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Complementary and alternative asthma treatments and their association with asthma control: a population-based study

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Conflict of interest

The authors declare no conflict of interest.

Original publication

The work of this manuscript contains original unpublished work, which is not being submitted for publication elsewhere at the same time.

Ethics approval

This study was approved by the Human Ethics board of the University of British Columbia.

Contributorship Statement

MF, MS, CM, LL, and WH designed the Economic Burden of Asthma (EBA) study, whose data is used in the present research. MS and RR designed the case report forms. MF and WC proposed the research question. WC conceptualized the study design, was the main analyst, and wrote the first draft of the manuscript. MF, MS, CM, LL, RR, and WH were involved in

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the acquisition of the data. CM and LL critically revised the manuscript. All authors approved the final version of the manuscript.

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ABSTRACT

Background: Many patients with asthma spend time and resources consuming complementary and alternative medicines (CAMs). This study explores whether CAM utilization is associated with asthma control and the intake of asthma controller medications.

Methods: Data were collected from the baseline visit of a prospective cohort study of adult individuals with self-reported physician-diagnosed asthma from British Colombia, Canada. We assessed CAM use over the previous 12 months, level of asthma control as defined by the Global Initiative for Asthma (GINA), and the self-reported intake of controller medications. Multivariate logistic regression was performed to study the relationship between any usage of CAMs (outcome), asthma control and controller medication usage, adjusted for potential confounders.

Results: The study sample included 486 patients with asthma (mean age=52 years; 67.3% female). A total of 179 (36.8%) of the sample reported CAM usage in the past 12 months. Breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) were the most popular CAMs reported. After adjustment, female sex (OR: 1.66; 95% CI: 1.09-2.52) and uncontrolled asthma(vs. controlled asthma, OR: 2.25, 95% CI: 1.30-3.89) were associated with a higher likelihood of using any CAMs in the past 12 months. Controller medication use was not associated with CAM usage in general and in the subgroups defined by asthma control.

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Conclusion: Clinicians and policy makers need to be aware of the high prevalence of CAM use in patients with asthma and its association with lack of asthma control.

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ARTICLE SUMMARY

Article Focus

- How does the use of complementary and alternative medicines (CAMs) in treating asthma relate to the clinical control of asthma and the use of conventional asthma controller therapies?

Key Messages

- Our study demonstrated that CAMs were commonly used to treat asthma
- The CAM usage was inversely associated with asthma control whereas unrelated to the use of controller medications.
- Given the uncertain benefits and potential side effects of CAMs and possible drug interactions, it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use.

Strengths and Limitations

- This is one of the few population-based studies investigating the association between CAM usage, the use of conventional asthma therapies and asthma control. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function. Various subgroup and sensitivity analyses added to the robustness and credibility of our results.
- However, the study is based on self-reports and thus the results are subject to recall bias. Also, the cross-sectional design of this study prevents the evaluation of whether CAMs played a causal role in changing the level of asthma control.

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INTRODUCTION

Asthma is a chronic disease of the airways associated with high health care resource utilization, productivity loss, and reduced quality of life (1). Proper management can lead to clinically controlled asthma which, compared to uncontrolled asthma, is associated with lower usage of health care resources and better quality of life (2). Clinical guidelines recommend anti-inflammatory medications as the primary controller treatment for asthma. In particular, inhaled corticosteroids (ICSs) are considered as the foundation therapy for treating asthma (3).

In addition to conventional treatments, many patients with asthma use complementary and alternative medicines (CAMs) in an attempt to improve their asthma symptoms (4). The CAMs are generally defined as "a group a diverse medical and healthcare systems, practices and products that are not generally considered to be part of conventional medicine" (5). The reported prevalence rates of CAM usage in treating asthma is quite varied, ranging from 4% to 79% (6). Breathing techniques, homeopathy, and herbal medicines are reportedly the most popular CAMs among patients with asthma (6). Despite the common use of CAMs, individuals often do not disclose CAM usage to health care professionals (7,8).

In general, the effectiveness of CAMs in treating asthma is unknown and most likely is minimal, whereas some CAMs are associated with certain risks(4,9,10). The resources

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individuals spend in seeking and using CAMs may potentially draw from the resources they possess to support evidence-based care for their asthma. Understanding the reasons behind individuals' consuming CAMs can thus help care providers offer informed advice to patients. Two of the important factors in determining what makes patients consume CAMs are the association between CAM use and the level of asthma control as well as the usage of conventional controller therapies. There is evidence indicating an association between CAM usages and poor control in work-related asthma (11). Nonetheless, few studies have attempted to determine the association between the usage of CAMs and controller medications as a function of asthma control. Hypothetically, CAMs can play either a complementary or a substitute role in relation with conventional therapies. In a complementary role patients use CAMs in addition to their conventional treatments in an attempt to reduce asthma-related impairment. A substitute role for CAMs indicates that individuals use CAMs as a replacement for conventional therapies if they do not perceive benefit from conventional therapies (or do not seek conventional therapies due to lack of belief in their effect or due to their prohibitive cost). The objective of this study was to explore the association between CAM use, asthma control, and the use of controller medications in a random sample of adult patients with asthma. Specifically, we hypothesized that lack of asthma control will be associated with higher usage of CAMs, and that individuals use CAMs to complement their conventional therapies.

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METHODS

Study Subjects and Data

Data were collected from the baseline visit of a prospective, longitudinal cohort study with the ultimate goal of estimating the economic burden of asthma. Study subjects were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (population of 603,502 and 179,839, respectively, in 2011 (12)). The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a 10 pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next 12 months, and those in whom a methacholine challenge test was contraindicated were not eligible. Consenting individuals attended the study centers for the baseline visit, during which a comprehensive questionnaire was administered to collect information on the demographic and socio-economic status, asthma-related symptoms, and use of CAMs and conventional medications. Patients also underwent spirometry by a trained technician. For the purposes of this sub-study, we restricted the sample to adults 18 years and older.

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Demographics and socio-economic status

The socio-demographic characteristics included age at baseline, sex, ethnicity (self-reported and defined as Caucasian, Asian which included Mandarin, Japanese, Korean, Arabic and Persian, or other ethnicities), education (self-reported and categorized as less than post-secondary education versus post-secondary education), and annual household income (self-reported and categorized as low versus high at a cutoff value of $60,000 CAD).

CAM use

The usage of CAMs in the past 12 months was assessed with the question "*In the past 12 months, have you received any alternative therapy for your asthma? Check all that apply*", followed by a list including nine options: 1) massage, osteopathy or other manipulative techniques; 2) herbal treatment; 3) acupuncture; 4) homeopathy; 5) breathing exercises; 6) vitamins or other supplements; 7) chiropractic; 8) dieting programs; and 9) naturopathy. The interviewer provided verbal explanation and examples to clarify the options. There was also a miscellaneous category with free text, capturing any other modality that could be considered a CAM. This free text field was evaluated by three investigators who decided whether each stated item was a CAM. Approved items then entered into the analysis as the 'other' category.

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Asthma control

Asthma control was defined according to the Global Initiative for Asthma (GINA) criteria (3). Patients were classified as controlled, partially controlled, or uncontrolled based on asthma symptoms during the past three months (daytime symptoms, limitation of activity, nocturnal symptoms and need for rescue medication) as well as the ratio of forced expiratory volume in one second (FEV1) to its predicted value. We used the NHANES III standards to calculate the predicted FEV1 (13).

Controller medication use

Asthma medications during the past 12 months were documented in a self-reported prescription medication chart. For each medication we evaluated the intensity of intake through questions "how many months?" and "how many days a week?". Using these two questions, we measured the intake of controller medication and converted the intensity of intake to proportions of days covered (PDC) (14). Low intake was defined as PDC<50%, moderate intake as 50%≤PDC<80%, and high intake as PDC≥80%.

Statistical analysis

All analyses were performed using Stata/IC (version 12.1., College Station, Texas, United States). The criterion for statistical significance was a two-tailed p-value (p) of less than 0.05. The distribution of variables across groups was compared with Pearson chi-square tests for categorical variables and Student's t-tests for continuous variables. We report the

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frequency of use of any CAMs, individual CAM categories, as well as the concomitant use of different types of CAMs.

Logistic regression was performed to evaluate the association between CAM use and asthma control, controller medication use, and potential confounders. Unadjusted analysis involved performing the logistic regression with the dependent variable being any use of CAMs (versus no use), and individual covariates as the single dependent variable. For the adjusted analysis, we used the same logistic regression model with any use of CAMs (versus no use) as the dependent variable, with independent variables including the level of asthma control (dummy-coded to represent partially controlled and uncontrolled versus controlled asthma), controller medication use (the abovementioned PDC categories) as independent variables of interest. We also controlled for sex, ethnicity, age at baseline, annual household income and education status by entering such variables as additional independent variables in the regression model. The hypothesis of the complementary versus substitute role of CAMs with regard to conventional controller medications was evaluated by interpreting the coefficient for controller medication use: a positive coefficient indicates a complementary role for CAMs, whereas a negative one points towards CAMs playing a substitute role.

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Sensitivity and subgroup analyses

In order to investigate whether the association between controller medication use and use of CAMs was different across asthma control levels, we fitted separate regression models using the aforementioned logistic model within each level of asthma control. In addition, to more efficiently exploit the information on CAM use provided by participants, we used a negative binomial regression model with the dependent variable being the number of different types of CAMs used by the individual (all independent variables similar to those of the logistic model described previously). In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to “yes” or “no” options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values. In another sensitivity analysis, the logistic regression analysis was repeated by removing the 'other' category of CAMs.

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RESULTS

Characteristics of study subjects

Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study. The average age was 52.3 years (SD=14.7) at study entry, and 67.3% were female (Table 1). Participants were likely to be Caucasian (82.1%), have attended college (75.3%), and have annual household income greater than $60,000 (72.2%). The mean baseline FEV1 was 2.61 (SD=0.87). The distribution of individuals across controlled, partially controlled, and uncontrolled asthma was 20.0%, 38.5% and 41.6%, respectively. Of all adults, 42.0%, 15.2%, and 42.8% had low, medium, and high intake of controller medications, respectively.

<<Table 1 here>>

The overall prevalence of the use of any CAMs in the past 12 months was 179/486 (36.8%; 95% CI: 32.5% - 41.1%). Excluding the 'other' category, which comprised 16.3% of CAM usage, a majority of the individuals (18.3%) reported using one type of CAMs, while 7.6% used two different CAMs, and 9.3% used more than two types of CAMs. The most frequent CAMs were breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) (Figure 1).

<<Figure 1 here>>

Association between CAM use, asthma control, and controller medication intake

Results of both unadjusted and adjusted logistic regressions are provided in Table 2. Only female sex and uncontrolled asthma were associated with a higher chance of using any CAMs

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in the unadjusted analysis. After adjustment, the same two variables, female sex (odds ratio (OR) 1.66; 95% CI 1.09; 2.52) and uncontrolled asthma (uncontrolled vs. controlled asthma OR 2.25; 95% CI 1.30; 3.89), were significantly associated with CAM utilization. Partially controlled asthma and controller medication intake were not associated with CAM usage.

<<Table2 here>>

Subgroup and sensitivity analyses

Results of the subgroup and sensitivity analyses are reported in Appendix Table A1-A3. Controller medication use was not associated with CAM use within the strata of controlled, partially controlled, or uncontrolled individuals. No change was observed in the overall study results when indeterminate answers to asthma symptoms were treated as missing values, when the multivariate logistic regression model was replaced with a negative binomial model, and when the 'other' category of CAMs were removed from the analysis.

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DISCUSSION

Using a population-based sample, we described the patterns of CAM usage in adults with asthma, and further examined the association between CAM use, asthma control, and controller medication intake. In our study, 37% of adults with asthma reported using any CAMs in the past 12 months. We also found that patients with uncontrolled asthma had a higher likelihood of reporting any use of CAMs, compared with patients with controlled asthma, after adjusting for potential confounders. Our study therefore suggests that the use of CAMs in patients with asthma is high, and is associated with worse asthma control. On the other hand, CAM usage was unrelated to the intake of controller medication in the overall study population, as well as within the subgroups defined by asthma control. As such we could not discern any complementary or substitute role of CAMs in relation to conventional controller therapies. In addition to our limited sample size to discover such a relationship, it might be the case that users of CAMs are a mixture of those who consume CAMs as a complement versus those who use them as substitute to their conventional controller therapies.

Our estimates of the prevalence of CAM use is in line with recent survey-based estimates (Behavioral Risk Factor Surveillance System) for 38% -40% for any use of CAMs in the U.S (11,15). Our findings on the association between CAM use and socio-demographic factors (e.g., age, education, household income, ethnicity) are generally consistent with published findings (6,15–17): several previous studies also reported a greater possibility of receiving

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CAMs among females with asthma as compared to males (6,16,17), but a recent U.S. study did not find a statistically significant association (15). Such discrepancies may be explained by our limited sample size as well as differences in data collection methods and in the types of CAMs being reported in these studies.

Marino and Shen found asthma emergency room visits and disability days, as surrogates for lack of asthma control, to be positively related with CAM use in adults (15). However, a Northern California study of adult patients reported no association between self-assessed asthma severity and CAM use (16). Using a validated and internationally accepted measure of asthma control (3), our analysis showed an inverse association between asthma control and usage of CAMs. Similar results have been observed in samples of individuals with work-related asthma (11). On the other hand, the link between CAM usage and adherence to asthma controller medications is inconsistent in the literature and likely confounded by asthma control. Two inner-city studies in the U.S reported decreased adherence to asthma controller therapy among adult CAM users (18,19) whereas a recent longitudinal analysis found no effect of CAMs on future adherence to controller medication in pediatric asthma patients (20).

Compared to previous studies (11,15,16,18,19), our study has several strengths. Based on a random sample, the estimates of CAM use and the association with asthma control are population-based. We estimated asthma control using internationally accepted standards

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based on measures of asthma impairment and lung function (3). Various subgroup and sensitivity analyses added to the robustness and credibility of our results. However, this study is not without limitations. First, both CAM use and controller medication intake were based on self-reports and thus are subject to recall bias, which may affect the precision of measurement and thereby increase the noise in finding an association We provided a list of nine pre-specified types of CAMs to participants to ensure homogeneity in the definition of CAMs across all individuals and to increase the accuracy of recall; however, individuals might have been less likely to report other forms of CAMs. Finally, using a cross-sectional design, we were not able to evaluate whether CAMs played a causal role in changing the level of asthma control.

Despite these limitations, our findings have important clinical implications. The extent of CAM use among the population of patients with asthma gives policy makers an estimate of the overall burden of CAM usage at the population level. The resources individuals spend consuming CAMs represent an opportunity cost because such resources could have been spent in evidence-based treatments or other activities. In addition, given the uncertain benefits, potential side effects and possible drug interactions of CAMs (4), it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use. CAM use might be a sign of patients' lack of satisfaction with asthma treatment, prompting the care provider to reevaluate asthma management. Future research is required to evaluate the economic impact of CAM use, to further examine other potential factors

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determining the use of CAMs such as individuals' value systems and beliefs, access to care, health literacy, and quality of life, and to rigorously study the causal interactions between CAM use, asthma control, and use of controller medications.

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Table legend

Table 1. Characteristics of study population based the pattern of use of CAMs in the last twelve months.

Table 2. Logistic regression with past 12 month CAM usage

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Table 1. Characteristics of the study population: overall and by CAM use

Variables	Overall (N=486)	Used Any CAMs		*p-value* *
		Yes (N=179)	No (N=307)	
Age, *mean(SD)*	52.3 (14.7)	52.3 (13.6)	52.1 (15.2)	0.88
Gender, *N (%)*				0.007#
Female	327 (67.3)	134 (74.9)	193 (62.9)	
Male	159 (32.7)	45 (25.1)	114 (37.1)	
Education, *N(%))*				
Less than post-secondary education	120 (24.7)	43 (24.0)	77 (25.1)	0.79
Post-secondary education	366 (75.3)	136 (76.0)	230 (74.9)	
Ethnicity, *N(%)*				0.62
Caucasian	399 (82.1)	143 (79.9)	256 (83.4)	
Asian	67 (13.8)	28 (15.6)	39 (12.7)	
Other	20 (4.1)	8 (4.5)	12 (3.9)	
Household income, *N(%)*				0.13
<$60,000	135 (27.8)	57 (31.8)	78 (25.4)	
≥$60,000	351 (72.2)	122 (68.2)	229 (74.6)	
Baseline FEV1 (L), *mean(SD)*	2.61 (0.87)	2.51 (0.86)	2.67 (0.87)	0.06
Asthma control level, *N(%)*				<0.001#
Controlled	97 (20.0)	26 (14.5)	71 (23.1)	
Partially controlled	187 (38.5)	58 (32.4)	129 (42.0)	
Uncontrolled	202 (41.6)	95 (53.1)	107 (34.9)	
Controller medication intake, *N(%)*				
PDC <50% (Low)	204 (42.0)	66 (36.9)	138 (45.0)	0.21
50%≤PDC<80% (Moderate)	74 (15.2)	31 (17.3)	43 (14.0)	
PDC ≥80% (High)	208 (42.8)	82 (45.8)	126 (41.0)	

Mean, mean values; SD, standard deviation of mean values; N, total number; %, percentage; FEV1: Forced Expiratory Volume at 1 second, L: liter; SD: Standard Deviation, CAMs: Complementary and Alternative Medicines, PDC: proportions of days covered by conventional controller medications.

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*p values are associated with independent-sample t-test for continuous variables and chi-square test for categorical variables.

Significant at 0.05 level

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Table 2. Logistic regression with past 12 month CAM usage

Variables	Any CAM use, *OR (95% CI); p-value*	
	Unadjusted[a]	Adjusted[b]
Age	1.00 (0.99;1.01); p=0.88	1.00 (0.98;1.01); p=0.70
Gender		
Male	Reference	Reference
Female	**1.76 (1.17;2.65); p=0.007#**	**1.66 (1.09;2.52); p=0.019#**
Household income		
<$60,000	Reference	Reference
≥$60,000	0.73 (0.49;1.09); p=0.13	0.80 (0.52;1.23); p=0.31
Education		
Less than post-secondary education	Reference	Reference
Post-secondary education	1.06 (0.69;1.63); p=0.79	1.07 (0.68;1.69); p=0.77
Ethnicity		
Caucasian	Reference	Reference
Asian	1.29 (0.76;2.18); p=0.35	1.31 (0.76;2.28); p=0.32
Other	1.19 (0.48; 2.99); p=0.71	1.14 (0.44;2.96); p=0.78
Asthma control level		
Controlled	Reference	Reference
Partially controlled	1.23 (0.71;2.12); p=0.46	1.26 (0.72;2.19); p=0.42
Uncontrolled	**2.42 (1.43; 4.11); p=0.001#**	**2.25 (1.30;3.89); p=0.004#**
Intake of controller medication		
Low	Reference	Reference
Moderate	1.51 (0.87;2.61); p=0.14	1.22 (0.69;2.16); p=0.49
High	1.36 (0.91; 2.04); p=0.14	1.10 (0.71;1.71); p=0.67

[a]Univariate logistic regression; [b]Multivariate logistic regression;

OR, odds ratios; CI, confidence interval.

Significant at 0.05 level

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Figure legend

Figure 1. Frequencies of past 12-month CAM usage in treating asthma, by CAM types

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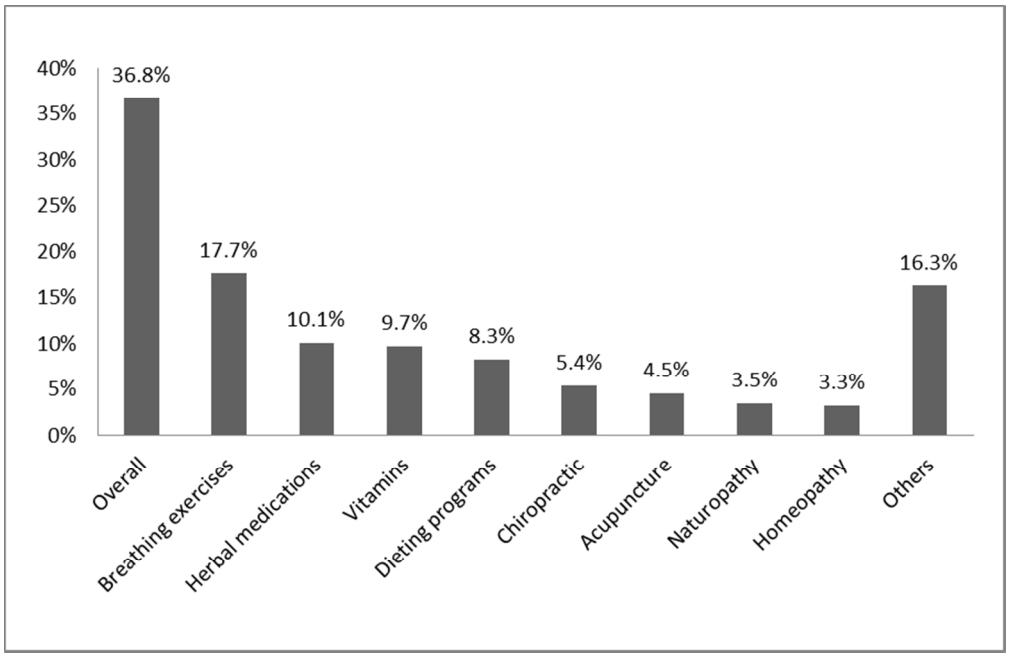

Frequencies of past 12-month CAM usage in treating asthma, by CAM types.
239x155mm (96 x 96 DPI)

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Table A1. Subgroup analysis: multivariate logistic regression results for subgroups based on control level

Variables	CAM usage by asthma control level, *OR (95% CI), p*		
	Controlled (N=91)	Partially Controlled (N=187)	Uncontrolled (N=202)
Age	1.01 (0.98;1.05), p=0.43	1.00 (0.97;1.01), p=0.33	1.00 (0.98-1.02), p=0.81
Gender			
Male	Reference	Reference	Reference
Female	1.77 (0.58;5.41), p=0.31	1.88 (0.95;3.72), p=0.07	1.31 (0.68-2.52), p=0.43
Household income			
<$60,000	Reference	Reference	Reference
≥$60,000	0.57 (0.18;1.76), p=0.32	0.52 (0. 23;1.14), p=0.10	1.18 (0.63-2.20), p=0.60
Education			
Less than post-secondary education	Reference	Reference	Reference
Post-secondary education	1.13 (0.38;3.38), p=0.83	1.86 (0.77;4.47), p=0.17	0.77 (0.39-1.52), p=0.46
Ethnicity			
Caucasian	Reference	Reference	Reference
Asian	1.50 (0.38;5.70), p=0.56	1.02 (0.40;2.60), p=0.96	1.33 (0.59-3.01), p=0.49
Other	NA	1.92 (0.31;11.83), p=0.48	1.95 (0.44-8.61), p=0.38
Intake of controller medication			
Low	Reference	Reference	Reference
Moderate	0.92 (0.15-5.74), p=0.93	1.08 (0.43;2.70), p=0.87	1.70 (0.73-3.99), p=0.22
High	0.70 (0.22-2.19), p=0.54	0.80 (0.38;1.68), p=0.56	1.57 (0.79-3.11), p=0.20

OR, odds ratios; CI, confidence interval.

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Table A2. Multivariate negative binomial regression predicting counts of using different types of CAMs in the past 12 months in asthmatics

Independent Variables	Number of different CAMs being used			
	B	*SE B*	*Exp(B)*	*p*
Age	-0.01	0.01	0.99	0.10
Gender				
Male	Reference			
Female	**0.57**	**0.19**	**1.77**	**0.002**
Household income				
<$6,000	Reference			
≥$6,000	**-0.36**	**0.18**	**0.70**	**0.046**
Education years (centered)				
Less than post-secondary education	Reference			
Post-secondary education	0.25	0.20	1.28	0.22
Ethnicity				
Caucasian	Reference			
Asian	0.01	0.24	1.01	0.96
Other	0.52	0.36	1.68	0.16
Asthma control level				
Controlled	Reference			
Partially controlled	0.42	0.25	1.53	0.09
Uncontrolled	**0.77**	**0.25**	**2.15**	**0.002**
Intake of controller medication				
Low	Reference			
Moderate	0.17	0.25	1.18	0.51
High	0.18	0.19	1.20	0.34
	Likelihood-ratio χ^2 (10) =34.05, p<0.001 Likelihood-ratio test of alpha=0: p<0.001			

B, unstandardized regression coefficients; SE B, standard error of B; Exp(B), exponential of B.

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Table A3

Sensitivity analyses

1) The same multivariate logistic regression, as used in the main analysis, was repeated by excluding all other CAMs being listed in the miscellaneous option so as to restrict potential biases in misclassifying non-CAMs into CAMs. Regression results did not vary substantially between the 2 models. Uncontrolled asthma and female sex were significant factors predictive of CAM usage (OR=2.29, 95% CI: 1.31; 4.02 and OR=1.55, 95% CI: 1.01; 2.37) whereas other variables were not associated.
2) In the main analyses, asthma control was calculated with the assumption that any response to a GINA symptom criterion as "don't know" was treated as no symptoms. To address bias that could have been introduced by this assumption on asthma control and covariates, we treated the "don't know" response to GINA criteria as missing data in asthma control, hence we identified 18 out of 486 missing data (3.7%) in the re-defined asthma control variable. Multinomial logistic regression was performed to multiply impute missing values in re-defined asthma control using all other variables in the original logistic regression model. 5 datasets were generated from multiple imputations and applied to regression estimation. Appendix Table A3 shows that multiple imputations did not substantially alter the regression results predictive of CAM usage.

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Table A3. Sensitivity analysis based on coding of controller medication intake, adjustment for demographics and multiple imputations: predicting whether utilized any CAMs.

	CAM usage, *multivariate OR (95% CI), p values*		
Independent variables of interest	Original model[a]	Other CAMs excluded[b]	Multiple imputation model[c]
Age	1.00 (0.98;1.01); p=0.70	1.00 (0.98; 1.01); p=0.67	1.00 (0.98; 1.01); p=0.73
Gender			
Male	Reference		
Female	**1.66 (1.09; 2.53); p=0.019**	**1.55 (1.01; 2.37); p=0.044**	**1.63 (1.07; 2.50); p=0.023**
Household income			
<$60,000	Reference		
≥$60,000	0.80 (0.52; 1.23); p=0.31	0.78 (0.50; 1.21); p=0.27	0.81 (0.52; 1.26); p=0.35
Education			
Less than post-secondary education	Reference		
Post-secondary education	1.07 (0.68; 1.69); p=0.77	1.05 (0.66; 1.67); p=0.83	1.09 (0.69; 1.72); p=0.72
Ethnicity			
Caucasian	Reference		
Asian	1.31 (0.76; 2.28); p=0.32	1.27 (0.73; 2.22); p=0.40	1.34 (0.77; 2.32); p=0.30
Other	1.14 (0.44; 2.96); p=0.78	1.20 (0.46; 3.10); p=0.71	1.18 (0.45; 3.05); p=0.74
Asthma control level			
Controlled	Reference		
Partially controlled	1.26 (0.72; 2.19); p=0.42	1.30 (0.74; 2.30); p=0.36	1.36 (0.75-2.47); p=0.31
Uncontrolled	**2.25 (1.30; 3.89); p=0.004**	**2.29 (1.31; 4.02); p=0.004**	**2.49 (1.38-4.49); p=0.002**
Intake of controller medication			
Low	Reference		
Moderate	1.22 (0.69; 2.16); p=0.49	1.28 (0.72; 2.27); p=0.41	1.22 (0.69; 2.16); p=0.49
High	1.10 (0.71; 1.71); p=0.67	1.17 (0.75; 1.82); p=0.50	1.10 (0.70-1.70); p=0.70

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[a] The original multivariate model as displayed in Table 2, which studied the association of past 12 month CAM usage with asthma control and controller medication intake and controlled for age, gender, household income, education, ethnicity and lung function.

[b] This model repeated the original multivariate model by excluding all other CAMs from the past 12 month CAM uses.

[c] Multiple imputation was conducted using methods described in Appendix 3 with the assumption that asthma control values were missing at random. 5 datasets generated from multiple imputations were applied to regression estimation. The same control variables included in the original multivariate model were used in the multiple imputation and subsequent logistic regression

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Abstract (page 4): "Data were collected from the baseline visit of a prospective cohort study of adult individuals with self-reported physician-diagnosed asthma from British Colombia, Canada"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Abstract (page 4-5) has provided this information in the methods and results section.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Introduction (page 7-8) has provided this information.
Objectives	3	State specific objectives, including any prespecified hypotheses Introduction (page 8): "The objective of this study was to explore the association between CAMs use, asthma control, and the use of controller medications in a random sample of adult patients with asthma."
Methods		
Study design	4	Present key elements of study design early in the paper Methods (Page 9, first paragraph): "Data were collected from the baseline visit of a prospective, longitudinal cohort study with the ultimate goal of estimating the economic burden of asthma."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Methods (Page 9): The first section under the heading "Study Subjects and Data" has provided such information.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Methods (Page 9): Patient enrolment and eligibility criteria: "Study subjects were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (population of 603,502 and 179,839, respectively, in 2011 (12)). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a 10 pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next 12 months, and those in whom a methacholine challenge test was contraindicated were neither eligible." Method of follow up was described in the rest of this paragraph.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed The current study is a non-matched longitudinal cohort study thus such information is not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Outcomes, predictors and potential confounders are defined in the Methods section (page 10-11) under the headings "CAMs use", "Asthma control", "Controller medication use" and "Demographics and socio-economic status", respectively.

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		Diagnostic criteria is not applicable but this study included "Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified." (Methods: page 9, "Study Subjects and Data").
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Such information has been provided in Methods (page 10-11) under the headings of "Demographics and socio-economic status", "CAMs use", "Asthma control", "Controller medication use".
Bias	9	Describe any efforts to address potential sources of bias The last paragraph of the Methods section (page 13) titled "Sensitivity and subgroup analyses" describes our effort to address potential sources of bias: we performed sensitivity analysis to test the impact of missing values and the definition of CAMs on the main results of the study. We also used subgroup analyses and other regression model to further exploit the information on CAM use. Correlation matrix is provided for exploration of interactions between study variables. Results of these exploratory analyses are reported in the Supplemental Materials.
Study size	10	Explain how the study size was arrived at The first paragraph of the Methods section (page 9) has the corresponding description: "The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate)".
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Outcome, predictor and confounding variables are clearly defined in the Methods section (page 10-11). Detailed information on the how to handle these variables is described in Methods (page 11-12) under the "Statistical analysis" heading.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Such information is described in Methods (page 11-12) under the "Statistical analysis" heading.
		(*b*) Describe any methods used to examine subgroups and interactions Such information is described in Methods (page 13) under the "Sensitivity and subgroup analysis" heading: "In order to investigate whether the association between controller medication use and use of CAMs was different across asthma control levels, we fitted separate regression models using the aforementioned logistic model within each level of asthma control."
		(*c*) Explain how missing data were addressed Methods (page 13) under the "Sensitivity and subgroup analysis" heading: "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values". Details of methods are described in the Supplemental Materials (Appendix Table 3A).
		(*d*) If applicable, explain how loss to follow-up was addressed The information is not applicable because the current analysis is focused on data from the baseline visit.

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		(*e*) Describe any sensitivity analyses Methods (Page 13, "Sensitivity and subgroup analysis"): "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values. In another sensitivity analysis, the logistic regression analysis was repeated by removing the 'other' category of CAMs." Details of these sensitivity analyses are reported in the Supplemental Materials (Appendix Table 3A).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Results (page 14, first paragraph): "Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study."
		(b) Give reasons for non-participation at each stage Please note that in the Results section (page 14, first paragraph) under the heading "Characteristics of study subjects", it states: "Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study." Hereby it is indicated that age is the reason for non-participation, in that paediatric patients with asthma are not included in this analysis.
		(c) Consider use of a flow diagram We considered this option but we believe the information provided in the results section (see Item 13-a) adequately and concisely illustrates the study flow.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Such information is given in Table 1, page 24-25.
		(b) Indicate number of participants with missing data for each variable of interest We used data from the baseline visit of this cohort study which does not report any missing data, as fields in the survey were required to be filled with valid responses. A sensitivity analysis treated responses of "I do not know" as missing values (Methods: page 13 and Supplemental Materials: Appendix Table 3A): "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values."
		(c) Summarise follow-up time (eg, average and total amount) This item is not applicable as the current study is a cross-sectional analysis on the baseline data.
Outcome data	15*	Report numbers of outcome events or summary measures over time Table 2: Logistic regression with past 12 month CAM usage (page 26); Figure 1: Frequencies of past 12 month CAM usage in treating asthma, by CAM types.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

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		Table 2: Logistic regression with past 12 month CAM usage (page 26)
		(*b*) Report category boundaries when continuous variables were categorized The category boundaries are already reported in the tables (Table 1: page 24-25; Table 2: page 26) and the texts of the Results section (page 14-15). For example, we used a cutoff of $60,000 to categorize annual household incomes.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period This is not relevant in our study because we provided odds ratios as estimation outcomes.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Summary of findings on sensitivity and subgroup analyses are summarized in the last paragraph of the Results section (page 15, "Sensitivity and subgroup analyses"): "Results of the subgroup and sensitivity analyses are reported in Appendix Table A1-A3. Controller medication use was not associated with CAM use within the strata of controlled, partially controlled, or uncontrolled individuals. No change was observed in the overall study results when indeterminate answers to asthma symptoms were treated as missing values, when the multivariate logistic regression model was replaced with a negative binomial, and when the 'other' category of CAMs were removed from the analysis. " Details of the information are provided in Supplemental Materials, Appendix Table A1-A4.
Discussion		
Key results	18	Summarise key results with reference to study objectives Summary of key findings is provided in the Discussion (page 16, first paragraph).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Discussion (page 18, first paragraph): "First, both CAM use and controller medication intake were based on self-reports and thus are subject to recall bias, which may affect the precision of measurement and thereby increase the noise in finding an association We provided a list of nine pre-specified types of CAMs to participants to ensure homogeneity in the definition of CAMs across all individuals and to increase the accuracy of recall; however, individuals might have been less likely to report other forms of CAMs. Finally, using a cross-sectional design, we were not able to evaluate whether CAMs played a causal role in changing the level of asthma control."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Discussion (page 18, second paragraph to page 19): "The resources individuals spend consuming CAMs represent an opportunity cost because such resources could have been spent in evidence-based treatments or other activities. In addition, given the uncertain benefits, potential side effects and possible drug interactions of CAMs (4), it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use. CAM use might be a sign of patients' lack of satisfaction with asthma treatment, prompting the care provider to reevaluate asthma management. Future research is required to evaluate the economic impact of CAM use, to further examine other potential factors determining the use of CAMs such as individuals' value systems and beliefs, access to care, health literacy, and quality of life, and to rigorously study the causal interactions between CAM use, asthma control, and use of controller medications. "
Generalisability	21	Discuss the generalisability (external validity) of the study results Discussion (page 17, third paragraph to page 18, first paragraph): "Based on a random sample, the estimates of CAM use and the association with asthma control are population-based. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function (3). Various subgroup and sensitivity analyses added to the robustness and credibility of our results."
Other information		

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Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Funding information (page 1): "This study is part of a peer-reviewed grant funded through GlaxoSmithKline's Collaborative Innovative Research Fund (CIRF). None of the sponsors played a role in the study design, data analysis, interpretation or publication of the results."

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Complementary and alternative asthma treatments and their association with asthma control: a population-based study

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Complementary and alternative asthma treatments and their association with asthma control: a population-based study

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Conflict of interest

The authors declare no conflict of interest.

Original publication

The work of this manuscript contains original unpublished work, which is not being submitted for publication elsewhere at the same time.

Ethics approval

This study was approved by the Human Ethics board of the University of British Columbia.

Contributorship Statement

MF, MS, CM, LL, and WH designed the Economic Burden of Asthma (EBA) study, whose data is used in the present research. MS and RR designed the case report forms. MF and WC proposed the research question. WC conceptualized the study design, was the main analyst, and wrote the first draft of the manuscript. MF, MS, CM, LL, RR, and WH were involved in

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the acquisition of the data. CM and LL critically revised the manuscript. All authors approved the final version of the manuscript.

Data sharing statement

The analytical dataset and statistical codes are shared with BMJ Editorial Board for peer review purposes.

Word count (excluding title page, abstract, key message, references, figures, tables and appendices)**:** 2,638 words.

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ABSTRACT

Objectives: Many patients with asthma spend time and resources consuming complementary and alternative medicines (CAMs). This study explores whether CAM utilization is associated with asthma control and the intake of asthma controller medications.

Design: Population-based, prospective cross-sectional study.

Setting: General population residing in two census areas in the province of British Columbia, Canada. Recruitment was based on random-digit dialing of both landlines and cell phones.

Participants: 486 patients with self-reported physician-diagnosis of asthma (mean age 52 years; 67.3% female).

Primary and secondary outcome measures: We assessed CAM use over the previous 12 months, level of asthma control as defined by the Global Initiative for Asthma (GINA), and the self-reported intake of controller medications. Multivariate logistic regression was performed to study the relationship between any usage of CAMs (outcome), asthma control and controller medication usage, adjusted for potential confounders.

Results: A total of 179 (36.8%) of the sample reported CAM usage in the past 12 months. Breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) were the most popular CAMs reported. After adjustment, female sex (OR: 1.66; 95% CI: 1.09-2.52) and uncontrolled asthma (vs. controlled asthma, OR: 2.25, 95% CI: 1.30-3.89) were associated with a higher likelihood of using any CAMs in the past 12 months. Controller medication use was not associated with CAM usage in general and in the subgroups defined by asthma

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control.

Conclusion: Clinicians and policy makers need to be aware of the high prevalence of CAM use in patients with asthma and its association with lack of asthma control.

Word count (excluding section titles): 234/250 words

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ARTICLE SUMMARY

Article Focus

- How does the use of complementary and alternative medicines (CAMs) in treating asthma relate to the clinical control of asthma and the use of conventional asthma controller therapies?

Key Messages

- Our study demonstrated that CAMs were commonly used to treat asthma
- The CAM usage was inversely associated with asthma control whereas unrelated to the use of controller medications.
- Given the uncertain benefits and potential side effects of CAMs and possible drug interactions, it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use.

Strengths and Limitations

- This is one of the few population-based studies investigating the association between CAM usage, the use of conventional asthma therapies and asthma control. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function. Various subgroup and sensitivity analyses added to the robustness and credibility of our results.
- However, the study is based on self-reports and thus the results are subject to recall bias. Also, the cross-sectional design of this study prevents the evaluation of whether CAMs played a causal role in changing the level of asthma control.

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INTRODUCTION

Asthma is a chronic disease of the airways associated with high health care resource utilization, productivity loss, and reduced quality of life (1). Proper management can lead to clinically controlled asthma which, compared to uncontrolled asthma, is associated with lower usage of health care resources and better quality of life (2). Clinical guidelines recommend anti-inflammatory medications as the primary controller treatment for asthma. In particular, inhaled corticosteroids (ICSs) are considered as the foundation therapy for treating asthma (3).

In addition to conventional treatments, many patients with asthma use complementary and alternative medicines (CAMs) in an attempt to improve their asthma symptoms (4). The CAMs are generally defined as "a group a diverse medical and healthcare systems, practices and products that are not generally considered to be part of conventional medicine" (5). The reported prevalence rates of CAM usage in treating asthma is quite varied, ranging from 4% to 79% (6). Breathing techniques, homeopathy, and herbal medicines are reportedly the most popular CAMs among patients with asthma (6). Despite the common use of CAMs, individuals often do not disclose CAM usage to health care professionals (7,8).

In general, the effectiveness of CAMs in treating asthma is unknown and most likely is minimal, whereas some CAMs are associated with certain risks (4,9,10). The resources

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individuals spend in seeking and using CAMs may potentially draw from the resources they possess to support evidence-based care for their asthma. Understanding the reasons behind individuals' consuming CAMs can thus help care providers offer informed advice to patients. Two of the important factors in determining what makes patients consume CAMs are the association between CAM use and the level of asthma control as well as the usage of conventional controller therapies. There is evidence indicating an association between CAM usages and poor control in work-related asthma (11). Nonetheless, few studies have attempted to determine the association between the usage of CAMs and controller medications as a function of asthma control. Hypothetically, CAMs can play either a complementary or a substitute role in relation with conventional therapies. In a complementary role patients use CAMs in addition to their conventional treatments in an attempt to reduce asthma-related impairment. A substitute role for CAMs indicates that individuals use CAMs as a replacement for conventional therapies if they do not perceive benefit from conventional therapies (or do not seek conventional therapies due to lack of belief in their effect or due to their prohibitive cost). The objective of this study was to explore the association between CAM use, asthma control, and the use of controller medications in a random sample of adult patients with asthma. Specifically, we hypothesized that lack of asthma control will be associated with higher usage of CAMs, and that individuals use CAMs to complement their conventional therapies.

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METHODS

Study Subjects and Data

Data were collected from the baseline visit of a prospective, longitudinal cohort study with the ultimate goal of estimating the economic burden of asthma. Study subjects were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (population of 603,502 and 179,839, respectively, in 2011 (12)). The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a 10 pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next 12 months, and those in whom a methacholine challenge test was contraindicated were not eligible. Consenting individuals attended the study centers for the baseline visit, during which a comprehensive questionnaire was administered to collect information on the demographic and socio-economic status, asthma-related symptoms, and use of CAMs and conventional medications. Patients also underwent spirometry by a trained technician. For the purposes of this sub-study, we restricted the sample to adults 18 years and older.

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Demographics and socio-economic status

The socio-demographic characteristics included age at baseline, sex, ethnicity (self-reported and defined as Caucasian, Asian which included Mandarin, Japanese, Korean, Arabic and Persian, or other ethnicities), education (self-reported and categorized as less than post-secondary education versus post-secondary education), and annual household income (self-reported and categorized as low versus high at a cutoff value of $60,000 CAD).

CAM use

The usage of CAMs in the past 12 months was assessed with the question "*In the past 12 months, have you received any alternative therapy for your asthma? Check all that apply*", followed by a list including nine options: 1) massage, osteopathy or other manipulative techniques; 2) herbal treatment; 3) acupuncture; 4) homeopathy; 5) breathing exercises; 6) vitamins or other supplements; 7) chiropractic; 8) dieting programs; and 9) naturopathy. The interviewer provided verbal explanation and examples to clarify the options. There was also a miscellaneous category with free text, capturing any other modality that could be considered a CAM. This free text field was evaluated by three investigators who decided whether each stated item was a CAM. Approved items then entered into the analysis as the 'other' category.

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Asthma control

Asthma control was defined according to the Global Initiative for Asthma (GINA) criteria (3). Patients were classified as controlled, partially controlled, or uncontrolled based on asthma symptoms during the past three months (daytime symptoms, limitation of activity, nocturnal symptoms and need for rescue medication) as well as the ratio of forced expiratory volume in one second (FEV1) to its predicted value. We used the NHANES III standards to calculate the predicted FEV1 (13).

Controller medication use

Asthma medications during the past 12 months were documented in a self-reported prescription medication chart. For each medication we evaluated the intensity of intake through questions "how many months?" and "how many days a week?". Using these two questions, we measured the intake of controller medication and converted the intensity of intake to proportions of days covered (PDC) (14). Low intake was defined as PDC<50%, moderate intake as 50%≤PDC<80%, and high intake as PDC≥80%.

Statistical analysis

All analyses were performed using Stata/IC (version 12.1., College Station, Texas, United States). The criterion for statistical significance was a two-tailed p-value (p) of less than 0.05. The distribution of variables across groups was compared with Pearson chi-square tests for categorical variables and Student's t-tests for continuous variables. We report the

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frequency of use of any CAMs, individual CAM categories, as well as the concomitant use of different types of CAMs.

Logistic regression was performed to evaluate the association between CAM use and asthma control, controller medication use, and potential confounders. Unadjusted analysis involved performing the logistic regression with the dependent variable being any use of CAMs (versus no use), and individual covariate of interest as the single independent variable. For the adjusted analysis, we used the same logistic regression model with any use of CAMs (versus no use) as the dependent variable, with independent variables including the level of asthma control (dummy-coded to represent partially controlled and uncontrolled versus controlled asthma), controller medication use (the abovementioned PDC categories) as independent variables of interest. We also controlled for sex, ethnicity, age at baseline, annual household income and education status by entering such variables as additional independent variables in the regression model. The hypothesis of the complementary versus substitute role of CAMs with regard to conventional controller medications was evaluated by interpreting the coefficient for controller medication use: a positive coefficient (indicating an odds ratio (OR) of more than one) indicates a complementary role for CAMs, whereas a negative one (indicating an OR of less than one) points towards CAMs playing a substitute role.

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Sensitivity and subgroup analyses

In order to investigate whether the association between controller medication use and use of CAMs was different across asthma control levels, we fitted separate regression models using the aforementioned logistic model within each level of asthma control. In addition, to more efficiently exploit the information on CAM use provided by participants, we used a negative binomial regression model with the dependent variable being the number of different types of CAMs used by the individual (all independent variables similar to those of the logistic model described previously). In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to “yes” or “no” options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values. In another sensitivity analysis, the logistic regression analysis was repeated by removing the 'other' category of CAMs.

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RESULTS

Characteristics of study subjects

Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study. The average age was 52.3 years (SD=14.7) at study entry, and 67.3% were female (Table 1). Participants were likely to be Caucasian (82.1%), have attended college (75.3%), and have annual household income greater than $60,000 (72.2%). The mean baseline FEV1 was 2.61 (SD=0.87). The distribution of individuals across controlled, partially controlled, and uncontrolled asthma was 20.0%, 38.5% and 41.6%, respectively. Of all adults, 42.0%, 15.2%, and 42.8% had low, medium, and high intake of controller medications, respectively.

<<Table 1 here>>

The overall prevalence of the use of any CAMs in the past 12 months was 179/486 (36.8%; 95% CI: 32.5% - 41.1%). Excluding the 'other' category, which comprised 16.3% of CAM usage, a majority of the individuals (18.3%) reported using one type of CAMs, while 7.6% used two different CAMs, and 9.3% used more than two types of CAMs. The most frequent CAMs were breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) (Figure 1).

<<Figure 1 here>>

Association between CAM use, asthma control, and controller medication intake

Results of both unadjusted and adjusted logistic regressions are provided in Table 2. Only female sex and uncontrolled asthma were associated with a higher chance of using any CAMs

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in the unadjusted analysis. After adjustment, the same two variables, female sex (OR1.66; 95% CI 1.09 - 2.52) and uncontrolled asthma (uncontrolled vs. controlled asthma OR 2.25; 95% CI 1.30 - 3.89), were significantly associated with CAM utilization. Partially controlled asthma and controller medication intake were not associated with CAM usage.

<<Table2 here>>

Subgroup and sensitivity analyses

Results of the subgroup and sensitivity analyses are reported in Appendix Table A1-A3. Controller medication use was not associated with CAM use within the strata of controlled, partially controlled, or uncontrolled individuals. No change was observed in the overall study results when indeterminate answers to asthma symptoms were treated as missing values, when the multivariate logistic regression model was replaced with a negative binomial model, and when the 'other' category of CAMs were removed from the analysis.

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DISCUSSION

Using a population-based sample, we described the patterns of CAM usage in adults with asthma, and further examined the association between CAM use, asthma control, and controller medication intake. In our study, 37% of adults with asthma reported using any CAMs in the past 12 months. We also found that patients with uncontrolled asthma had a higher likelihood of reporting any use of CAMs, compared with patients with controlled asthma, after adjusting for potential confounders. Our study therefore suggests that the use of CAMs in patients with asthma is high, and is associated with worse asthma control. In addition, we found breathing exercise, a modality often used by patients with more severe asthma, to be the most common type of CAM. This, combined with a lower baseline FEV1 (P=0.06) among CAM users compared with non-users, might indicate that CAM users tended to have more severe asthma.

On the other hand, CAM usage was unrelated to the intake of controller medication in the overall study population, as well as within the subgroups defined by asthma control. As such we could not discern any complementary or substitute role of CAMs in relation to conventional controller therapies. In addition to our limited sample size to discover such a relationship, it might be the case that users of CAMs are a mixture of those who consume CAMs as a complement versus those who use them as substitute to their conventional controller therapies.

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Our estimates of the prevalence of CAM use is in line with recent survey-based estimates (Behavioral Risk Factor Surveillance System) for 38% -40% for any use of CAMs in the U.S (11,15). Our findings on the association between CAM use and socio-demographic factors (e.g., age, education, household income, ethnicity) are generally consistent with published findings (6,15–17): several previous studies also reported a greater possibility of receiving CAMs among females with asthma as compared to males (6,16,17), but a recent U.S. study did not find a statistically significant association (15). Such discrepancies may be explained by our limited sample size as well as differences in data collection methods and in the types of CAMs being reported in these studies.

Marino and Shen found asthma emergency room visits and disability days, as surrogates for lack of asthma control, to be positively related with CAM use in adults (15). However, a Northern California study of adult patients reported no association between self-assessed asthma severity and CAM use (16). Using a validated and internationally accepted measure of asthma control (3), our analysis showed an inverse association between asthma control and usage of CAMs. Similar results have been observed in samples of individuals with work-related asthma (11). On the other hand, the link between CAM usage and adherence to asthma controller medications is inconsistent in the literature and likely confounded by asthma control. Two inner-city studies in the U.S reported decreased adherence to asthma controller therapy among adult CAM users (18,19) whereas a recent longitudinal analysis found no effect of CAMs on future adherence to controller medication in pediatric asthma

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patients (20).

Compared to previous studies (11,15,16,18,19), our study has several strengths. Based on a random sample, the estimates of CAM use and the association with asthma control are population-based. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function (3). Various subgroup and sensitivity analyses added to the robustness and credibility of our results. However, this study is not without limitations. First, both CAM use and controller medication intake were based on self-reports and thus are subject to recall bias, which may affect the precision of measurement and thereby increase the noise in finding an association We provided a list of nine pre-specified types of CAMs to participants to ensure homogeneity in the definition of CAMs across all individuals and to increase the accuracy of recall; however, individuals might have been less likely to report other forms of CAMs. Finally, using a cross-sectional design, we were not able to evaluate whether CAMs played a causal role in changing the level of asthma control.

Despite these limitations, our findings have important clinical implications. The extent of CAM use among the population of patients with asthma gives policy makers an estimate of the overall burden of CAM usage at the population level. The resources individuals spend consuming CAMs represent an opportunity cost because such resources could have been spent in evidence-based treatments or other activities. Given the uncertain benefits, potential

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side effects and possible drug interactions of CAMs (4), it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use. We found the use of CAMs to be associated with uncontrolled asthma. Overall, CAM use might be a sign of patients' lack of satisfaction with asthma treatment, prompting the care provider to reevaluate asthma management. Future research is required to evaluate the economic impact of CAM use, to further examine other potential factors determining the use of CAMs such as individuals' value systems and beliefs, access to care, health literacy, and quality of life, and to rigorously study the causal interactions between CAM use, asthma control, and use of controller medications.

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Table legend

Table 1. Characteristics of study population based the pattern of use of CAMs in the last twelve months.

Table 2. Logistic regression with past 12 month CAM usage

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Table 1. Characteristics of the study population: overall and by CAM use

Variables	Overall (N=486)	Used Any CAMs		*p-value* *
		Yes (N=179)	No (N=307)	
Age, *mean(SD)*	52.3 (14.7)	52.3 (13.6)	52.1 (15.2)	0.88
Gender, *N (%)*				0.007#
Female	327 (67.3)	134 (74.9)	193 (62.9)	
Male	159 (32.7)	45 (25.1)	114 (37.1)	
Education, *N(%))*				
Less than post-secondary education	120 (24.7)	43 (24.0)	77 (25.1)	0.79
Post-secondary education	366 (75.3)	136 (76.0)	230 (74.9)	
Ethnicity, *N(%)*				0.62
Caucasian	399 (82.1)	143 (79.9)	256 (83.4)	
Asian	67 (13.8)	28 (15.6)	39 (12.7)	
Other	20 (4.1)	8 (4.5)	12 (3.9)	
Household income, *N(%)*				0.13
<$60,000	135 (27.8)	57 (31.8)	78 (25.4)	
≥$60,000	351 (72.2)	122 (68.2)	229 (74.6)	
Baseline FEV1 (L), *mean(SD)*	2.61 (0.87)	2.51 (0.86)	2.67 (0.87)	0.06
Asthma control level, *N(%)*				<0.001#
Controlled	97 (20.0)	26 (14.5)	71 (23.1)	
Partially controlled	187 (38.5)	58 (32.4)	129 (42.0)	
Uncontrolled	202 (41.6)	95 (53.1)	107 (34.9)	
Controller medication intake, *N(%)*				
PDC <50% (Low)	204 (42.0)	66 (36.9)	138 (45.0)	0.21
50%≤PDC<80% (Moderate)	74 (15.2)	31 (17.3)	43 (14.0)	
PDC ≥80% (High)	208 (42.8)	82 (45.8)	126 (41.0)	

Mean, mean values; SD, standard deviation of mean values; N, total number; %, percentage; FEV1: Forced Expiratory Volume at 1 second, L: liter; SD: Standard Deviation, CAMs: Complementary and Alternative Medicines, PDC: proportions of days covered by conventional controller medications.

*p values are associated with independent-sample t-test for continuous variables and chi-square test for categorical variables.

Significant at 0.05 level

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Table 2. Logistic regression with past 12 month CAM usage

Variables	Any CAM use, *OR (95% CI); p-value*	
	Unadjusted[a]	Adjusted[b]
Age	1.00 (0.99;1.01); p=0.88	1.00 (0.98;1.01); p=0.70
Gender		
Male	Reference	Reference
Female	**1.76 (1.17;2.65); p=0.007#**	**1.66 (1.09;2.52); p=0.019#**
Household income		
<$60,000	Reference	Reference
≥$60,000	0.73 (0.49;1.09); p=0.13	0.80 (0.52;1.23); p=0.31
Education		
Less than post-secondary education	Reference	Reference
Post-secondary education	1.06 (0.69;1.63); p=0.79	1.07 (0.68;1.69); p=0.77
Ethnicity		
Caucasian	Reference	Reference
Asian	1.29 (0.76;2.18); p=0.35	1.31 (0.76;2.28); p=0.32
Other	1.19 (0.48; 2.99); p=0.71	1.14 (0.44;2.96); p=0.78
Asthma control level		
Controlled	Reference	Reference
Partially controlled	1.23 (0.71;2.12); p=0.46	1.26 (0.72;2.19); p=0.42
Uncontrolled	**2.42 (1.43; 4.11); p=0.001#**	**2.25 (1.30;3.89); p=0.004#**
Intake of controller medication		
Low	Reference	Reference
Moderate	1.51 (0.87;2.61); p=0.14	1.22 (0.69;2.16); p=0.49
High	1.36 (0.91; 2.04); p=0.14	1.10 (0.71;1.71); p=0.67

[a]Univariate logistic regression; [b]Multivariate logistic regression;
OR, odds ratios; CI, confidence interval.
Significant at 0.05 level

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Figure legend

Figure 1. Frequencies of past 12-month CAM usage in treating asthma, by CAM types

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Complementary and alternative asthma treatments and their association with asthma control: a population-based study

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Conflict of interest

The authors declare no conflict of interest.

Original publication

The work of this manuscript contains original unpublished work, which is not being submitted for publication elsewhere at the same time.

Ethics approval

This study was approved by the Human Ethics board of the University of British Columbia.

Contributorship Statement

MF, MS, CM, LL, and WH designed the Economic Burden of Asthma (EBA) study, whose data is used in the present research. MS and RR designed the case report forms. MF and WC proposed the research question. WC conceptualized the study design, was the main analyst, and wrote the first draft of the manuscript. MF, MS, CM, LL, RR, and WH were involved in

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the acquisition of the data. CM and LL critically revised the manuscript. All authors approved the final version of the manuscript.

Data sharing statement

The analytical dataset and statistical codes are shared with BMJ Editorial Board for peer review purposes.

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ABSTRACT

Objectives: Many patients with asthma spend time and resources consuming complementary and alternative medicines (CAMs). This study explores whether CAM utilization is associated with asthma control and the intake of asthma controller medications.

Design: Population-based, prospective cross-sectional study.

Setting: General population residing in two census areas in the province of British Columbia, Canada. Recruitment was based on random-digit dialing of both landlines and cell phones.

Participants: 486 patients with self-reported physician-diagnosis of asthma (mean age 52 years; 67.3% female).

Primary and secondary outcome measures: We assessed CAM use over the previous 12 months, level of asthma control as defined by the Global Initiative for Asthma (GINA), and the self-reported intake of controller medications. Multivariate logistic regression was performed to study the relationship between any usage of CAMs (outcome), asthma control and controller medication usage, adjusted for potential confounders.

Results: A total of 179 (36.8%) of the sample reported CAM usage in the past 12 months. Breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) were the most popular CAMs reported. After adjustment, female sex (OR: 1.66; 95% CI: 1.09-2.52) and uncontrolled asthma (vs. controlled asthma, OR: 2.25, 95% CI: 1.30-3.89) were associated with a higher likelihood of using any CAMs in the past 12 months. Controller medication use was not associated with CAM usage in general and in the subgroups defined by asthma

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control.

Conclusion: Clinicians and policy makers need to be aware of the high prevalence of CAM use in patients with asthma and its association with lack of asthma control.

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ARTICLE SUMMARY

Article Focus

- How does the use of complementary and alternative medicines (CAMs) in treating asthma relate to the clinical control of asthma and the use of conventional asthma controller therapies?

Key Messages

- Our study demonstrated that CAMs were commonly used to treat asthma
- The CAM usage was inversely associated with asthma control whereas unrelated to the use of controller medications.
- Given the uncertain benefits and potential side effects of CAMs and possible drug interactions, it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use.

Strengths and Limitations

- This is one of the few population-based studies investigating the association between CAM usage, the use of conventional asthma therapies and asthma control. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function. Various subgroup and sensitivity analyses added to the robustness and credibility of our results.
- However, the study is based on self-reports and thus the results are subject to recall bias. Also, the cross-sectional design of this study prevents the evaluation of whether CAMs played a causal role in changing the level of asthma control.

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INTRODUCTION

Asthma is a chronic disease of the airways associated with high health care resource utilization, productivity loss, and reduced quality of life (1). Proper management can lead to clinically controlled asthma which, compared to uncontrolled asthma, is associated with lower usage of health care resources and better quality of life (2). Clinical guidelines recommend anti-inflammatory medications as the primary controller treatment for asthma. In particular, inhaled corticosteroids (ICSs) are considered as the foundation therapy for treating asthma (3).

In addition to conventional treatments, many patients with asthma use complementary and alternative medicines (CAMs) in an attempt to improve their asthma symptoms (4). The CAMs are generally defined as "a group a diverse medical and healthcare systems, practices and products that are not generally considered to be part of conventional medicine" (5). The reported prevalence rates of CAM usage in treating asthma is quite varied, ranging from 4% to 79% (6). Breathing techniques, homeopathy, and herbal medicines are reportedly the most popular CAMs among patients with asthma (6). Despite the common use of CAMs, individuals often do not disclose CAM usage to health care professionals (7,8).

In general, the effectiveness of CAMs in treating asthma is unknown and most likely is minimal, whereas some CAMs are associated with certain risks (4,9,10). The resources

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individuals spend in seeking and using CAMs may potentially draw from the resources they possess to support evidence-based care for their asthma. Understanding the reasons behind individuals' consuming CAMs can thus help care providers offer informed advice to patients. Two of the important factors in determining what makes patients consume CAMs are the association between CAM use and the level of asthma control as well as the usage of conventional controller therapies. There is evidence indicating an association between CAM usages and poor control in work-related asthma (11). Nonetheless, few studies have attempted to determine the association between the usage of CAMs and controller medications as a function of asthma control. Hypothetically, CAMs can play either a complementary or a substitute role in relation with conventional therapies. In a complementary role patients use CAMs in addition to their conventional treatments in an attempt to reduce asthma-related impairment. A substitute role for CAMs indicates that individuals use CAMs as a replacement for conventional therapies if they do not perceive benefit from conventional therapies (or do not seek conventional therapies due to lack of belief in their effect or due to their prohibitive cost). The objective of this study was to explore the association between CAM use, asthma control, and the use of controller medications in a random sample of adult patients with asthma. Specifically, we hypothesized that lack of asthma control will be associated with higher usage of CAMs, and that individuals use CAMs to complement their conventional therapies.

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METHODS

Study Subjects and Data

Data were collected from the baseline visit of a prospective, longitudinal cohort study with the ultimate goal of estimating the economic burden of asthma. Study subjects were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (population of 603,502 and 179,839, respectively, in 2011 (12)). The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a 10 pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next 12 months, and those in whom a methacholine challenge test was contraindicated were not eligible. Consenting individuals attended the study centers for the baseline visit, during which a comprehensive questionnaire was administered to collect information on the demographic and socio-economic status, asthma-related symptoms, and use of CAMs and conventional medications. Patients also underwent spirometry by a trained technician. For the purposes of this sub-study, we restricted the sample to adults 18 years and older.

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Demographics and socio-economic status

The socio-demographic characteristics included age at baseline, sex, ethnicity (self-reported and defined as Caucasian, Asian which included Mandarin, Japanese, Korean, Arabic and Persian, or other ethnicities), education (self-reported and categorized as less than post-secondary education versus post-secondary education), and annual household income (self-reported and categorized as low versus high at a cutoff value of $60,000 CAD).

CAM use

The usage of CAMs in the past 12 months was assessed with the question "*In the past 12 months, have you received any alternative therapy for your asthma? Check all that apply*", followed by a list including nine options: 1) massage, osteopathy or other manipulative techniques; 2) herbal treatment; 3) acupuncture; 4) homeopathy; 5) breathing exercises; 6) vitamins or other supplements; 7) chiropractic; 8) dieting programs; and 9) naturopathy. The interviewer provided verbal explanation and examples to clarify the options. There was also a miscellaneous category with free text, capturing any other modality that could be considered a CAM. This free text field was evaluated by three investigators who decided whether each stated item was a CAM. Approved items then entered into the analysis as the 'other' category.

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Asthma control

Asthma control was defined according to the Global Initiative for Asthma (GINA) criteria (3). Patients were classified as controlled, partially controlled, or uncontrolled based on asthma symptoms during the past three months (daytime symptoms, limitation of activity, nocturnal symptoms and need for rescue medication) as well as the ratio of forced expiratory volume in one second (FEV1) to its predicted value. We used the NHANES III standards to calculate the predicted FEV1 (13).

Controller medication use

Asthma medications during the past 12 months were documented in a self-reported prescription medication chart. For each medication we evaluated the intensity of intake through questions "how many months?" and "how many days a week?". Using these two questions, we measured the intake of controller medication and converted the intensity of intake to proportions of days covered (PDC) (14). Low intake was defined as PDC<50%, moderate intake as 50%≤PDC<80%, and high intake as PDC≥80%.

Statistical analysis

All analyses were performed using Stata/IC (version 12.1., College Station, Texas, United States). The criterion for statistical significance was a two-tailed p-value (p) of less than 0.05. The distribution of variables across groups was compared with Pearson chi-square tests for categorical variables and Student's t-tests for continuous variables. We report the

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frequency of use of any CAMs, individual CAM categories, as well as the concomitant use of different types of CAMs.

Logistic regression was performed to evaluate the association between CAM use and asthma control, controller medication use, and potential confounders. Unadjusted analysis involved performing the logistic regression with the dependent variable being any use of CAMs (versus no use), and individual covariate of interest as the single independent variable. For the adjusted analysis, we used the same logistic regression model with any use of CAMs (versus no use) as the dependent variable, with independent variables including the level of asthma control (dummy-coded to represent partially controlled and uncontrolled versus controlled asthma), controller medication use (the abovementioned PDC categories) as independent variables of interest. We also controlled for sex, ethnicity, age at baseline, annual household income and education status by entering such variables as additional independent variables in the regression model. The hypothesis of the complementary versus substitute role of CAMs with regard to conventional controller medications was evaluated by interpreting the coefficient for controller medication use: a positive coefficient (indicating an odds ratio (OR) of more than one) indicates a complementary role for CAMs, whereas a negative one (indicating an OR of less than one) points towards CAMs playing a substitute role.

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Sensitivity and subgroup analyses

In order to investigate whether the association between controller medication use and use of CAMs was different across asthma control levels, we fitted separate regression models using the aforementioned logistic model within each level of asthma control. In addition, to more efficiently exploit the information on CAM use provided by participants, we used a negative binomial regression model with the dependent variable being the number of different types of CAMs used by the individual (all independent variables similar to those of the logistic model described previously). In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to “yes” or “no” options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values. In another sensitivity analysis, the logistic regression analysis was repeated by removing the 'other' category of CAMs.

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RESULTS

Characteristics of study subjects

Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study. The average age was 52.3 years (SD=14.7) at study entry, and 67.3% were female (Table 1). Participants were likely to be Caucasian (82.1%), have attended college (75.3%), and have annual household income greater than $60,000 (72.2%). The mean baseline FEV1 was 2.61 (SD=0.87). The distribution of individuals across controlled, partially controlled, and uncontrolled asthma was 20.0%, 38.5% and 41.6%, respectively. Of all adults, 42.0%, 15.2%, and 42.8% had low, medium, and high intake of controller medications, respectively.

<<Table 1 here>>

The overall prevalence of the use of any CAMs in the past 12 months was 179/486 (36.8%; 95% CI: 32.5% - 41.1%). Excluding the 'other' category, which comprised 16.3% of CAM usage, a majority of the individuals (18.3%) reported using one type of CAMs, while 7.6% used two different CAMs, and 9.3% used more than two types of CAMs. The most frequent CAMs were breathing exercises (17.7%), herbal medicines (10.1%), and vitamins (9.7%) (Figure 1).

<<Figure 1 here>>

Association between CAM use, asthma control, and controller medication intake

Results of both unadjusted and adjusted logistic regressions are provided in Table 2. Only female sex and uncontrolled asthma were associated with a higher chance of using any CAMs

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in the unadjusted analysis. After adjustment, the same two variables, female sex (OR1.66; 95% CI 1.09 - 2.52) and uncontrolled asthma (uncontrolled vs. controlled asthma OR 2.25; 95% CI 1.30 - 3.89), were significantly associated with CAM utilization. Partially controlled asthma and controller medication intake were not associated with CAM usage.

<<Table2 here>>

Subgroup and sensitivity analyses

Results of the subgroup and sensitivity analyses are reported in Appendix Table A1-A3. Controller medication use was not associated with CAM use within the strata of controlled, partially controlled, or uncontrolled individuals. No change was observed in the overall study results when indeterminate answers to asthma symptoms were treated as missing values, when the multivariate logistic regression model was replaced with a negative binomial model, and when the 'other' category of CAMs were removed from the analysis.

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DISCUSSION

Using a population-based sample, we described the patterns of CAM usage in adults with asthma, and further examined the association between CAM use, asthma control, and controller medication intake. In our study, 37% of adults with asthma reported using any CAMs in the past 12 months. We also found that patients with uncontrolled asthma had a higher likelihood of reporting any use of CAMs, compared with patients with controlled asthma, after adjusting for potential confounders. Our study therefore suggests that the use of CAMs in patients with asthma is high, and is associated with worse asthma control. In addition, we found breathing exercise, a modality often used by patients with more severe asthma, to be the most common type of CAM. This, combined with a lower baseline FEV1 (P=0.06) among CAM users compared with non-users, might indicate that CAM users tended to have more severe asthma.

On the other hand, CAM usage was unrelated to the intake of controller medication in the overall study population, as well as within the subgroups defined by asthma control. As such we could not discern any complementary or substitute role of CAMs in relation to conventional controller therapies. In addition to our limited sample size to discover such a relationship, it might be the case that users of CAMs are a mixture of those who consume CAMs as a complement versus those who use them as substitute to their conventional controller therapies.

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Our estimates of the prevalence of CAM use is in line with recent survey-based estimates (Behavioral Risk Factor Surveillance System) for 38% -40% for any use of CAMs in the U.S (11,15). Our findings on the association between CAM use and socio-demographic factors (e.g., age, education, household income, ethnicity) are generally consistent with published findings (6,15–17): several previous studies also reported a greater possibility of receiving CAMs among females with asthma as compared to males (6,16,17), but a recent U.S. study did not find a statistically significant association (15). Such discrepancies may be explained by our limited sample size as well as differences in data collection methods and in the types of CAMs being reported in these studies.

Marino and Shen found asthma emergency room visits and disability days, as surrogates for lack of asthma control, to be positively related with CAM use in adults (15). However, a Northern California study of adult patients reported no association between self-assessed asthma severity and CAM use (16). Using a validated and internationally accepted measure of asthma control (3), our analysis showed an inverse association between asthma control and usage of CAMs. Similar results have been observed in samples of individuals with work-related asthma (11). On the other hand, the link between CAM usage and adherence to asthma controller medications is inconsistent in the literature and likely confounded by asthma control. Two inner-city studies in the U.S reported decreased adherence to asthma controller therapy among adult CAM users (18,19) whereas a recent longitudinal analysis found no effect of CAMs on future adherence to controller medication in pediatric asthma

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patients (20).

Compared to previous studies (11,15,16,18,19), our study has several strengths. Based on a random sample, the estimates of CAM use and the association with asthma control are population-based. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function (3). Various subgroup and sensitivity analyses added to the robustness and credibility of our results. However, this study is not without limitations. First, both CAM use and controller medication intake were based on self-reports and thus are subject to recall bias, which may affect the precision of measurement and thereby increase the noise in finding an association We provided a list of nine pre-specified types of CAMs to participants to ensure homogeneity in the definition of CAMs across all individuals and to increase the accuracy of recall; however, individuals might have been less likely to report other forms of CAMs. Finally, using a cross-sectional design, we were not able to evaluate whether CAMs played a causal role in changing the level of asthma control.

Despite these limitations, our findings have important clinical implications. The extent of CAM use among the population of patients with asthma gives policy makers an estimate of the overall burden of CAM usage at the population level. The resources individuals spend consuming CAMs represent an opportunity cost because such resources could have been spent in evidence-based treatments or other activities. Given the uncertain benefits, potential

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side effects and possible drug interactions of CAMs (4), it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use. We found the use of CAMs to be associated with uncontrolled asthma. Overall, CAM use might be a sign of patients' lack of satisfaction with asthma treatment, prompting the care provider to reevaluate asthma management. Future research is required to evaluate the economic impact of CAM use, to further examine other potential factors determining the use of CAMs such as individuals' value systems and beliefs, access to care, health literacy, and quality of life, and to rigorously study the causal interactions between CAM use, asthma control, and use of controller medications.

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Table legend

Table 1. Characteristics of study population based the pattern of use of CAMs in the last twelve months.

Table 2. Logistic regression with past 12 month CAM usage

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Table 1. Characteristics of the study population: overall and by CAM use

Variables	Overall (N=486)	Used Any CAMs		*p-value* *
		Yes (N=179)	No (N=307)	
Age, *mean(SD)*	52.3 (14.7)	52.3 (13.6)	52.1 (15.2)	0.88
Gender, *N (%)*				0.007#
Female	327 (67.3)	134 (74.9)	193 (62.9)	
Male	159 (32.7)	45 (25.1)	114 (37.1)	
Education, *N(%))*				
Less than post-secondary education	120 (24.7)	43 (24.0)	77 (25.1)	0.79
Post-secondary education	366 (75.3)	136 (76.0)	230 (74.9)	
Ethnicity, *N(%)*				0.62
Caucasian	399 (82.1)	143 (79.9)	256 (83.4)	
Asian	67 (13.8)	28 (15.6)	39 (12.7)	
Other	20 (4.1)	8 (4.5)	12 (3.9)	
Household income, *N(%)*				0.13
<$60,000	135 (27.8)	57 (31.8)	78 (25.4)	
≥$60,000	351 (72.2)	122 (68.2)	229 (74.6)	
Baseline FEV1 (L), *mean(SD)*	2.61 (0.87)	2.51 (0.86)	2.67 (0.87)	0.06
Asthma control level, *N(%)*				<0.001#
Controlled	97 (20.0)	26 (14.5)	71 (23.1)	
Partially controlled	187 (38.5)	58 (32.4)	129 (42.0)	
Uncontrolled	202 (41.6)	95 (53.1)	107 (34.9)	
Controller medication intake, *N(%)*				
PDC <50% (Low)	204 (42.0)	66 (36.9)	138 (45.0)	0.21
50%≤PDC<80% (Moderate)	74 (15.2)	31 (17.3)	43 (14.0)	
PDC ≥80% (High)	208 (42.8)	82 (45.8)	126 (41.0)	

Mean, mean values; SD, standard deviation of mean values; N, total number; %, percentage; FEV1: Forced Expiratory Volume at 1 second, L: liter; SD: Standard Deviation, CAMs: Complementary and Alternative Medicines, PDC: proportions of days covered by conventional controller medications.

*p values are associated with independent-sample t-test for continuous variables and chi-square test for categorical variables.

Significant at 0.05 level

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Table 2. Logistic regression with past 12 month CAM usage

Variables	Any CAM use, *OR (95% CI); p-value*	
	Unadjusted[a]	Adjusted[b]
Age	1.00 (0.99;1.01); p=0.88	1.00 (0.98;1.01); p=0.70
Gender		
Male	Reference	Reference
Female	**1.76 (1.17;2.65); p=0.007#**	**1.66 (1.09;2.52); p=0.019#**
Household income		
<$60,000	Reference	Reference
≥$60,000	0.73 (0.49;1.09); p=0.13	0.80 (0.52;1.23); p=0.31
Education		
Less than post-secondary education	Reference	Reference
Post-secondary education	1.06 (0.69;1.63); p=0.79	1.07 (0.68;1.69); p=0.77
Ethnicity		
Caucasian	Reference	Reference
Asian	1.29 (0.76;2.18); p=0.35	1.31 (0.76;2.28); p=0.32
Other	1.19 (0.48; 2.99); p=0.71	1.14 (0.44;2.96); p=0.78
Asthma control level		
Controlled	Reference	Reference
Partially controlled	1.23 (0.71;2.12); p=0.46	1.26 (0.72;2.19); p=0.42
Uncontrolled	**2.42 (1.43; 4.11); p=0.001#**	**2.25 (1.30;3.89); p=0.004#**
Intake of controller medication		
Low	Reference	Reference
Moderate	1.51 (0.87;2.61); p=0.14	1.22 (0.69;2.16); p=0.49
High	1.36 (0.91; 2.04); p=0.14	1.10 (0.71;1.71); p=0.67

[a]Univariate logistic regression; [b]Multivariate logistic regression;
OR, odds ratios; CI, confidence interval.
Significant at 0.05 level

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Figure legend

Figure 1. Frequencies of past 12-month CAM usage in treating asthma, by CAM types

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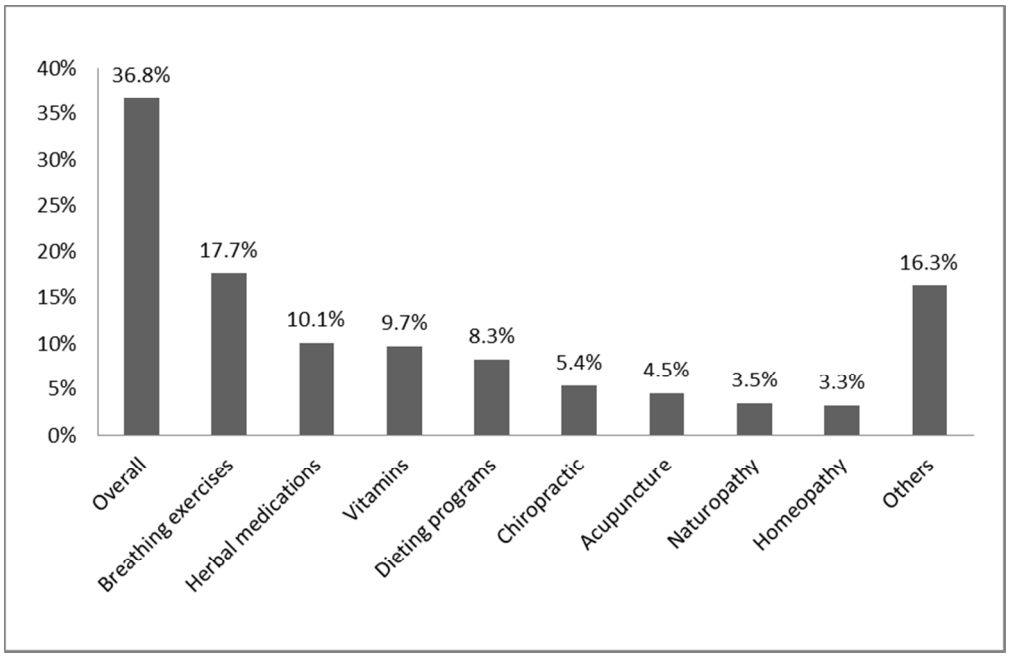

Frequencies of past 12-month CAM usage in treating asthma, by CAM types.
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Table A1. Subgroup analysis: multivariate logistic regression results for subgroups based on control level

Variables	CAM usage by asthma control level, *OR (95% CI), p*		
	Controlled (N=91)	Partially Controlled (N=187)	Uncontrolled (N=202)
Age	1.01 (0.98;1.05), p=0.43	1.00 (0.97;1.01), p=0.33	1.00 (0.98-1.02), p=0.81
Gender			
Male	Reference	Reference	Reference
Female	1.77 (0.58;5.41), p=0.31	1.88 (0.95;3.72), p=0.07	1.31 (0.68-2.52), p=0.43
Household income			
<$60,000	Reference	Reference	Reference
≥$60,000	0.57 (0.18;1.76), p=0.32	0.52 (0. 23;1.14), p=0.10	1.18 (0.63-2.20), p=0.60
Education			
Less than post-secondary education	Reference	Reference	Reference
Post-secondary education	1.13 (0.38;3.38), p=0.83	1.86 (0.77;4.47), p=0.17	0.77 (0.39-1.52), p=0.46
Ethnicity			
Caucasian	Reference	Reference	Reference
Asian	1.50 (0.38;5.70), p=0.56	1.02 (0.40;2.60), p=0.96	1.33 (0.59-3.01), p=0.49
Other	NA	1.92 (0.31;11.83), p=0.48	1.95 (0.44-8.61), p=0.38
Intake of controller medication			
Low	Reference	Reference	Reference
Moderate	0.92 (0.15-5.74), p=0.93	1.08 (0.43;2.70), p=0.87	1.70 (0.73-3.99), p=0.22
High	0.70 (0.22-2.19), p=0.54	0.80 (0.38;1.68), p=0.56	1.57 (0.79-3.11), p=0.20

OR, odds ratios; CI, confidence interval.

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Table A2. Multivariate negative binomial regression predicting counts of using different types of CAMs in the past 12 months in asthmatics

Independent Variables	Number of different CAMs being used			
	B	*SE B*	*Exp(B)*	*p*
Age	-0.01	0.01	0.99	0.10
Gender				
Male	Reference			
Female	**0.57**	**0.19**	**1.77**	**0.002**
Household income				
<$6,000	Reference			
≥$6,000	**-0.36**	**0.18**	**0.70**	**0.046**
Education years (centered)				
Less than post-secondary education	Reference			
Post-secondary education	0.25	0.20	1.28	0.22
Ethnicity				
Caucasian	Reference			
Asian	0.01	0.24	1.01	0.96
Other	0.52	0.36	1.68	0.16
Asthma control level				
Controlled	Reference			
Partially controlled	0.42	0.25	1.53	0.09
Uncontrolled	**0.77**	**0.25**	**2.15**	**0.002**
Intake of controller medication				
Low	Reference			
Moderate	0.17	0.25	1.18	0.51
High	0.18	0.19	1.20	0.34
	Likelihood-ratio χ^2 (10) =34.05, p<0.001 Likelihood-ratio test of alpha=0: p<0.001			

B, unstandardized regression coefficients; SE B, standard error of B; Exp(B), exponential of B.

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Table A3

Sensitivity analyses

1) The same multivariate logistic regression, as used in the main analysis, was repeated by excluding all other CAMs being listed in the miscellaneous option so as to restrict potential biases in misclassifying non-CAMs into CAMs. Regression results did not vary substantially between the 2 models. Uncontrolled asthma and female sex were significant factors predictive of CAM usage (OR=2.29, 95% CI: 1.31; 4.02 and OR=1.55, 95% CI: 1.01; 2.37) whereas other variables were not associated.
2) In the main analyses, asthma control was calculated with the assumption that any response to a GINA symptom criterion as "don't know" was treated as no symptoms. To address bias that could have been introduced by this assumption on asthma control and covariates, we treated the "don't know" response to GINA criteria as missing data in asthma control, hence we identified 18 out of 486 missing data (3.7%) in the re-defined asthma control variable. Multinomial logistic regression was performed to multiply impute missing values in re-defined asthma control using all other variables in the original logistic regression model. 5 datasets were generated from multiple imputations and applied to regression estimation. Appendix Table A3 shows that multiple imputations did not substantially alter the regression results predictive of CAM usage.

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Table A3. Sensitivity analysis based on coding of controller medication intake, adjustment for demographics and multiple imputations: predicting whether utilized any CAMs.

	CAM usage, *multivariate OR (95% CI), p values*		
Independent variables of interest	Original model[a]	Other CAMs excluded[b]	Multiple imputation model[c]
Age	1.00 (0.98;1.01); p=0.70	1.00 (0.98; 1.01); p=0.67	1.00 (0.98; 1.01); p=0.73
Gender			
Male	Reference		
Female	**1.66 (1.09; 2.53); p=0.019**	**1.55 (1.01; 2.37); p=0.044**	**1.63 (1.07; 2.50); p=0.023**
Household income			
<$60,000	Reference		
≥$60,000	0.80 (0.52; 1.23); p=0.31	0.78 (0.50; 1.21); p=0.27	0.81 (0.52; 1.26); p=0.35
Education			
Less than post-secondary education	Reference		
Post-secondary education	1.07 (0.68; 1.69); p=0.77	1.05 (0.66; 1.67); p=0.83	1.09 (0.69; 1.72); p=0.72
Ethnicity			
Caucasian	Reference		
Asian	1.31 (0.76; 2.28); p=0.32	1.27 (0.73; 2.22); p=0.40	1.34 (0.77; 2.32); p=0.30
Other	1.14 (0.44; 2.96); p=0.78	1.20 (0.46; 3.10); p=0.71	1.18 (0.45; 3.05); p=0.74
Asthma control level			
Controlled	Reference		
Partially controlled	1.26 (0.72; 2.19); p=0.42	1.30 (0.74; 2.30); p=0.36	1.36 (0.75-2.47); p=0.31
Uncontrolled	**2.25 (1.30; 3.89); p=0.004**	**2.29 (1.31; 4.02); p=0.004**	**2.49 (1.38-4.49); p=0.002**
Intake of controller medication			
Low	Reference		
Moderate	1.22 (0.69; 2.16); p=0.49	1.28 (0.72; 2.27); p=0.41	1.22 (0.69; 2.16); p=0.49
High	1.10 (0.71; 1.71); p=0.67	1.17 (0.75; 1.82); p=0.50	1.10 (0.70-1.70); p=0.70

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[a] The original multivariate model as displayed in Table 2, which studied the association of past 12 month CAM usage with asthma control and controller medication intake and controlled for age, gender, household income, education, ethnicity and lung function.

[b] This model repeated the original multivariate model by excluding all other CAMs from the past 12 month CAM uses.

[c] Multiple imputation was conducted using methods described in Appendix 3 with the assumption that asthma control values were missing at random. 5 datasets generated from multiple imputations were applied to regression estimation. The same control variables included in the original multivariate model were used in the multiple imputation and subsequent logistic regression

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Abstract (page 4): "Data were collected from the baseline visit of a prospective cohort study of adult individuals with self-reported physician-diagnosed asthma from British Colombia, Canada"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Abstract (page 4-5) has provided this information in the methods and results section.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Introduction (page 7-8) has provided this information.
Objectives	3	State specific objectives, including any prespecified hypotheses Introduction (page 8): "The objective of this study was to explore the association between CAMs use, asthma control, and the use of controller medications in a random sample of adult patients with asthma."
Methods		
Study design	4	Present key elements of study design early in the paper Methods (Page 9, first paragraph): "Data were collected from the baseline visit of a prospective, longitudinal cohort study with the ultimate goal of estimating the economic burden of asthma."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Methods (Page 9): The first section under the heading "Study Subjects and Data" has provided such information.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Methods (Page 9): Patient enrolment and eligibility criteria: "Study subjects were recruited via random digit dialing from Vancouver and Central Okanagan, two representative census subdivisions in British Columbia, Canada (population of 603,502 and 179,839, respectively, in 2011 (12)). Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified. Individuals were not eligible if they were unable to provide informed consent due to language difficulties or cognitive impairment, reported a 10 pack-year smoking history or greater, or had plans to leave the study area during the follow-up period. Pregnant women, those who planned to become pregnant in the next 12 months, and those in whom a methacholine challenge test was contraindicated were neither eligible." Method of follow up was described in the rest of this paragraph.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed The current study is a non-matched longitudinal cohort study thus such information is not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Outcomes, predictors and potential confounders are defined in the Methods section (page 10-11) under the headings "CAMs use", "Asthma control", "Controller medication use" and "Demographics and socio-economic status", respectively.

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		Diagnostic criteria is not applicable but this study included "Subjects aged 1 to 85 years old with a parental or a self-reported physician diagnosis of asthma, plus a parental or a self-reported record of asthma-related healthcare resource usage in the past 5 years, were initially identified." (Methods: page 9, "Study Subjects and Data").
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Such information has been provided in Methods (page 10-11) under the headings of "Demographics and socio-economic status", "CAMs use", "Asthma control", "Controller medication use".
Bias	9	Describe any efforts to address potential sources of bias The last paragraph of the Methods section (page 13) titled "Sensitivity and subgroup analyses" describes our effort to address potential sources of bias: we performed sensitivity analysis to test the impact of missing values and the definition of CAMs on the main results of the study. We also used subgroup analyses and other regression model to further exploit the information on CAM use. Correlation matrix is provided for exploration of interactions between study variables. Results of these exploratory analyses are reported in the Supplemental Materials.
Study size	10	Explain how the study size was arrived at The first paragraph of the Methods section (page 9) has the corresponding description: "The sample size of the original cohort was designed to provide reliable estimate of the prevalence of asthma (with 95% confidence bound being within 10% of the point estimate)".
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Outcome, predictor and confounding variables are clearly defined in the Methods section (page 10-11). Detailed information on the how to handle these variables is described in Methods (page 11-12) under the "Statistical analysis" heading.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Such information is described in Methods (page 11-12) under the "Statistical analysis" heading.
		(*b*) Describe any methods used to examine subgroups and interactions Such information is described in Methods (page 13) under the "Sensitivity and subgroup analysis" heading: "In order to investigate whether the association between controller medication use and use of CAMs was different across asthma control levels, we fitted separate regression models using the aforementioned logistic model within each level of asthma control."
		(*c*) Explain how missing data were addressed Methods (page 13) under the "Sensitivity and subgroup analysis" heading: "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values". Details of methods are described in the Supplemental Materials (Appendix Table 3A).
		(*d*) If applicable, explain how loss to follow-up was addressed The information is not applicable because the current analysis is focused on data from the baseline visit.

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		(*e*) Describe any sensitivity analyses Methods (Page 13, "Sensitivity and subgroup analysis"): "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values. In another sensitivity analysis, the logistic regression analysis was repeated by removing the 'other' category of CAMs." Details of these sensitivity analyses are reported in the Supplemental Materials (Appendix Table 3A).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Results (page 14, first paragraph): "Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study."
		(b) Give reasons for non-participation at each stage Please note that in the Results section (page 14, first paragraph) under the heading "Characteristics of study subjects", it states: "Among the 622 individuals who completed the baseline visit, there were 486 adults with asthma who comprised the sample for the present study." Hereby it is indicated that age is the reason for non-participation, in that paediatric patients with asthma are not included in this analysis.
		(c) Consider use of a flow diagram We considered this option but we believe the information provided in the results section (see Item 13-a) adequately and concisely illustrates the study flow.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Such information is given in Table 1, page 24-25.
		(b) Indicate number of participants with missing data for each variable of interest We used data from the baseline visit of this cohort study which does not report any missing data, as fields in the survey were required to be filled with valid responses. A sensitivity analysis treated responses of "I do not know" as missing values (Methods: page 13 and Supplemental Materials: Appendix Table 3A): "In assessing the presence of asthma symptoms as part of the definition of asthma control, in addition to "yes" or "no" options, a third category of 'I do not know' was also available to respondents. In the main analysis it was assumed that those who chose the latter option had not experienced the corresponding symptom. In a sensitivity analysis we treated such values as missing and performed multiple imputations on these values."
		(c) Summarise follow-up time (eg, average and total amount) This item is not applicable as the current study is a cross-sectional analysis on the baseline data.
Outcome data	15*	Report numbers of outcome events or summary measures over time Table 2: Logistic regression with past 12 month CAM usage (page 26); Figure 1: Frequencies of past 12 month CAM usage in treating asthma, by CAM types.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

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		Table 2: Logistic regression with past 12 month CAM usage (page 26)
		(*b*) Report category boundaries when continuous variables were categorized The category boundaries are already reported in the tables (Table 1: page 24-25; Table 2: page 26) and the texts of the Results section (page 14-15). For example, we used a cutoff of $60,000 to categorize annual household incomes.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period This is not relevant in our study because we provided odds ratios as estimation outcomes.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Summary of findings on sensitivity and subgroup analyses are summarized in the last paragraph of the Results section (page 15, "Sensitivity and subgroup analyses"): "Results of the subgroup and sensitivity analyses are reported in Appendix Table A1-A3. Controller medication use was not associated with CAM use within the strata of controlled, partially controlled, or uncontrolled individuals. No change was observed in the overall study results when indeterminate answers to asthma symptoms were treated as missing values, when the multivariate logistic regression model was replaced with a negative binomial, and when the 'other' category of CAMs were removed from the analysis. " Details of the information are provided in Supplemental Materials, Appendix Table A1-A4.
Discussion		
Key results	18	Summarise key results with reference to study objectives Summary of key findings is provided in the Discussion (page 16, first paragraph).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Discussion (page 18, first paragraph): "First, both CAM use and controller medication intake were based on self-reports and thus are subject to recall bias, which may affect the precision of measurement and thereby increase the noise in finding an association We provided a list of nine pre-specified types of CAMs to participants to ensure homogeneity in the definition of CAMs across all individuals and to increase the accuracy of recall; however, individuals might have been less likely to report other forms of CAMs. Finally, using a cross-sectional design, we were not able to evaluate whether CAMs played a causal role in changing the level of asthma control."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Discussion (page 18, second paragraph to page 19): "The resources individuals spend consuming CAMs represent an opportunity cost because such resources could have been spent in evidence-based treatments or other activities. In addition, given the uncertain benefits, potential side effects and possible drug interactions of CAMs (4), it is important for physicians to be aware of CAM usage among their patients and understand the reasons of use. CAM use might be a sign of patients' lack of satisfaction with asthma treatment, prompting the care provider to reevaluate asthma management. Future research is required to evaluate the economic impact of CAM use, to further examine other potential factors determining the use of CAMs such as individuals' value systems and beliefs, access to care, health literacy, and quality of life, and to rigorously study the causal interactions between CAM use, asthma control, and use of controller medications. "
Generalisability	21	Discuss the generalisability (external validity) of the study results Discussion (page 17, third paragraph to page 18, first paragraph): "Based on a random sample, the estimates of CAM use and the association with asthma control are population-based. We estimated asthma control using internationally accepted standards based on measures of asthma impairment and lung function (3). Various subgroup and sensitivity analyses added to the robustness and credibility of our results."
Other information		

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Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Funding information (page 1): "This study is part of a peer-reviewed grant funded through GlaxoSmithKline's Collaborative Innovative Research Fund (CIRF). None of the sponsors played a role in the study design, data analysis, interpretation or publication of the results."

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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