

Beta2-adrenergic agonist use and the risk of multiple sclerosis: a total population-based case-control study

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Abstract

Objective: The aim of this study was to investigate whether the use of fenoterol, a beta2-adrenergic agonist, was associated with multiple sclerosis (MS) risk by conducting a total population-based case-control study in Taiwan.

Methods: A total of 578 patients with newly diagnosed MS who had a severely disabling disease (SDD) certificate between January 1, 2002 and December 1, 2008 comprised the case group. These cases were compared with 2890 gender-, age-, residence-, and insurance premium-matched controls. Fenoterol use was analyzed using a conditional logistic regression model that controlled for asthma, chronic obstructive pulmonary disease (COPD), salbutamol and steroid use.

Results: Compared with the group of people who did not use fenoterol, the adjusted odds ratios were 0.67 (95% confidence interval (CI) = 0.48–0.93, $p = 0.016$) for the group prescribed fenoterol below 2.25 cumulative defined daily dose (cDDD) and 0.49 (95% CI = 0.33–0.71, $p < 0.001$) for the group with a cumulative fenoterol use of more than 2.25 cDDD. The dose-response relationship was similar within the non-asthma patients. The associations were similar between males and females, but differences between age groups were observed.

Conclusions: The results of this study suggest that fenoterol use may reduce the risk of MS.

Keywords: Multiple sclerosis, fenoterol, case-control study

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. An increase in the prevalence and incidence of MS has been observed in Europe, Iran, and possibly worldwide.^{1–4} Because there is no cure for MS, disease-modifying therapies (DMTs) have become the standard treatment. The DMT drugs for MS include interferon beta 1-a, interferon beta 1-b, glatiramer acetate, natalizumab, and mitoxantrone.⁵ Treatment with any of the DMT drugs is associated with favorable clinical and economic outcomes, including a lower risk of MS-related medical costs and hospitalization,⁵ reduced loss of brain volume,⁶ reduced incidence of MS relapse,⁷ and improved survival.⁸

The beta2-adrenergic receptor agonists, fenoterol and salbutamol, have been used for many years in

the treatment of bronchospasm in patients with asthma and chronic obstructive pulmonary disease (COPD). Studies have provided increasing evidence that beta2-adrenergic agonists might have immunomodulatory properties both in vitro and in vivo, in various animal models as well as in humans.^{9–11} An experimental study showed that beta2-adrenergic agonists, focused on salbutamol, have the potential to improve clinical outcomes in patients with MS as an add-on treatment to glatiramer acetate therapy.¹²

Based on our research, little is known about the association between beta2-adrenergic agonists and MS incidence. We investigated whether the use of beta2-adrenergic agonists, particularly fenoterol, was associated with MS risk by conducting a total population-based case-control study in Taiwan.

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Methods

National Health Insurance (NHI) in Taiwan

In 1995, the NHI program, a government-run insurance program with a single-payer insurance system, was established in Taiwan. By December 2010, 23.074 million people were enrolled nationwide, with a coverage rate of 99.6%. The registration of all cases of severely disabling diseases (SDD), such as chronic renal failure, myasthenia gravis, cancer, and MS, are required by the Bureau of NHI before SDD certification can be granted. In 2008, 37,099 medical doctors and 553 neurology specialists were registered in Taiwan. In addition, 790,621 people had SDD certificates in 2008, which constituted 3.4% of the total population.

Sample

This was a total population-based case-control study. The National Health Insurance Research Database (NHIRD), which contains outpatient, ambulatory, hospital inpatient care, and dental records, was used in this study. The MS cases were identified according to the International Classification of Diseases, ninth revision (ICD-9), code number 340. The study period to include incident MS patients (2002–2008) was dependent on all SDD and NHIRD databases published since 1996. The medical claim data from 1996 to 2001 were used to verify that our MS patients were new cases. The diagnoses of MS, based on Poser's criteria¹³ and McDonald's criteria,¹⁴ were provided by a practicing clinical neurologist, and the diagnosed patients' medical records were sent to the Bureau of NHI. A group of neurology specialists at Taiwan's Bureau of NHI validated the medical records of MS patients according to Poser's criteria¹³ and McDonald's criteria.¹⁴ Because patients with SDD certificates are eligible for exemption from insurance premiums and co-payments, the approval of SDD certificates requires the strict evaluation of the Bureau of NHI. In this study, the diagnoses of all MS patients were verified by linking the encrypted identification numbers with the SDD certificates. Overall, 578 new MS cases from January 1, 2002 to December 31, 2008 were included in this study. These cases were compared with 2890 gender-, age-, residence-, and insurance premium-matched controls. Residence was categorized as rural or urban. The insurance premium was a proxy indicator of economic status and was classified into one of four categories: fixed premium and dependent, less than New Taiwan Dollar (NTD) 20,000 monthly, NTD 20,000–40,000 monthly, and NTD 40,000 or more monthly (one USD = 32.1 NTD in 2008). The fixed premium group was composed of people receiving social welfare support, and included low-income people and veterans. The

dependent insurance premium group comprised people with family members who did not have a job or income. The analysis data were provided from NHIRD without personal identification, and institutional review board (IRB) approval was unnecessary.

Statistical analyses

Fenoterol use in the five years prior to the index date was analyzed using a conditional logistic regression model that controlled for asthma, COPD, salbutamol use, and steroid use according to a matched case-control design. The defined daily dose (DDD) recommended by the World Health Organization (WHO) is a unit for assessing dose of drug on the same standard. Cumulative DDD (cDDD), which indicates the exposed duration, was estimated as the sum of dispensed DDD of drug to compare their use to the risk of MS. The index date was defined as the first diagnosis of MS, and the drug use was classified according to the cDDD. To reveal the possible dose-response relationship between fenoterol use and MS incidence, the use of fenoterol was classified into one of three categories: no use, less than 2.25 cDDD, and more than 2.25 cDDD. The cut-off value, 2.25 cDDD, was the median fenoterol dose in our patients. For the classification of salbutamol use and steroid use, the patients' median doses were also used as cut-off values. The model was tested first among the total group of patients, then among subgroups according to gender and age (one–24 years, 25–44 years, and > 45 years). In order to reveal the potential impact of controlling for asthma/COPD during analyses on the association between fenoterol and MS, an adjusted model without controlling for asthma/COPD was also performed. Analyses were carried out using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

Sensitivity analyses

To validate the robustness of the main study findings, which is the association between fenoterol and MS incidence, we performed a sensitivity analysis defining the use of fenoterol as a binary variable (any single use vs no use) and comparing to the main findings. Moreover, to remove asthma's effect on the risk of MS, another sensitivity analysis focusing on the non-asthmatic patients was performed. The analysis of patients with asthma could not be performed because of the number of asthmatic patients in this study was small. The analysis of patients with COPD also could not be performed because of the small number of COPD patients in this study. Therefore, the influence of COPD on the association between fenoterol and MS was adjusted in the regression model. Another

beta2-adrenergic agonist, salbutamol, has been demonstrated to improve clinical outcomes in patients with MS.^{9,12} Instead of investigating the association between fenoterol and the risk of MS by controlling salbutamol, a sensitivity analysis was performed to reveal the effect of combining fenoterol and salbutamol as an overall drug group. Finally, analysis was also stratified among non-steroid-use patients and steroid-use patients, respectively.

Results

Sample characteristics

Results for the demographic and clinical characteristics of patients are summarized in Table 1. Because of the matched design, the age, sex, residence and insurance premium distributions of the MS and non-MS group were equivalent. The mean age of our MS patients was 37.55 ± 13.17 years (mean $\pm$ standard deviation, SD). Among the 578 new MS patients, 444 patients were female and 134 patients were male, and the female-to-male ratio was 3.3. The proportion of MS for the diagnosis age period of 25–44 years was predominantly higher than that for the other diagnosis ages. Ninety-nine patients (17.13%) lived in rural areas and 479 (82.87%) lived in urban areas. Regarding the proxy index of economic status (insurance premium), nearly a quarter of the cases were listed as receiving social support or as a dependent member of a family. Of the 578 patients, 101 (17.5%) used fenoterol, 59 used fenoterol less than 2.25 DDD, and 42 used fenoterol more than 2.25 DDD. The cut-off value 2.25 DDD was the median fenoterol-use dose in our 707 fenoterol-using patients, of whom 101 belonged to the MS group and 606 belonged to the non-MS group. According to a chi-square test, the proportion of fenoterol use in MS patients was slightly lower, but not significantly, than that in non-MS patients ($p = 0.098$). The salbutamol use proportion was similar between MS and non-MS patients ($p = 0.988$). The steroid use proportion of MS patients was significantly higher than that of non-MS patients ($p < 0.001$). The prevalence of asthma was 6.4% in the MS group, which was higher than in the non-MS group, which was 3.74% ($p = 0.004$); however, the prevalence of COPD was similar in the MS and non-MS groups ($p = 0.437$).

Respiratory diseases among fenoterol-use patients

As shown in Table 2, of 707 fenoterol-use patients in this study, most of the patients use fenoterol to treat acute respiratory diseases, including 235 (33%) acute upper respiratory infections, 189 (28%) acute

bronchitis and bronchiolitis and 85 (12%) acute laryngitis and tracheitis, etc. Only 44 (6%) patients used fenoterol to treat asthma and 20 (3%) patients used fenoterol to treat COPD. Additionally, according to Table 1 and Table 2, seven (19%) of 37 asthma patients among MS group and 37 (34%) of 108 asthma patients among the non-MS group used fenoterol to treat asthma. Two (33%) of six COPD patients among the MS group and 18 (86%) of 21 COPD patients among the non-MS group used fenoterol to treat COPD. Fenoterol was not used in all of the asthma or COPD patients in this study.

Factors associated with MS incidence

Results for the associations of interest are summarized in Table 3. The unadjusted conditional logistic regression model showed significant factors associated with MS incidence, including low-dose fenoterol use, high-dose steroid use, and asthma. In the fully adjusted model (adjusted model 2), the final independent predictors were similar to the unadjusted results, with the exception that asthma had a non-significant effect on the risk of MS. Compared with the no-fenoterol-use group, the adjusted odds ratios were 0.67 (95% confidence interval (CI) = 0.48–0.93, $p = 0.016$) for the group prescribed fenoterol below 2.25 DDD and 0.49 (95% CI = 0.33–0.71, $p < 0.001$) for the group with cumulative fenoterol use of more than 2.25 DDD. The unadjusted and the fully adjusted conditional logistic regression results showed that salbutamol use had a non-significant association with MS incidence. In the adjusted model 1, without controlling for asthma/COPD, the association between fenoterol and MS was similar to the main finding.

Sensitivity and subgroup analyses

The effects of fenoterol on MS risk observed by analyzing the variable fenoterol as a binary variable (fenoterol use vs no use) were similar to that in the main findings in this study. Compared with the no-fenoterol-use group, the adjusted odds ratio was 0.58 (95% CI = 0.45–0.76, $p < 0.001$) for the group prescribed fenoterol. Moreover, data analysis conducted according to subgroup revealed that, among non-asthmatic patients, the dose-response relationship between fenoterol and MS incidence remained. The results that focused on non-steroid- or steroid-use patients also supported the negative association between fenoterol use and MS incidence. When fenoterol and salbutamol was combined as an overall drug group, the dose-response relationship between fenoterol and/or salbutamol and MS incidence also remained. The adjusted

Table 1. Demographic and clinic characteristic of multiple sclerosis (MS) and non-MS in Taiwan, 2002–2008.

Characteristic	MS, <i>n</i> = 578 (%)	Non-MS, <i>n</i> = 2890 (%)	Chi-square <i>p</i> value
MS diagnosis age (year)			
1–24	107 (18.51)	535 (18.51)	1.000
25–44	300 (51.90)	1500 (51.90)	
45+	171 (29.58)	855 (29.58)	
Sex			
Female	444 (76.82)	2220 (76.82)	1.000
Male	134 (23.18)	670 (23.18)	
Residence			
Rural	99 (17.13)	495 (17.13)	1.000
Urban	479 (82.87)	2395 (82.87)	
Insurance premium			
Fixed premium and dependent	157 (27.16)	785 (27.16)	1.000
Less than NTD ^a 20,000	152 (26.30)	760 (26.30)	
NTD20,000 ~40,000	202 (34.95)	1010 (34.95)	
NTD40,000 or more	67 (11.59)	335 (11.59)	
Fenoterol use (cDDD ^b)			
0	477 (82.53)	2284 (79.03)	0.098
Less than 2.25	59 (10.21)	319 (11.04)	
More than 2.25	42 (7.27)	287 (9.93)	
Salbutamol use (cDDD)			
0	522 (90.31)	2616 (90.52)	0.988
Less than 2.37	28 (4.84)	137 (4.74)	
More than 2.37	28 (4.84)	137 (4.74)	
Fenoterol and/or salbutamol (cDDD) use (%)			
0	437 (75.61)	2123 (73.46)	0.195
Less than 2.50	79 (13.67)	377 (13.04)	
More than 2.50	62 (10.73)	390 (13.49)	
Steroid use (cDDD)			
0	175 (30.28)	1468 (50.80)	<0.001
Less than 11.00	109 (18.86)	808 (27.96)	
More than 11.00	294 (50.87)	614 (21.25)	
Asthma ^c			
No	541 (93.60)	2782 (96.26)	0.004
Yes	37 (6.40)	108 (3.74)	
COPD ^d			
No	572 (98.96)	2869 (99.27)	0.437
Yes	6 (1.04)	21 (0.73)	

^a1US\$ = 32.1 New Taiwan Dollars (NTD) in 2008. ^bcDDD: cumulative defined daily dose. ^cInternational Classification of Diseases, ninth revision (ICD-9):493. ^dCOPD: chronic obstructive pulmonary disease, ICD-9:491, 492, 494, 496.

odds ratios were 0.80 (95% CI = 0.60–1.06, *p* = 0.119) for the group prescribed with fenoterol and/or salbutamol below 2.50 DDD and 0.54 (95% CI = 0.39–0.74, *p* < 0.001) for the group with a cumulative fenoterol and/or salbutamol use of more than 2.50 DDD. The main effects were similar between males and females, but were observed only in patients aged less than 45 years (Table 4).

Discussion

Based on our research, the present study is the first to assess the association between fenoterol and MS risk in a population-based study. Using data from the total population of Taiwan, our findings indicate that the incidence of MS was negatively associated with fenoterol use. This association was observed after controlling for age, sex, residence, economic status,

Table 2. Comorbidity respiratory diseases among fenoterol use patients ($n = 707$) in this study.

Diseases (ICD-9)	Patients		
	Total	MS ($n = 578$)	Non-MS ($n = 2890$)
Acute upper respiratory infections (465)	235	28	207
Acute bronchitis and bronchiolitis (466)	189	35	154
Acute laryngitis and tracheitis (464)	85	19	66
Asthma (493)	44	7	37
Acute nasopharyngitis (460)	42	6	36
Acute tonsillitis (463)	39	6	33
Acute sinusitis (461)	37	6	31
Acute pharyngitis (462)	31	5	26
COPD ^a (491, 492, 494, 496)	20	2	18
Others ^b	79	15	64

ICD-9: International Classification of Diseases, ninth revision. ^aCOPD: chronic obstructive pulmonary disease. ^bIncluding chronic pharyngitis and nasopharyngitis (472), chronic sinusitis (473), peritonsillar abscess (475), allergic rhinitis (477), other diseases of upper respiratory tract (478), other bacterial pneumonia (482), bronchopneumonia (485), pneumonia (486), influenza (487), bronchitis (490), pleurisy (511) and other diseases of respiratory system (519).

Table 3. Association between fenoterol use and multiple sclerosis risk in a population-based case-control study^a, Taiwan, 2002–2008.

Variable	Unadjusted analysis		Adjusted analysis model 1		Adjusted analysis model 2	
	Odds ratio (95% CI ^b)	<i>p</i> value	Odds ratio (95% CI ^b)	<i>p</i> value	Odds ratio (95% CI ^b)	<i>p</i> value
Fenoterol use (cDDD ^c)						
0	1.00		1.00		1.00	
Less than 2.25	0.88 (0.65–1.18)	0.395	0.73 (0.54–0.96)	0.019	0.67 (0.48–0.93)	0.016
More than 2.25	0.70 (0.50–0.98)	0.039	0.51 (0.36–0.73)	<0.001	0.49 (0.33–0.72)	<0.001
Salbutamol use (cDDD)						
0	1.00		1.00		1.00	
Less than 2.37	1.02 (0.67–1.56)	0.912	1.02 (0.68–1.57)	0.502	0.98 (0.62–1.54)	0.930
More than 2.37	1.02 (0.67–1.56)	0.912	1.01 (0.69–1.66)	0.753	0.90 (0.57–1.45)	0.675
Steroid use (cDDD)						
0	1.00		1.00		1.00	
Less than 11.00	1.15 (0.89–1.48)	0.284	1.28 (0.99–1.66)	0.063	1.20 (0.93–1.55)	0.159
More than 11.00	3.99 (3.23–4.93)	<0.001	4.86 (3.89–6.06)	<0.001	4.35 (3.49–5.42)	<0.001
Asthma						
No	1.00				1.00	
Yes	1.80 (1.21–2.66)	0.003			1.37 (0.89–2.10)	0.156
COPD						
No	1.00				1.00	
Yes	1.49 (0.57–3.91)	0.415			0.85 (0.30–2.39)	0.759

COPD: chronic obstructive pulmonary disease. ^aMatched age, sex, residence and insurance premium. ^bCI: confidence interval. ^ccDDD: cumulative defined daily dose.

asthma, COPD, salbutamol use and steroid use. This association was observed both in men and women. The association was significant only in patients less than 45 years old. Furthermore, we found that, after controlling for fenoterol use and steroid use, asthma was not associated with MS risk.

Although an experimental study showed that salbutamol potentially improves clinical outcomes in patients after the onset of MS,¹² our main findings showed that fenoterol (but not salbutamol) has the potential to reduce MS risk before MS is diagnosed. Although both fenoterol and salbutamol belong to the same drug

Table 4. Stratified analyses of association between fenoterol use and multiple sclerosis risk in a population-based case-control study^a, Taiwan, 2002–2008.

Subgroup	Fenoterol use category	Adjusted odds ratio (95% CI ^b)	<i>p</i> value
Total	0 cDDD ^c	1.00	
	Less than 2.25 cDDD	0.67 (0.48–0.93)	0.016
	More than 2.25 cDDD	0.49 (0.33–0.71)	<0.001
	No use	1.00	
	Any fenoterol use	0.58 (0.45–0.76)	<0.001
Non-asthma	0 cDDD	1.00	
	Less than 2.25 cDDD	0.66 (0.46–0.94)	0.020
	More than 2.25 cDDD	0.49 (0.33–0.74)	<0.001
	No use	1.00	
	Any fenoterol use	0.58 (0.44–0.77)	<0.001
Non-steroid use	0 cDDD	1.00	
	Less than 2.25 cDDD	0.17 (0.05–0.55)	0.003
	More than 2.25 cDDD	1.17 (0.54–2.55)	0.694
	No use	1.00	
	Any fenoterol use	0.51 (0.27–0.96)	0.038
Steroid use	0 cDDD	1.00	
	Less than 2.25 cDDD	0.99 (0.70–1.41)	0.961
	More than 2.25 cDDD	0.57 (0.37–0.88)	0.010
	No use	1.00	
	Any fenoterol use	0.68 (0.49–0.89)	0.016
Male	0 cDDD	1.00	
	Less than 2.25 cDDD	0.40 (0.18–0.91)	0.028
	More than 2.25 cDDD	0.34 (0.14–0.83)	0.017
Female	0 cDDD	1.00	
	Less than 2.25 cDDD	0.76 (0.53–1.08)	0.127
	More than 2.25 cDDD	0.54 (0.35–0.83)	0.005
Aged 1–24	0 cDDD	1.00	
	Less than 2.25 cDDD	0.45 (0.20–1.03)	0.057
	More than 2.25 cDDD	0.38 (0.14–1.07)	0.066
Aged 25–44	0 cDDD	1.00	
	Less than 2.25 cDDD	0.73 (0.47–1.12)	0.145
	More than 2.25 cDDD	0.39 (0.22–0.69)	0.001
Aged 45+	0 cDDD	1.00	
	Less than 2.25 cDDD	0.75 (0.39–1.44)	0.386
	More than 2.25 cDDD	0.72 (0.39–1.32)	0.286

^aControlling by age, sex, residence and insurance premium, asthma, chronic obstructive pulmonary disease (COPD), salbutamol use and steroid use. ^bCI: confidence interval. ^ccDDD: cumulative defined daily dose.

class (both are beta2-adrenergic agonists), ample functional diversity exists between them. First, cyclic-adenosine monophosphate (cAMP) was significantly stimulated by fenoterol, but not salbutamol, in a dose-dependent manner to an extent of 65% and 13% ($p < 0.04$), respectively.¹⁵ Immune-system-related factors are crucial in the pathogenesis of MS. Interleukin 4 (IL-4), a helper T cell (2TH)

cytokine, is involved in the regulation of immune responses. The functional polymorphisms of IL-4 possibly play a crucial role in the pathogenesis of MS,¹⁶ and the changes in IL-4 and IL-12 levels are the manifestations of inflammatory reactions connected with MS relapse.¹⁷ Fenoterol (1 μ M) potentiated IL-4-induced immunoglobulin (Ig)E production and IgE messenger ribonucleic acid (mRNA)

expression.¹⁸ Fenoterol stimulates the production of cAMP, suggesting that it may be therapeutically effective in treating oxidative-stress-associated MS.

Second, fenoterol inhibited platelet-activating-factor (PAF)-induced O₂ generation by eosinophils significantly more than salbutamol did. Fenoterol, but not salbutamol, significantly inhibited PAF-induced eosinophil adhesion. Fenoterol inhibited O₂ generation and degranulation more effectively than did salbutamol; these effects may include a component involving cellular adhesion. Inhibition might also include a component not mediated by beta2 adrenoceptors.¹⁹ A recent study reported the implication of a PAF receptor A224D mutation in the susceptibility to relapsing–remitting MS in the Tunisian population.²⁰

Third, at high concentrations, fenoterol significantly inhibited both formyl-Met-Leu-Phe- and phorbol-myristate-acetate-induced superoxide generation by neutrophils. By contrast, salbutamol partially inhibited the generation induced by the former stimulus but not by the latter.²¹ Oxygen radical production was induced by formyl-Met-Leu-Phe, Trp-Lys-Tyr-Met-Val-Met-NH₂, or phorbol myristate acetate. In patients with severe MS, the production of superoxide anions was significantly lower for all three inducers of radical formation ($p = 0.004$), indicating a protective role of oxygen radicals in autoimmunity.²²

MS development may reflect factors that relate to a general immunoinflammatory upregulation of immune activity. Therefore, steroid use showed a positive dose-response relationship with MS in this study. Asthma was positively associated with MS without controlling for fenoterol in our study. However, the association between asthma and MS was not observed when considering fenoterol. This is because fenoterol has been prescribed preferentially to patients with severe asthma.²³ Concerning asthma and MS, previous researchers produced discordant results by case-control study, including positive,²⁴ negative²⁵ and absent^{26–28} associations. Although ours is a larger total population-based study than previous studies, the association between asthma and MS is still unclear in the literature and needs further study. Among non-asthma patients and controlling for COPD, the main finding did not change. Moreover, the controlling of asthma/COPD on the association between fenoterol and MS was limited. MS epidemiology studies have focused on childhood and adolescent exposure as being most relevant for developing MS.²⁹ Our study also showed that

fenoterol was associated with a reduction in the risk of MS in ages less than 45 years.

The major strength of this study is its large size. Based on research, this is the first national population study to explore the association between fenoterol and MS. This study was implemented using the total population of Taiwanese citizens seen in general medical practice; therefore, the findings are likely to be applicable to the general population. This study has several limitations. In epidemiological studies, the time of first symptom onset is the traditional starting point for MS. Exposure at or before the time of first symptom onset is epidemiologically the most relevant. However, our study database did not contain information on first symptom onset. The database also did not contain certain crucial predictors, such as the symptoms of MS, and the leading distinguishing factors of MS patient subtypes were not available. An important confounding factor that was also not addressed in this study is smoking; our study database did not contain information on cigarette smoking. Another limitation of this study is that MS is a rare disease in Taiwan, and even though this was a seven-year total population-based study, only 578 new MS cases were verified.

In summary, the results of this study demonstrated a 51% risk reduction for MS in people who used more than 2.25 DDD of fenoterol in a five-year period compared with people who did not use fenoterol. Our study suggests that fenoterol has a potential role in the prevention of MS. This was an observational population-based study. Therefore, we recommend a randomized clinical trial to confirm our findings.

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Conflict of interest

None declared.

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