

ASSOCIATED DISEASES

Seasonal and Regional Variations of Asthma and Association with Osteoporosis: Possible Role of Vitamin D in Asthma

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Background. Based on the evidence that vitamin D is involved in the development of immune system and vitamin D receptor gene is associated with asthma, we supposed that vitamin D is related to the development of asthma. **Methods.** Asthma patients were identified from the Swedish Hospital Discharge Register and the hospitalization rate was examined by different seasons and regions. Standardized incidence ratios (SIRs) for asthma were examined among patients hospitalized for osteoporosis compared with the general population. **Results.** A total of 172,384 patients were hospitalized for asthma in Sweden during 1965–2007. More patients were hospitalized in winter and North Sweden than in summer and South Sweden. The risk of asthma after osteoporosis was significantly increased, giving an overall SIR of 2.93. The risk was higher in male patients when compared with female subjects. Patients hospitalized for osteoporosis at age younger than 55 showed a high risk. Reversing the analyses and examining the risk of osteoporosis after hospitalization of asthma, SIR was significantly increased (3.54). **Conclusion.** Our study suggests that vitamin D, as indicated by the high risk of asthma after osteoporosis and the seasonal and regional variations of hospitalization, could play an important role for the development of asthma.

Keywords asthma, incidence, osteoporosis, seasonal variation

INTRODUCTION

Asthma is an increasing common disorder, affecting 5–10% of the population. It is characterized by recurrent bronchospasms, breathing difficulties, dyspnea, and wheezing (1–3). The prevalence of asthma has increased during the past decades (4). An improved hygiene and a dramatic drop in exposure to viral and bacterial infections are thought to explain part of the increase (5–7). Recent studies suggested that vitamin D could play a potential role for the inception and expression of asthma (8), based on the evidence that vitamin D is involved in the development of immune system and the lung (9, 10), and the association between the polymorphisms of vitamin D receptor gene and asthma (11, 12).

Vitamin D plays an important role in the maintenance of organ systems, and its deficiency in adults could lead to osteoporosis and increase the risk of fracture (13, 14). Many studies demonstrated that vitamin D levels in the body showed highly seasonal and geographic variations, with a high 25-OH D level in the summer and autumn and in south locations than in winter and in north locations (15–17). Therefore, if asthma is really associated with vitamin D, the incidence of asthma should show seasonal and regional variations and the subsequent risk of asthma among osteoporosis patients could be higher when compared with the general population. In

this study, we will test this hypothesis, using the nationwide Swedish Hospital Discharge Register, which covered approximately 172,384 asthma patients hospitalized in Sweden during 1965–2007.

PATIENTS AND METHODS

Data used in this study were retrieved from the MigMed2 database, located at the Center for Primary Health Care Research at the Lund University. MigMed2 is a comprehensive database that contains individual-level information on all people in Sweden, including age, sex, occupation, geographical region of residence, hospital diagnoses and date of hospital admission, country of birth, dates of emigration and immigration, and causes of death. This unique database was constructed using several national Swedish data registers, including but not limited to the total population register, the multigeneration register (18), the death register (19), the Swedish hospital discharge register (1986–2001) (19), and the immigration register. Information retrieved from the various registers in the MigMed2 database was linked at the individual level through the national 10-digit civic registration number assigned to each person in Sweden for his or her lifetime. Before inclusion in the MigMed2 database, civic registration numbers were replaced by serial numbers to ensure the anonymity of all individuals.

We used the Swedish Hospital Discharge Register, founded in 1964–1965 by the National Board of Health and Welfare with a complete nationwide coverage since 1987, to identify patients hospitalized with asthma. These patients were retrieved from the registry according to

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the seventh (1964–1968 code 241), eighth (1969–1986 code 493), ninth (1987–1996 code 493), and tenth ICD code (1997 code J45 and J46). Codes for osteoporosis were 7230 (ICD8), 733A (ICD9), and M80-82 (ICD10), respectively.

There are 21 counties in Sweden, and they are divided into three geographic regions according to their latitudes, including south (Skåne, Halland, Kronoberg, Blekinge), middle (Västra Götaland, Östergötland, Gotland, Kalmar, Jönköping, Stockholm, Uppsala, Södermanland, Värmland, Örebro, Västmanland, Dalarna, Gävleborg), and north regions (Västernorrland, Jämtland, Västerbotten, Norrbotten). Standardized incidence ratios (SIRs) with 95% confidence intervals were calculated as the ratio of observed to expected number of cases (20). The expected numbers were calculated by the incidence rates for all individuals without a history of asthma, and the rates were standardized by 5-year age, gender, period (5 years group), socioeconomic status (manual worker, blue collar, professional, private, farmer, and other), and residential area (21). Person-years were calculated from the first date of hospitalization for osteoporosis until diagnosis of asthma, death, emigration, or closing date (31 December 2007), whichever came first. Confidence intervals (95%) were determined assuming a Poisson distribution and they were rounded to the nearest two decimals (21). All analyses were performed using the SAS statistical package (version 9.1; SAS Institute, Cary, NC, USA). This study was approved by the Ethics Committee at Lund University.

RESULTS

A total of 172,384 patients were hospitalized for asthma in Sweden during 1965–2007; among them 90,040 (52%) were men and 82,344 (48%) were women. Figure 1 shows the seasonal and regional hospitalization rates for asthma. More patients were hospitalized in winter than in summer. Individuals living in North Sweden had a higher hospitalization rate than those living in south region. The hospitalization rate was higher for individuals at age older than 59 years.

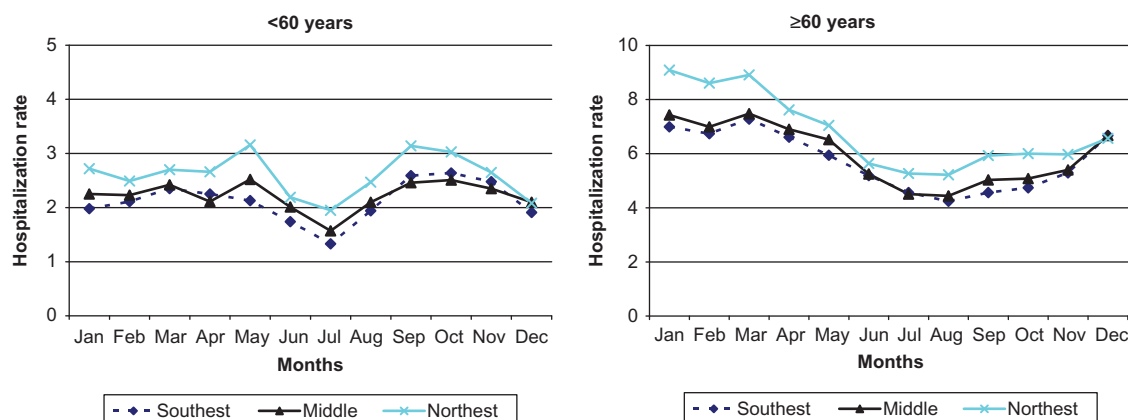


FIGURE 1.—Seasonal and regional variation of asthma in Sweden.

A total of 31,179 patients were hospitalized for osteoporosis in Sweden, among them 381 patients developed subsequent asthma, giving an overall SIR of 2.93 (Table 1). The risk was higher in male patients when compared with female subjects. The risk of asthma was somewhat higher during the first year after hospitalization for osteoporosis, probably because of a concomitant diagnosis. The increased risk for asthma was significant during the whole follow-up period. Patients diagnosed in the 1980s and at age younger than 55 years showed a high risk. We then reversed the analyses and calculated the risk of osteoporosis after the hospitalization for asthma. A total of 1354 patients were diagnosed with osteoporosis after asthma, with a SIR of 3.54. Risk of osteoporosis was significant during the whole follow-up time and the whole study periods.

DISCUSSION

In this nationwide study, 172,384 asthma patients were identified from the Swedish Hospital Discharge Register. The incidence of asthma showed seasonal and regional variations, and it was more common in winter and North Sweden than in summer and South Sweden. Asthma was highly associated with osteoporosis. Strengths of our study include its population-based character of hospitalized asthma patients, a large number of cases, and the completeness of follow-up of patients. All the data were based on the nationwide database in Sweden guaranteeing reliable data. A limitation of this study is that it is a retrospective cohort study; thus some individual factors, such as vitamin D levels in the body, treatment, smoking history, and physical activity, are missing in our database, leading to possible bias. Future prospective cohort studies with measurement of vitamin D in the body before the diagnosis of asthma are highly needed to confirm our findings.

Vitamin D can be provided both from endogenous sources (synthesized in the skin under the reaction to sunlight) and from the diet or diet supplements (13). Previous studies have shown that summer sunshine may contribute more vitamin D stores in the body than diet

TABLE 1.—Associations between asthma and osteoporosis in Sweden by follow-up interval, sex, age, and hospitalization period.

	Male				Female				All			
	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Risk of asthma after osteoporosis												
All	49	4.13	3.05	5.46	332	2.81	2.52	3.13	381	2.93	2.64	3.24
Follow-up interval (years)												
<1	14	5.26	2.87	8.85	101	5.08	4.14	6.17	115	5.10	4.21	6.12
1–4	23	4.17	2.64	6.26	135	2.50	2.10	2.96	158	2.66	2.26	3.11
5–9	6	2.68	0.96	5.87	58	2.01	1.53	2.60	64	2.06	1.58	2.63
>= 10	6	4.14	1.49	9.08	38	2.47	1.75	3.39	44	2.61	1.90	3.51
Age at hospitalization (year)												
<55	3	2.31	0.44	6.84	11	4.56	2.26	8.19	14	3.77	2.06	6.35
>= 55	46	4.35	3.19	5.81	332	2.81	2.52	3.13	367	2.91	2.62	3.22
Hospitalization period												
1970s	12	4.24	2.18	7.44	44	2.54	1.85	3.41	56	2.78	2.10	3.61
1980s	13	4.59	2.43	7.87	113	3.51	2.90	4.22	126	3.60	3.00	4.29
1990s	14	4.09	2.23	6.88	117	2.84	2.35	3.41	131	2.94	2.46	3.49
Risk of osteoporosis after asthma												
All	246	5.14	4.52	5.83	1108	3.31	3.11	3.51	1354	3.54	3.35	3.73
Follow-up interval (years)												
<1	17	5.71	3.32	9.15	101	4.85	3.95	5.89	118	4.95	4.10	5.93
1–4	74	7.01	5.51	8.81	306	4.07	3.62	4.55	380	4.43	3.99	4.90
5–9	42	3.77	2.72	5.11	270	3.41	3.02	3.85	312	3.46	3.09	3.87
>= 10	113	4.88	4.02	5.87	431	2.69	2.45	2.96	544	2.97	2.73	3.23
Age at hospitalization (year)												
<60	66	4.23	3.27	5.39	281	3.04	2.7	3.42	347	3.22	2.89	3.57
>= 60	180	5.59	4.80	6.47	827	3.41	3.18	3.65	1007	3.66	3.44	3.89
Hospitalization period												
1970s	56	5.35	4.04	6.95	199	2.84	2.46	3.26	255	3.17	2.79	3.58
1980s	97	4.96	4.02	6.05	436	3.34	3.03	3.67	533	3.55	3.25	3.86
1990s	54	5.41	4.06	7.06	277	3.52	3.12	3.69	331	3.73	3.34	4.16

Note. Bold type, 95% CI does not include 1.00. Underline type, 99% CI does not include 1.00.

does (15), which may partly explain the seasonal and geographic variations of vitamin D in the body (22, 23). In this study hospitalization for asthma was more common in winter, when the sunlight is poor and vitamin D level is low. Other factors, such as winter virus infection and bronchiolitis, may also contribute part of the increased risk of asthma during winter. It should be noted that pollens, most common in spring or early summer, can precipitate asthma attack, which may explain somewhat the high risk of asthma in May among patients hospitalized at age less than 60 years. The effects of viral infection and pollen exposure could not be totally excluded in this study because this information was not available in our database. However, the risk of asthma was highly increased among individuals in North Sweden during the whole year, strongly suggesting a vitamin D effect. Unfortunately, this was an ecological study and we had no data on vitamin D levels among these asthma patients, which may have limited value in assessing whether there is a true relationship between vitamin D and asthma.

Osteoporosis is a disease of the bone that may lead to high risk of fracture. It is common in women after menopause, which is highly related to estrogen deficiency following menopause, leading to rapid reduction of bone mineral density (24). Another important risk factor for osteoporosis is vitamin D deficiency (24). In this study the subsequent risk of asthma after osteoporosis was significantly increased, suggesting that vitamin D deficiency

could be related to the development of asthma. The high risk of asthma (SIR = 4.56) among women hospitalized of osteoporosis before age 55 years and among male patients (4.13) can partly exclude the contribution of estrogen deficiency to osteoporosis. Osteoporosis can also occur among individuals with particular hormonal disorders as a result of medications (24), specifically glucocorticoids. However, no evidence showed that glucocorticoid treatment can increase the risk of asthma. Inflammatory and immune responses associated with vitamin D could also contribute to our observation, which cannot be totally excluded. Osteopenia is much more common than osteoporosis; however, in Sweden individuals with osteopenia were normally treated in outpatient clinics, not in hospitals, which preclude our analyses about the association of osteopenia with asthma.

The risk of osteoporosis after the hospitalization of asthma was also significantly increased; this highly suggested that the association between asthma and osteoporosis was a true finding. Inhaled corticosteroids are the most effective medications available for patients with persistent asthma (25). Unfortunately, treatments or medication information is unavailable in our database, thus their adverse effect can not be excluded. The effects of inhaled corticosteroids on bone remains debated, whereas the adverse effects of oral corticosteroids have been well documented (26). It is also noteworthy that the diagnostic criteria and treatment for asthma patients have changed

during the follow-up period (27), but the increased risk of osteoporosis after the hospitalization of asthma remained constant during the whole study period, suggesting that the effect of corticosteroid treatment on osteoporosis could be weak. Other individual factors, such as smoking and physical activity, could somewhat confound the association, but the adjustment of socioeconomic status can partly lessen their effects.

In summary, our study suggest that vitamin D, as indicated by the high risk of asthma after osteoporosis and the seasonal and regional variation of asthma, could play an important role in the development of asthma.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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