

Original article

Are overweight asthmatics more difficult to control?

The relationship between asthma and obesity appears to be quite complex. The aim of this study was to assess the effect of excess weight on asthma control evolution in a cohort of asthmatics. A prospective database was set up, which enrolled adult asthmatics with persistent (mild, moderate or severe) asthma. The control of asthma was defined as a binary variable, acceptable or unacceptable. In order to evaluate the effect of body mass index (BMI; < 25 or ≥ 25), data were analysed using a continuous time homogeneous Markov model in which the forces ruling the transition between the two health states were estimated. The following confounding covariates were also evaluated in the model: severity of asthma, current treatment with oral corticosteroids (OCS) and history of OCS over the year preceding inclusion. About 406 asthmatics were included who made a total of 1639 consultations; the median length of follow up was 182 days. Using a univariate model, overweight patients had a lower risk of transiting from the unacceptable to the acceptable health state ($RR = 0.45$; $P < 0.01$). The effect of weight remained significant ($RR = 0.53$; $P < 0.01$) in the multivariate model including the other covariates. Moreover, transition probabilities stabilized more rapidly for patients with BMI < 25 (200 vs 300 days). In this study, we thus demonstrated that there is an association between excess weight and transition from unacceptable to acceptable control. Because control of asthma clearly drives asthma management, this finding has consequences for defining original new strategies for managing asthma in overweight patients.

**P. Saint-Pierre¹, A. Bourdin²,
P. Chanez², J.-P. Daures¹, P. Godard²**

¹Institut Universitaire de Recherche Clinique, Laboratoire de Biostatistique, Montpellier; ²Service de Pneumologie and INSERM U454, CHU Hôpital Arnaud de Villeneuve, Montpellier, France

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Philippe Saint-Pierre
Institut Universitaire de Recherche Clinique
Laboratoire de Biostatistique
641 Av. G. Giraud
34093 Montpellier
France

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Obesity and asthma are two increasingly important population health issues in industrialized countries. The prevalence of obesity has increased dramatically over the last few decades. For example, a recent study in the USA indicated that 65% of the general population are overweight [body mass index (BMI) ≥ 25 kg/m²] and 31% are obese (BMI ≥ 30 kg/m²) (1). In several European countries (UK, Germany, Poland), the overall percentage of the population with obesity is over 15%. The increased prevalence of obesity has been observed in both men and women in children and adults (2). Asthma is also a major public health problem which affects more than 17 million people in the USA and as many as 300 million people of all ages and all ethnic backgrounds worldwide (3).

Several recent studies have demonstrated an association between BMI and asthma symptoms, both in adults (4–9) and children (10–15), suggesting that excess weight and obesity are potential risk factors for asthma. Moreover, BMI has been observed to be associated with asthma severity (16, 17) in adults, although conflicting results have been reported in children (18). In addition, weight reduction has been shown to improve lung function, symptoms, morbidity and health status in obese

patients with asthma (7). Last but not least, data from a recent study (19) have suggested that obesity could be a systemic inflammatory disease, implying a potential aetiological link between asthma and obesity involving a shared inflammatory pathway.

Asthma control has emerged as the cornerstone of the management of this condition (20). Various strategies have been proposed to assess control over different time periods. Asthma control is usually determined from a composite selection of items including exacerbations, brief symptoms, use of short-acting β_2 -agonists, night awakenings and limitations in carrying out daily activities. Lung function measurements or variability in parameters such as forced expiratory volume in 1 s (FEV₁) are usually added to the scores. Levels of control have been defined using these items, with optimal or total control usually representing the 'ideal achievement' of asthma management, whilst a level of control, which requires a change in the management of a patient, is considered as unacceptable. We used control levels to define health states as described previously (21) and applied a Markov model in order to evaluate the influence of BMI on the evolution of asthma control.

Material and methods

Study subjects

This longitudinal follow-up study of asthmatic patients was conducted in four French university hospital outpatient clinics between 1994 and 2002. Adult asthmatic patients were enrolled prospectively and were required to have been diagnosed for at least 1 year, the diagnosis being confirmed according to National Heart, Lung and Blood Institute (NHLBI) guidelines (22). The conditions for entering the study have been described in detail in a previous report (21). Note that the results obtained in this study are potentially applicable to similar asthma patients, i.e. patients followed up in tertiary hospitals.

Study design

Asthmatic patients were followed up and treated according to international recommendations (22). Only patients with persistent asthma were included in the analysis. The database reflects the real-life activity of hospital outpatient clinics, where, for example, patients return at variable intervals even though they were scheduled to consult every 3 months or according to their perceived needs.

At each visit, a standard case report form (23) was completed, and the control of asthma (20) evaluated according to international GINA guidelines (22). Two control levels were used to define the subject's state at the time of the visit: acceptable control (state 1) and unacceptable control (state 2). Unacceptable control was defined according to Canadian guidelines (24). The BMI was calculated at each visit.

In the Markov analysis, several covariates were evaluated, categorized as binary variables.

- BMI at each consultation: BMI < 25 kg/m² (encoded by 0) and BMI ≥ 25 kg/m² (encoded by 1).
- Asthma severity, defined according to international and national recommendations and guidelines (22): nonsevere asthma (i.e. mild or moderate asthma; encoded by 0) and severe asthma (encoded by 1).
- The daily dose of oral corticosteroids (OCS) at each consultation: dose 0 mg (encoded by 0) and dose > 0 mg (encoded by 1).
- The total dose of OCS over the year preceding inclusion: dose ≤ 2 g (encoded by 0) and dose > 2 g (encoded by 1).

Modelling

Markov models allow the modelling of patient follow up as a succession of transitions between health states over time (25, 26). Figure 1 illustrates the continuous homogeneous Markov model used. The parameters q_{ij} (Fig. 1), associated with the transition from the state ' i ' to the state ' j ', which characterize the model are known

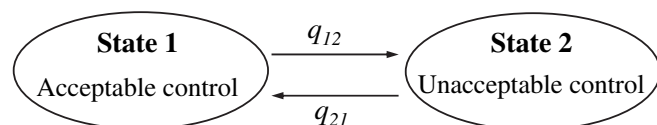


Figure 1. A two-state Markov model with state defined by asthma control. Arrows indicate transitions possible. The parameters q_{ij} are associated with transition from state ' i ' to state ' j '.

as transition forces. They are quantified as the rate of transition and expressed in number of transitions per day. The model was considered to be homogeneous, i.e. the transition forces are independent of time. In a proportional regression model, the relationship between transition forces and the covariates can be expressed as

$$q_{ij} = q_{ij0} \exp(\beta_{ij} z) \quad i \neq j$$

in which z is a vector of covariates, β_{ij} is a vector of regression coefficients and q_{ij0} represents the baseline intensity. A major interest lies in testing hypotheses of the form $\beta_{ijk} = 0$ using the Wald test. This postulates that there is no relationship between the transition from state i to state j and the k th covariate. The regression coefficients can be interpreted similarly to those in the Cox model. The parameters were assessed by maximum likelihood and standard deviations estimated using the delta method.

Statistical analysis

Bivariate relations between BMI, severity and control groups vs other factors were analysed by chi-squared or Kruskal–Wallis (KW) tests as appropriate. The Wald test was used to test if regression coefficients in the Markov model were statistically different from zero. Analysis was carried out using the S-PLUS 6 software package for Windows.

Results

About 406 patients were included in this study, who made a total of 1639 consultations; the median length of follow up was 182 days (interquartile range = 91–446, mean = 384). In a first analysis, we assessed the relationship between BMI, asthma severity and asthma control at inclusion, and their demographic and clinical determinants. Patient characteristics at baseline were described as a function of BMI (< 25 and ≥ 25) and are summarized in Table 1. Table 2 describes patient characteristics at inclusion as a function of asthma severity (mild–moderate and severe asthma). Several variables correlated with severity, BMI and control state. As expected, FEV₁, the presence of exacerbations and the daily dose of inhaled corticosteroids (ICS) were correlated positively to severity (Table 2). Moreover, there was a clear relationship between BMI and severity, with more overweight patients in the severe asthma group (47.2% vs 32.7%; $P < 0.01$). Severity, daily dose of OCS and dose of OCS during the previous year were all correlated positively with BMI (Table 1).

In a second step, we modelled the follow-up data using the Markov model presented in Fig. 1. A univariate Markov model was first fitted with BMI or one of three associated variables: severity, OCS dose, history of OCS. The estimates of regression coefficients, SDs and P -values using the Wald test are summarized in Table 3. All the coefficients relating to transitions from the unacceptable state to the acceptable state were significantly inferior to

Table 1. Patient characteristics at baseline according to BMI

Variables	Body mass index		P-value†
	<25 (n = 260)	≥25 (n = 146)	
Age	38.1 ± 16.4	49.3 ± 13.7	<0.01
Female	160 (61.5)	72 (49.3)	0.02
Severe asthma	48 (18.5)	43 (29.5)	0.01
Atopy*	145 (55.9)	55 (37.7)	<0.01
Rhinitis	196 (75.4)	95 (65.1)	0.02
At least one exacerbation	74 (28.5)	51 (34.9)	0.17
Duration of asthma (years)	16.5 ± 12.8	20.1 ± 16.9	0.16
FEV ₁	79.3 ± 21.9	73.8 ± 22.5	0.03
OCS dose in previous year >2 g	27 (10.4)	27 (18.5)	0.03
Inhaled steroid dose >0	158 (60.8)	107 (73.3)	0.01
Inhaled steroid dose >500	128 (49.2)	93 (63.7)	<0.01
Oral steroid dose >0	36 (13.8)	37 (25.3)	<0.01
Inhaled steroid dose	693.6 ± 720.1	972.3 ± 813.2	<0.01
Smoking status			
Never smoked	183 (70.4)	107 (73.3)	0.78
Former smoker	45 (17.3)	24 (16.4)	
Current smoker	32 (12.3)	15 (10.3)	

Data are presented as mean ± SD or number (%).

*Skin test reactivity to one or more allergens.

†P-values calculated with the Kruskal–Wallis or chi-squared tests.

FEV₁, forced expiratory volume in 1 s; OCS, oral corticosteroid; BMI, body mass index.

Table 2. Patient characteristics at baseline according to asthma severity

Variables	Asthma severity		P-value†
	Mild–moderate (n = 315)	Severe (n = 91)	
Age	41.4 ± 16.5	44.7 ± 15.8	0.12
Female	188 (59.7)	44 (48.3)	0.05
BMI	23.8 ± 4.6	25.3 ± 4.9	<0.01
BMI < 25	212 (67.3)	48 (52.8)	0.01
Atopy*	162 (51.4)	38 (41.8)	0.1
Rhinitis	223 (73.8)	68 (74.7)	0.86
At least one exacerbation	95 (30.2)	30 (33)	0.61
Duration of asthma (years)	17.6 ± 14.5	18.4 ± 14.9	0.78
FEV ₁	83.8 ± 17.3	55.1 ± 23.1	<0.01
OCS dose in previous year >2 g	20 (6.3)	34 (37.4)	<0.01
Inhaled steroid dose >0	192 (60.9)	73 (80.2)	<0.01
Inhaled steroid dose >500	153 (48.6)	68 (74.7)	<0.01
Oral steroid dose >0	37 (11.7)	36 (39.6)	<0.01
Inhaled steroid dose	696.5 ± 724.2	1130.8 ± 813	<0.01
Smoking status			
Never smoked	233 (74)	57 (62.6)	<0.01
Former smoker	43 (13.6)	26 (28.6)	
Current smoker	39 (12.4)	8 (8.8)	

Data are presented as mean ± SD or number (%).

*Skin test reactivity to one or more allergens.

†P-values calculated with the Kruskal–Wallis or chi-squared tests.

FEV₁, forced expiratory volume in 1 s; OCS, oral corticosteroid; BMI, body mass index.

0, the transitions thus being reduced for patients encoded by 1 in all four models. For BMI, the transition regression coefficient was -0.801 , which means that, in

terms of relative risk, an overweight patient had a risk divided by 2.23 of going from the unacceptable state to the acceptable state. The only variables that influenced transition from the acceptable to the unacceptable state were the dose of OCS during the year preceding inclusion and severity, which both accelerated the transition significantly.

In order to take into account potential interactions between BMI and the other variables, a multivariate model was performed including all four covariates (Table 3). In this model, only four coefficients were retained as statistically different from 0: the coefficients related to BMI ($\beta_{21} = -0.637$) and use of an OCS treatment ($\beta_{21} = -0.693$) for the transition from the unacceptable state to the acceptable state, and the coefficients related to severity ($\beta_{12} = 0.82$) and dose of OCS during the year preceding inclusion ($\beta_{12} = 0.498$) for the transition from the acceptable state to the unacceptable state. The main result is that, after adjustment on covariates associated with BMI, the transition from the unacceptable to the acceptable state was still reduced for overweight patients, the risk being divided by 1.89.

In order to evaluate the consequences of the model more fully, the curves representing the change in transition probability over time were analysed. These curves allow simple comparison of the transition probabilities for each covariate vector. For instance, Fig. 2A represents the transition probabilities for the two BMI groups from the unacceptable to the acceptable state for patients with covariates encoded as 0 (i.e. nonsevere asthma, without OCS treatment and with <2 g of OCS in the year preceding inclusion) and Fig. 2B represents the same transition probabilities for the covariates encoded as 1. In both groups, the probabilities of transition from the unacceptable to the acceptable state were lower for overweight patients. Moreover, as illustrated in Fig. 2A, the probability that patient with BMI < 25 would achieve acceptable control stabilized more quickly (200 days) than it did for overweight patients (300 days).

Discussion

In this study, the influence of BMI on the evolution of asthma control was evaluated. A single covariate Markov model was fitted in order to evaluate the influence of BMI on the evolution of asthma control. The results indicated that BMI > 25 kg/m² reduces the transition probability from the unacceptable state to the acceptable state. However, the reverse transition was not significantly affected by BMI.

As the influence of BMI in a single covariate model could have been fortuitous, a descriptive analysis of the data at inclusion were performed in order to identify any associations between BMI and other potential risk factors. The BMI was indeed positively associated with

Table 3. Estimation of regression coefficients β_{ij} (with estimated SDs and P -values for testing ' $\beta_{ij} = 0$ ' given in brackets) for the single covariate model (univariate model) and for the multivariate model with four covariates

Type of transition	Covariate	Univariate model, β (SD) (Wald, P -value)	Multivariate model, β (SD) (Wald, P -value)
Acceptable to unacceptable state (1 to >2)	BMI	−0.129 (0.247) (0.60)	−0.174 (0.278) (0.53)
	OCS during last year	0.651 (0.262) (0.01)	0.498 (0.299) (0.10)
	OCS	0.110 (0.269) (0.68)	−0.422 (0.305) (0.17)
	Severity	0.665 (0.272) (0.04)	0.820 (0.305) (<0.01)
Unacceptable to acceptable state (2 to >1)	BMI	−0.801 (0.184) (<0.01)	−0.637 (0.219) (<0.01)
	OCS during last year	−0.852 (0.212) (<0.01)	−0.312 (0.266) (0.24)
	OCS	−1.002 (0.209) (<0.01)	−0.693 (0.248) (<0.01)
	Severity	−0.726 (0.203) (<0.01)	−0.062 (0.255) (0.81)

OCS, oral corticosteroid; BMI, body mass index.

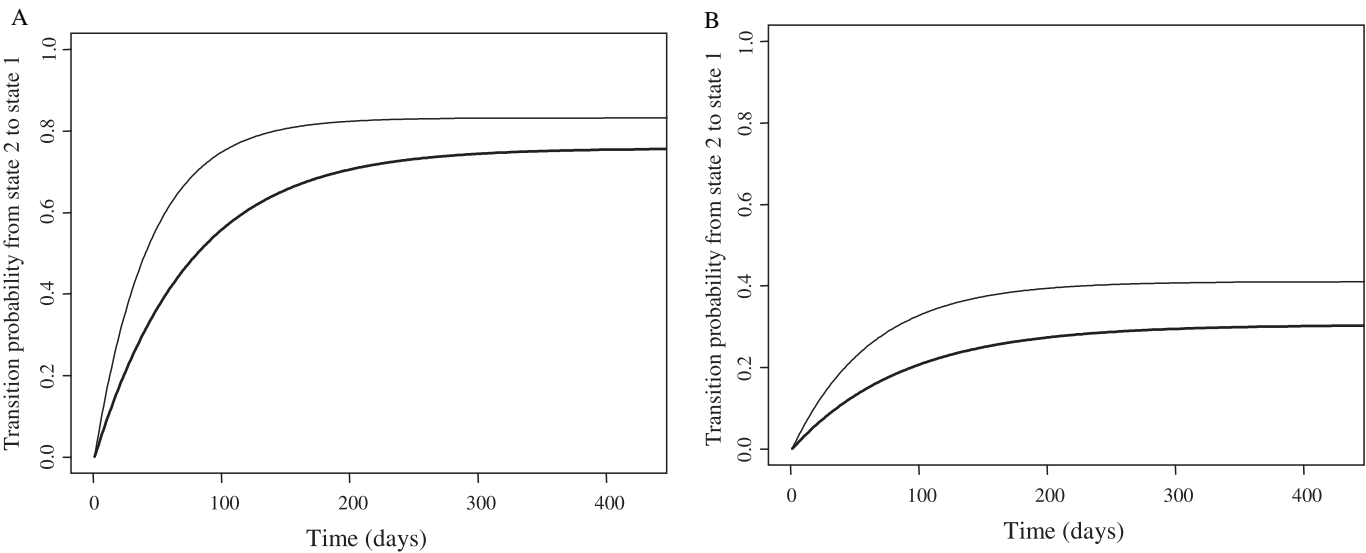


Figure 2. Transition probabilities from state 2 to state 1: (A) for patients with nonsevere asthma, without oral corticosteroid (OCS) treatment and with < 2 g of OCS in the year preceding inclusion; (B) for patients with severe asthma, with a OCS treatment and with more than 2 g of OCS in the year preceding inclusion. BMI < 25 (thin line); BMI ≥ 25 (thick line).

other variables, such as asthma severity, and treatment intensity and history.

In order to reduce potential bias introduced by confounding variables in the estimation of the relationship between BMI and asthma control, a multivariate model was evaluated, in which the daily dose of OCS and the total dose of OCS over the year preceding inclusion were included as covariates. Moreover, as severe asthma was associated with higher BMI (16, 17), severity was also included into the model.

The association between high BMI and poor asthma control was confirmed in the multivariate analysis. After adjustment for asthma severity, daily OCS dose and history of OCS use, high BMI was still associated with a lower probability of returning to acceptable control.

From a clinical point of view, the fact that BMI involved in one change (unacceptable to acceptable) but not in the other is surprising. This result is statistically

possible but it is difficult to find a clinical interpretation. Note that this result has to be taken carefully because it is obtained with an observational study. Therefore, it is necessary to perform further investigation in order to improve our knowledge of the relation between asthma control and BMI.

Obesity *per se* is known to induce respiratory symptoms, which mimic asthma and this fact has been used by some epidemiologists to question the relationship between asthma prevalence and obesity (27), in spite of the demonstration of bronchial hyperactivity in obese subjects with asthma (28). Although the estimation of asthma severity from patient self-report is the most significant limitation in epidemiological studies, this is not the case in our study when asthma diagnosis was ascertained clearly for each patient during a clinic visit. Moreover, the asthma patients in this database were principally overweight rather than obese, the number of obese patients (BMI > 30) being low ($n = 40$). This makes potential

confusion between symptoms of asthma and obesity much more improbable.

Excess weight could unconsciously lead to a less intensive treatment regimen being prescribed or to poorer compliance in order not to increase a potential adverse effect of treatments. However, such a bias should also be present in overweight patient with good asthma control, where suboptimal treatment would be expected to increase the probability escape from good asthma control, which was not observed.

During the planning of the study, the number of covariates that would be analysed and included in the model was considered carefully. There is a clear trade-off between the number of covariates assessed, the number of patients in the database and the number of health state transitions that can be analysed with appropriate power. For this reason, the number of health states was reduced to two in order to allow assessment of a larger number of covariates. This reduction of control to a simple binary variable is clinically relevant, because uncontrolled asthma is clearly different from controlled asthma. Moreover, the Canadian guidelines (24) recommend using this cut off point for adapting chronic treatment at each visit.

It was thus possible to evaluate four covariates. Smoking cessation was not assessed and this could be a source of bias as it could lead to an increased BMI. However, this should be a cause rather than a consequence of weight gain. Moreover, it is possible that smoking cessation increases the efficacy of ICS and thus improves control (29). The daily dose of ICS was not included as a variable in the model firstly because this is a part of the definition of severity and secondly because no association between ICS and BMI has been described although this aspect merits further study (30).

The Markov model is particularly useful in analysing risk factors in cohort studies and has been applied successfully to the study of lung cancer, HIV infection (25) and the cost of asthma (26). The results, in terms of relative risk and transition probability curves are practical and easy to understand. However, there are some inherent biases as a result of observational data (confusion, selection). Moreover, the Markov assumption is somewhat restrictive in that it supposes that the probability of changing state depends only on the current state and not on previous history of state transitions.

The time homogeneity assumption is also restrictive but necessary for the estimation and interpretation of

parameters. The model supposes that transition occurs at consultation time and that censoring is independent of the state process. However, our previous study (21) shows that the model is indeed well adapted to the data, despite these limitations. Moreover, in the two-state model, a comparison of observed and expected counts at different times using a chi-square test indicated a good fit for the model (results not shown).

Markov models with covariates are rarely used in the study of respiratory diseases. However, at a time when other parameters, such as biomarkers (level of bronchial hyperresponsiveness (31), assessment of eosinophils in sputum (32, 33) and nitric oxide (NO) in exhaled air (34)), are being investigated as tools for asthma management, such models could be very useful and promising to predict the potential of such criteria for maintaining patients at an acceptable level of control over a long period of time.

This study clearly demonstrated that overweight asthmatics may remain uncontrolled despite optimal pharmacological management and had may be less likely to achieve satisfactory control over a given period of time when compared to patients with a normal BMI.

This result should be kept in mind when implementing guidelines or in routine management of asthma. It certainly indicates that dietary advice is essential for the management of long-term asthma, along with pharmacological interventions. In asthmatic patients who are difficult to treat, more frequent and regular consultations may be required. Diet-oriented strategies should be investigated, especially in teenagers and young adults, to appreciate better their impact on asthma control and potentially on the natural history of the disease (35).

As recently reported, the link between obesity and asthma appears to be quite strong, even if definitive proof is still lacking (30). This study is in favour of a link between, on the one hand, severity and control of asthma and, on the other hand, weight. Excess weight appears to be an independent determinant of uncontrolled asthma. The consequences in terms of management of asthmatics are important.

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