depression and chronic disease at baseline in addition to the covariates in model I (n=16,819 due to missing of HADS).

[§]Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Table 4. Sensitivity analysis using a stricter definition for asthma[&] (n=14,939): The association of use of cod liver oil and multivitamin supplements with cumulative incidence of asthma over 11-year follow-up period, the HUNT Study, 1995-97 to 2006-08

Regular use of cod liver oil and multivitamin supplements the previous year	No.	Cases	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I*	Adjusted OR (95% CI) Model II [†]	Adjusted OR (95% CI) Model III [#]
Reference group [§]	12,175	238	2.0	1.00	1.00	1.00	1.00
Cod liver oil only	1,008	29	2.9	1.49 (1.00-2.20)	1.72 (1.16-2.56)	1.71 (1.15-2.54)	1.63 (1.09-2.44)
Multivitamin supplements only	861	26	3.0	1.56 (1.04-2.36)	1.50 (0.99-2.28)	1.49 (0.98-2.27)	1.43 (0.94-2.18)
Use of both	895	30	3.4	1.74 (1.18-2.56)	1.90 (1.28-2.83)	1.90 (1.28-2.83)	1.81 (1.21-2.70)

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; OR, odds ratio.

[&]stricter definition for asthma: participants who were free from wheeze and asthma at baseline reported asthma at follow-up in combination with use of asthma medication; participants who were free from wheeze and asthma both at baseline and at follow-up served as reference group.

*Model I adjusted for age, sex, smoking, physical activity, education, social benefit, economic difficulties, family history of asthma, and body mass index.

[†]Model II adjusted for alcohol consumption in addition to the covariates in Model I.

[#]Model III adjusted for HADS of anxiety and HADS of depression and chronic disease at baseline in addition to the covariates in model I (n=14,827 due to missing of HADS).

[§]Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Supplement table 1. The association of use of cod liver oil and multivitamin supplements with cumulative incidence of asthma over 11-year follow-up period, the HUNT Study, after excluding ever COPD, Chronic bronchitis or emphysema (n=16,711)

Regular use of cod liver oil and multivitamin supplements the previous year	No.	Cases	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I*	Adjusted OR (95% CI) Model II [†]	Adjusted OR (95% CI) Model III [#]
Reference group [§]	13,562	340	2.5	1.00	1.00	1.00	1.00
Cod liver oil only	1,143	39	3.4	1.37 (0.98-1.92)	1.55 (1.10-2.19)	1.55 (1.10-2.18)	1.49 (1.06-2.11)
Multivitamin supplements only	975	41	4.2	1.71 (1.23-2.38)	1.62 (1.16-2.27)	1.61 (1.15-2.26)	1.58 (1.12-2.22)
Use of both	1,031	39	3.8	1.53 (1.09-2.14)	1.61 (1.14-2.28)	1.61 (1.14-2.28)	1.56 (1.10-2.21)

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; OR, odds ratio.

*Model I adjusted for age, sex, smoking (current, former, never and unknown), light physical activity, education, social benefit, economic difficulties, family history of asthma, and body mass index.

[†]Model II adjusted for alcohol consumption in addition to the covariates in Model I.

[#]Model III adjusted for HADS of anxiety and HADS of depression and chronic disease at baseline in addition to the covariates in model I.

[§]Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Supplement table 2. The association of use of cod liver oil and multivitamin supplements with cumulative incidence of asthma over 11-year follow-up period, the HUNT Study, in subjects <40 years at baseline (n=8,024)

Regular use of cod liver oil and multivitamin supplements the previous year	No.	Cases	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I*	Adjusted OR (95% CI) Model II [†]	Adjusted OR (95% CI) Model III [#]
Reference group [§]	6,830	198	2.9	1.00	1.00	1.00	1.00
Cod liver oil only	425	17	4.0	1.40 (0.84-2.31)	1.61 (0.96-2.70)	1.60 (0.95-2.68)	1.56 (0.93-2.63)
Multivitamin supplements only	412	26	6.3	2.26 (1.48-3.44)	2.03 (1.32-3.12)	2.00 (1.30-3.08)	1.89 (1.22-2.93)
Use of both	357	17	4.8	1.67 (1.01-2.78)	1.63 (0.97-2.75)	1.66 (0.98-2.79)	1.52 (0.90-2.57)

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; OR, odds ratio.

*Model I adjusted for age, sex, smoking (current, former, never and unknown), light physical activity, education, social benefit, economic difficulties, family history of asthma, and body mass index.

[†]Model II adjusted for alcohol consumption in addition to the covariates in Model I.

[#]Model III adjusted for HADS of anxiety and HADS of depression and chronic disease at baseline in addition to the covariates in Model I.

[§]Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Supplement table 3. The association of use of cod liver oil and multivitamin supplements with cumulative incidence of asthma over 11-year follow-up period, the HUNT Study, in subjects with no chronic disease at baseline (n=14,332)

Regular use of cod liver oil and multivitamin supplements the previous year	No.	Cases	%	Crude OR (95% CI)	Adjusted OR (95% CI) Model I*	Adjusted OR (95% CI) Model II†	Adjusted OR (95% CI) Model III#
Reference group§	11,865	308	2.6	1.00	1.00	1.00	1.00
Cod liver oil only	939	36	3.8	1.50 (1.05-2.13)	1.71 (1.19-2.44)	1.71 (1.19-2.45)	1.71 (1.19-2.45)
Multivitamin supplements only	762	31	4.1	1.59 (1.09-2.32)	1.51 (1.03-2.21)	1.51 (1.02-2.21)	1.50 (1.02-2.20)
Use of both	766	30	3.9	1.53 (1.04-2.24)	1.68 (1.13-2.48)	1.68 (1.13-2.48)	1.67 (1.13-2.47)

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; OR, odds ratio.

*Model I adjusted for age, sex, smoking (current, former, never and unknown), light physical activity, education, social benefit, economic difficulties, family history of asthma, and body mass index.

†Model II adjusted for alcohol consumption in addition to the covariates in Model I.

#Model III adjusted for HADS of anxiety and HADS of depression in addition to the covariates in Model I.

§Reference group refers to non-users or daily intake of cod liver oil or multivitamin supplements <3 months.

Figure 1. A flow chart of study cohort

Figure 1

