

ORIGINAL ARTICLE

# The Relationship between Pharmaceutical Costs, Disease Severity, and Health-Related Quality of Life in Asthmatics in Swedish Primary Care

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The objective of this study is to explore the relationship between variables that may influence pharmaceutical costs in asthma and to generate a predictive model for these costs in primary health care. The understanding of these relationships is important since costs of drugs may place unnecessary economic burden on patients and society. During 2003, prospective clinical data were collected from 105 patients in 24 primary health care centers located in Stockholm. The relationships between cost of drugs and quality of life, lung function, and asthma severity were analyzed in a regression model. Twenty-three percent of the observed variation in pharmaceutical costs could be explained by asthma severity, disease-specific quality of life, and clinical practice. There was a weak inverse correlation between pharmaceutical costs, generic quality of life, and lung function. Even when severity was accounted for, there were large variations in costs between different primary health care units.

**Keywords** economics, asthma, drugs, HRQoL, primary care

## INTRODUCTION

The prevalence of asthma has increased worldwide. In Sweden the prevalence was estimated to be 6% to 8% in the late 1990s (1), yet, the hospitalizations and emergency visits have decreased. Most asthmatics are nowadays managed in primary care (2). According to a recent report (3), asthma is the 13th diagnosis on the top-20 list in primary care. Nevertheless, the studies that form the evidence base for treatment of asthma are usually performed in strictly selected patient groups, possibly with more severe asthma but less comorbidity, treated in chest clinics. Little is known about optimal pharmaceutical treatment and care in primary care asthmatics.

Evaluation of costs and benefits of treatments is essential for priority setting and development of health care programs and guidelines. When assessing the effects of pharmacotherapy for asthma in clinical trials, measurements of lung function, such as forced expiratory volume in 1 second (FEV<sub>1</sub>), are often used. Nevertheless, according to observations concerning chronic obstructive pulmonary disease (COPD), this outcome measure is not always fully reliable in primary care (4). Asthma seldom kills the patient but generally affects the quality of life of the patient over long periods of time, often several decades (5). However, health-related quality of life (HRQoL) is only weakly correlated to lung function in asthmatics (6). Therefore, measuring of HRQoL is a valuable complement to clinical assessments of disease severity to assess the health care needs, the effectiveness of intervention, and in cost-utility studies (7). During the last few years HRQoL has emerged as an outcome measure in clinical trials

but is not yet established in clinical practice. Using HRQoL questionnaires in clinical practice ensures focus on the patient rather than the disease (8). Indeed, the patients' own view on their asthma severity seems to correlate better with HRQoL measurements than with objective measures, such as FEV<sub>1</sub> (9).

Cisternas et al. show in their study that asthma-related costs are extensive and determined largely by pharmaceuticals and work loss (10). Barnes et al. have shown that the costs of asthma largely depend on suboptimal treatment, i.e., that medications are underutilized or incorrectly used (11). Mild to moderate asthmatic patient's pharmaceutical costs have previously been stated to make up approximately 37% of the total direct costs of asthma (11). In Sweden, the cost of asthma drugs has increased by nearly 300 % since 1980 (1). Since drugs are subsidized and the cost of drugs may place unnecessary economic burden on patients and on the health care system, an increased understanding of factors influencing pharmaceutical costs is important.

Therefore, the objective of this hypothesis-generating study is to explore the relationships between variables that may influence the pharmaceutical costs in asthmatic patients treated in primary care and to generate a predictive model for these costs. This article aims to answer the following questions:

- Is the cost of drugs related to asthma severity in primary care?
- Is the cost of drugs related to disease-specific health-related quality of life?
- Is the cost of drugs related to generic HRQoL?

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To our knowledge this is the first study exploring such relationships in asthmatic patients treated in primary care.

## METHODS

*Patient Selection and Study Population*

The present observational study was a part of a prospective multi-center study of quality of life among patients with asthma in 24 primary health care centers (PHCCs) located in the city and suburbs of Stockholm (12). Patients with different socioeconomic backgrounds and study centers with doctors and nurses with limited or no experience of research routines, i.e., ordinary general practices, were included. Patients 18 years of age and older who were considered by the general practitioner as having asthma were consecutively asked to participate in the study when they visited the enrolled primary health care centers (regardless of the reason for that particular visit). This patient selection allowed us to focus on asthmatics actually seeking care at PHCCs. Exclusion criteria were malignant disease, severe psychiatric disease, and dementia. Patients with inability to understand written Swedish were also excluded because patients were required to self-complete versions of HRQoL questionnaires.

A total of 117 patients between 18 to 86 years of age were included; 12 patients were excluded from the analysis; 9 patients did not complete the study; and 3 patients had missing data on drugs. The study group that could be evaluated thus comprised 105 patients (Figure 1).

*Study Design*

The patients visited the PHCC on one occasion, and HRQoL was estimated using the generic questionnaire Short Form-36 Health Survey (SF-36) (13) and the asthma-specific instrument Asthma Quality of Life Questionnaire with standardized activities, AQLQ(S) (14). Anti-asthmatic drugs and dosages used during the week preceding the visit were recorded. Pulmonary function was estimated using spirometry FEV<sub>1</sub> or peak expiratory flow (PEF) meters according to the local routines that were employed by the participating PHCCs for evaluation of their asthmatic patients. All variables for an individual were collected at the same time-point

since symptoms, quality of life, pulmonary function, and use of medication will vary over time.

*Costs*

Only costs of used drugs were explored in the present study. The cost of the daily dose of each drug was calculated per patient and summarized to total daily pharmaceutical costs per patient. If the name of the drug was recorded but not the dosage, we used the cost of a defined daily dose (DDD) of the drug (15). Unit costs for drugs were obtained from the Swedish pharmaceutical desk reference, FASS, 2003 (16); 1 USD = 8.1 SEK (2003).

*Asthma Severity*

Asthma severity was classified according to the Global Initiative for Asthma (GINA), guidelines (17). The GINA classification has four categories of severity and takes both symptoms and asthma treatment into account. The four categories of asthma severity are (1) intermittent, (2) mild persistent, (3) moderate persistent, and (4) severe persistent asthma.

*Health Related Quality of Life Instruments*

**SF-36.** SF-36 was included in this study as a generic measure of HRQoL to characterize the study population (18). It consists of eight multi-item domains, which may be combined into two summary scores reflecting two core aspects of HRQoL (physical and mental health). Calculations were performed using the algorithm provided by the developer (13). The score is from 0 to 100, where 100 indicate perfect health. The SF-36 has acceptable internal consistency and cross-sectional validity in asthma (19, 20).

**AQLQ(S).** Asthma-specific HRQoL, was assessed by the 32-item Asthma Quality-of-Life Questionnaire with standardized activities, AQLQ (S), which is be valid for measurements of health-related quality of life in asthma (12, 14). The AQLQ(S) yields a total score between 1 and 7, where 7 is the best and 1 is very poor.

*The Stockholm Formulary (Wise List)*

The Wise List is a manual for drug recommendations for care providers in Stockholm County. The rationale is to increase knowledge about rational and cost-effective use of drugs and to provide producer-independent drug information and education to prescribers and staff within the public health care system. In 2003, salbutamol, terbutaline, formoterol, ipratropiumbromide, budesonide, betamethasone, and prednisolone were recommended for the treatment of asthma.

*Clinical Practice*

For the explanatory variable Clinical Practice, we created several dummy variables that served as variables in regression analyses. The PHCCs themselves identified, by their own definitions, if they had an asthma practice (D<sub>1</sub>) or not. PHCCs performing spirometric evaluations on at least 75 % of their study patients were considered as performing spirometric evaluations (D<sub>2</sub>). Public or private provision of the primary health care centre (D<sub>3</sub>) was also taken into account. Finally, asthma severity (D<sub>4</sub>) according to the GINA classification was dummy coded. The most severe step was omitted and used as base in the regression. The remaining severity

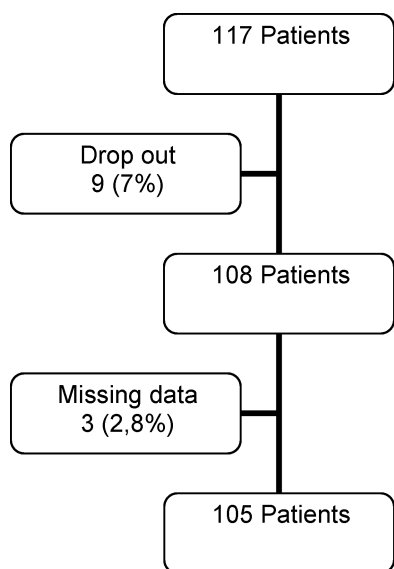


FIGURE 1.—Patients entered in the study.

steps were coded as follows: intermittent (D<sub>4\_1</sub>), mild (D<sub>4\_2</sub>), and moderate (D<sub>4\_3</sub>).

### Statistical Analysis

Correlations for descriptive purposes were calculated using Spearman correlation coefficients, since both the untransformed variable costs and asthma severity according to the GINA classification were heavily skewed. Before these variables were used in the main analysis, multiple regression, and correlation, cost data were transformed by taking the square root of costs. The distributions of the transformed costs were close to normal.

**Regression diagnostics.** Before other analyses, the data was examined to ensure that the assumptions for multiple regression were not violated. Histograms, normality plots, and scatter plots of predicted values versus residuals were made and examined. Before further analysis using a regression model, the relationships between variables were checked for multi-colinearity by calculating variance inflation factor values and tolerance values. Tolerance refers to the amount of variability of the selected independent variable that is not explained by the other independent variables. It is obtained by making each independent variable a dependent variable and using it in a regression against the remaining independent variables. Tolerance values approaching zero indicate that the variable is highly colinear with the other predictor variables. The variance inflation factor (VIF) is inversely related to the tolerance value: Large VIF values (a frequently used threshold is 10.0, which corresponds to a tolerance of 0.10) indicate a high degree of colinearity or multi-colinearity among the independent variables (21).

**Regression analysis.** A multiple linear regression model was used to explore the relationship between the dependent variable transformed total cost of drugs per day per patient and the independent variables asthma severity, AQLQ(S) total score, and use of spirometry. Univariate correlation analyses were first performed for a number of variables. Variables shown to be significantly associated in the correlation analysis ( $p < 0.05$ ) were included in a multivariate regression model. We built our regression model stepwise, using backward elimination, i.e., the model starts with all variables and eliminates one variable at a time. The model selected was based on the largest adjusted  $R^2$ , since adjusted  $R^2$  provides a better measure of "goodness of fit" than  $R^2$ . Adjusted  $R^2$  values take into account the fact that a regression model always fits the particular data on which it was developed better than it fits population data (22).

For data analysis, the computer program SPSS (release 12.01; SPSS Inc. Chicago, Ill, USA) was used.

### Ethics

All participating patients signed an informed consent. The study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

## RESULTS

### Descriptive Analysis

The demographic characteristics of the study population are shown in Table 1. The majority of patients were

TABLE 1.—Demographic characteristics of the study population.

|                                                         | Total              |
|---------------------------------------------------------|--------------------|
| Subjects, <i>n</i> (%)                                  | 105                |
| Sex M/F, <i>n</i> (%)                                   | 39/66 (37/63)      |
| Age, mean (range) year                                  | 48.1 (18–86)       |
| Lung function                                           |                    |
| FEV <sub>1</sub> , % predicted<br>(mean, <i>n</i> = 68) | 87.60              |
| PEF, % predicted<br>(mean, <i>n</i> = 32)               | 85.31              |
| Missing data, <i>n</i>                                  | 5                  |
| No medication, <i>n</i>                                 | 2                  |
| Total daily cost of drugs per patient SEK <sup>a</sup>  |                    |
| Mean                                                    | 13.66              |
| Median (interquartile range)                            | 10.94 (4.64;18.01) |
| Range                                                   | 0–75.34            |
| Asthma severity, % <sup>†</sup>                         |                    |
| Intermittent                                            | 1.9                |
| Mild                                                    | 7.6                |
| Moderate                                                | 20.0               |
| Severe                                                  | 70.5               |

<sup>a</sup>1 USD = 8.1 SEK (2003).

<sup>†</sup>Classification according to GINA guidelines.

female (63 %), 18 to 65 years of age (mean age 48 years).

The majority of patients (70.5 %) were classified as having severe asthma according to GINA guidelines. The pharmaceutical costs varied between 0 and 75.34 Swedish krona (SEK) (0–9.3 USD).

### Relationship between Costs and Asthma Severity

The correlation between the patient's total costs of asthma medication per day and asthma severity is presented in Figure 2. Among severe asthmatics, the cost of asthma medication per day ranged from 0.15 SEK to 75.34 SEK (0.02 – 9.18 USD), with a median of 12.59 SEK (1.55 USD).

The correlations between total costs of asthma medication per day and asthma severity (0.39), AQLQ(S) (0.35), and Short Form-36 Health Survey (SF36) Physical Index (0.23) are statistically significant. However, SF36 Mental Index (0.02), age (0.23), sex (0.075), PEF (0.18), and FEV<sub>1</sub> (–0.03) did not correlate statistically significantly with total costs of asthma medication.

Since the costs were skewed, we used transformed costs in the parametric correlation analysis (Table 2). Asthma severity, age, AQLQ(S), Physical Index of the SF36, and "using spirometry" correlated statistically significantly with the transformed costs. Gender influence could not be analyzed owing to the small sample size. The AQLQ(S) and the SF36 Physical Index correlated strongly with each other, but the correlation was not of the magnitude that one or the other should be left out of the regression analysis (Table 2).

A multiple linear regression model was used to describe the relationship between the dependent variable total transformed cost of asthma medication per day and the independent variables asthma severity, dummy variables labeled D<sub>4</sub>, AQLQ(S), and dummy D<sub>2</sub>, regressor variable for the explanatory variable clinical practice. The results of the regression analyses are summarized in Table 3. The model explains 23 % of the variation.

The colinearity statistics for the initial and final reduced model are summarized in Table 4. None of the tolerance or the VIF values implies any serious problems with colinearity.

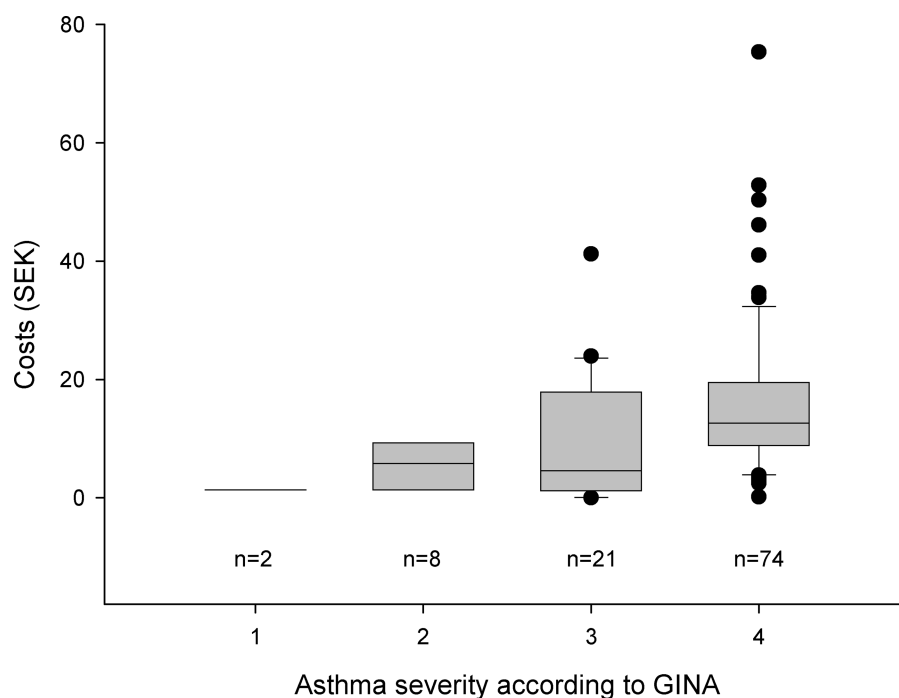


FIGURE 2.—Correlation between total costs of asthma medication per day and asthma severity according to GINA. Spearman's rho correlation coefficient = 0.39 ( $p = 0.01$ ).

### Impact of Clinical Practice

To study the impact of medical or clinical practice, we examined the cost of drugs per PHCC (Figure 3). Figure 3 shows the total cost of asthma medication per day (median) per PHCC. Three of the PHCCs (numbers 5, 14, and 21) show a larger median cost than the others. To go further and test whether the results would be different if the physicians implemented the Wise List correctly, we transformed the medication as recommended in the Wise List. The results did not change significantly (not shown). Eight of the patients used montelukast, which could not be substituted according to the Stockholm formulary since no other antileukotriene is currently registered in Sweden. The differences between total costs of asthma drugs for all patients compared to the costs if the drugs had been taken according to the Wise List were calculated. The difference

was minus SEK 30.21 (3.73 USD) per day for all patients together.

A possible cause for the difference between the PHCCs could be the case mix. Therefore, we examined the differences in costs for medication for severe asthma. However, the distribution of costs between different PHCCs was almost unchanged (Figure 4).

### DISCUSSION

We used a multiple linear regression for an explanatory approach, and the final model showed that 23% of the observed variation in pharmaceutical costs of asthma in primary care could be explained by asthma severity, disease-specific quality of life, and clinical practice.

In our study, the correlation between asthma severity and costs was strong. However, the pharmaceutical costs were

TABLE 2.—Correlations between asthma severity, AQLQ(S), age, sex, SF-36 Physical Index, SF-36 Mental Index, Asthma Practice ( $D_1$ ), spirometry usage ( $D_2$ ), principal ( $D_3$ ) and transformed Costs.

|                        | Transfor med costs | Asthma severity (GINA) | Age     | Sex   | AQLQ(s) Total score | SF-36 Physical | SF-36 Mental | $D_1$  | $D_2$ | $D_3$ |
|------------------------|--------------------|------------------------|---------|-------|---------------------|----------------|--------------|--------|-------|-------|
| Transformed costs      | 1.00               |                        |         |       |                     |                |              |        |       |       |
| Asthma severity (GINA) | 0.42**             | 1.00                   |         |       |                     |                |              |        |       |       |
| Age                    | 0.26**             | 0.16                   | 1.00    |       |                     |                |              |        |       |       |
| Sex                    | -0.09              | -0.15                  | -0.02   | 1.00  |                     |                |              |        |       |       |
| AQLQ(s) total score    | -0.35**            | -0.43**                | -0.22*  | -0.05 | 1.00                |                |              |        |       |       |
| SF-36 Physical Index   | -0.26**            | -0.33**                | -0.20*  | 0.04  | 0.64**              | 1.00           |              |        |       |       |
| SF-36 Mental Index     | -0.04              | -0.20*                 | 0.12    | -0.05 | 0.33**              | 0.05           | 1.00         |        |       |       |
| $D_1$                  | 0.09               | -0.02                  | 0.07    | -0.06 | 0.04                | 0.23*          | -0.04        | 1.00   |       |       |
| $D_2$                  | -0.30**            | -0.22*                 | -0.32** | 0.13  | 0.09                | 0.01           | -0.04        | -0.17  | 1.00  |       |
| $D_3$                  | 0.05               | 0.04                   | -0.15   | 0.16  | 0.01                | 0.14           | -0.09        | -0.24* | 0.25* | 1.00  |

\*Correlation is significant at the 0.05 level (2-tailed).

\*\*Correlation is significant.

TABLE 3.—Multiple linear regression models of cost of asthma medication.

| Parameter/<br>variable  | Initial model                       |       |                |                | Final reduced model                 |       |                |                |
|-------------------------|-------------------------------------|-------|----------------|----------------|-------------------------------------|-------|----------------|----------------|
|                         | $\beta$ Standardized<br>coefficient | SE    | <i>t</i> value | <i>p</i> value | $\beta$ Standardized<br>coefficient | SE    | <i>t</i> value | <i>p</i> value |
| Constant                | 4.754                               | 1.417 | 4.987          | <0.000         | 5.285                               | 0.683 | 7.733          | <0.000         |
| SF-36 Physical<br>Index | −0.038                              | 0.018 | −0.322         | 0.748          |                                     |       |                |                |
| AQLQ(s)                 | −0.131                              | 0.170 | −1.050         | 0.296          | −0.172                              | 0.130 | −1.800         | 0.075          |
| D <sub>2</sub>          | −0.218                              | 0.307 | −2.295         | 0.024          | −0.248                              | 0.286 | −2.797         | 0.006          |
| D <sub>4-1</sub>        | −0.160                              | 1.001 | −1.786         | 0.077          | −0.172                              | 0.988 | −1.948         | 0.054          |
| D <sub>4-2</sub>        | −0.208                              | 0.528 | −2.264         | 0.026          | −0.204                              | 0.524 | −2.240         | 0.027          |
| D <sub>4-3</sub>        | −0.207                              | 0.369 | −2.144         | 0.035          | −0.210                              | 0.367 | −2.192         | 0.031          |
| Age                     | 0.096                               | 0.009 | 1.000          | 0.320          |                                     |       |                |                |

only weakly correlated to health-related quality of life, as assessed by AQLQ(S) and SF-36 scores, or lung function in terms of PEF and FEV<sub>1</sub>.

Although costs correlated strongly with asthma severity, pharmaceutical costs per patient and day differed considerably between the PHCCs, even among patients with similar asthma severity. The cost of drugs in the health care sector (i.e., hospitals, primary health care centers) and for the patients can vary for different reasons, and the economic consequences can be substantial for patients with asthma as well as for the society (23). In Sweden, there is a uniform national ceiling on the total amount that a patient pays during a 12-month period (out-of-pocket ceiling) for health care, as well as for subsidized medications. Reimbursements for the visits are equal for all PHCCs in this study.

A multitude of factors, such as improper prescribing (24), compliance (25), use of generic drugs, guidelines, clinical practice (23), the meeting between patient and doctor (26), and gender (27) can influence pharmaceutical costs. There may thus be several explanations for the large variations in drug expenditures between different PHCCs. When analyzing only patients with severe asthma, the variation in costs between the PHCCs was highly fluctuating from SEK 0.15 to 30.85 per patient and day. In Figures 3 and 4, the median cost of drugs per PHCC is shown to vary considerably from one PHCC to another. One of the explanations can be differences in clinical practice. It is very likely that clinical practice has medical, economic, and equity consequences. Physicians have previously been shown to experience management of asthma in qualitatively different ways (23, 28). However, the existence of differences in clinical practice (24–26) does not tell us what is right or wrong—be it more or fewer medications (23). Even if we do not know what the adequate level of medication should be, the large variation by itself indicates

inefficiency. Other studies have shown similar results (23). Over- or underutilization of drugs can have a great impact on patients own costs and quality of life (11). Correct utilization of drugs is a question of importance to effective resource allocation of scarce resources in health care.

Interestingly, ability to perform pulmonary function tests at the PHCC influenced the pharmaceutical costs in the regression/correlation. We regard the possession of a spirometer as a marker of intention. However, being able to perform spirometric evaluations in a majority of patients indicates the presence of material prerequisites as well as competence. Performing spirometric tests might lead to better diagnoses and as a consequence better adjusted medications and lower pharmaceutical costs. This hypothesis remains to be tested in further research.

Another factor that can influence pharmaceutical costs is low degree of compliance with medication (29). Important factors can influence a patient's compliance such as age, gender, duration of the disease, the attitude of the staff, and information/education about asthma (30). It has been suggested that only 50% of patients with chronic diseases take their medicines (25). Stållberg reported, that 76% of the asthmatics claimed that they follow the prescriptions of the physician, although a large discrepancy was found between the prescriptions and the actual use of medicines (31). Another study found that 42% of the patients stated that they were non-compliers (30). Also, drugs can be prescribed but not collected from the pharmacy, and if collected from the pharmacy, not used in a correct way. It is important to note that the present study is based on the patients' own record of drugs actually used during the week preceding the visit. By collecting data during the visit we probably obtained the best possible data quality. The patients were asked about what kind of drugs they had actually been using the last week before the visit, not about what they had been prescribed. Further costs could be imposed by drugs that are collected but not used.

That the majority of patients in the study were women was an expected finding since this is often the case in asthma studies. However, it is remarkable that 70.5 % of the patients in the PHCCs were found to have severe asthma. In part, this reflects the skewed distribution of visits to PHCCs by patients with severe asthma, hence not reflecting the actual prevalence in the population. Also, it may be attributed to properties of the GINA classification, which is based on symptoms and drug use. Treatment with inhaled corticosteroids and long-acting beta<sub>2</sub> agonists early in the course of the disease, which is common in several countries including Sweden,

TABLE 4.—Colinearity statistics.

| Variable                | Initial model |                                 | Final reduced model |                                 |
|-------------------------|---------------|---------------------------------|---------------------|---------------------------------|
|                         | Tolerance     | Variance inflation factor (VIF) | Tolerance           | Variance inflation factor (VIF) |
| SF-36 Physical<br>Index | 0.538         | 1.860                           |                     |                                 |
| AQLQ(s)                 | 0.487         | 2.052                           | 0.818               | 1.222                           |
| D <sub>2</sub>          | 0.832         | 1.201                           | 0.949               | 1.053                           |
| D <sub>4-1</sub>        | 0.937         | 1.067                           | 0.954               | 1.048                           |
| D <sub>4-2</sub>        | 0.894         | 1.118                           | 0.901               | 1.110                           |
| D <sub>4-3</sub>        | 0.809         | 1.236                           | 0.810               | 1.234                           |
| Age                     | 0.823         | 1.215                           |                     |                                 |

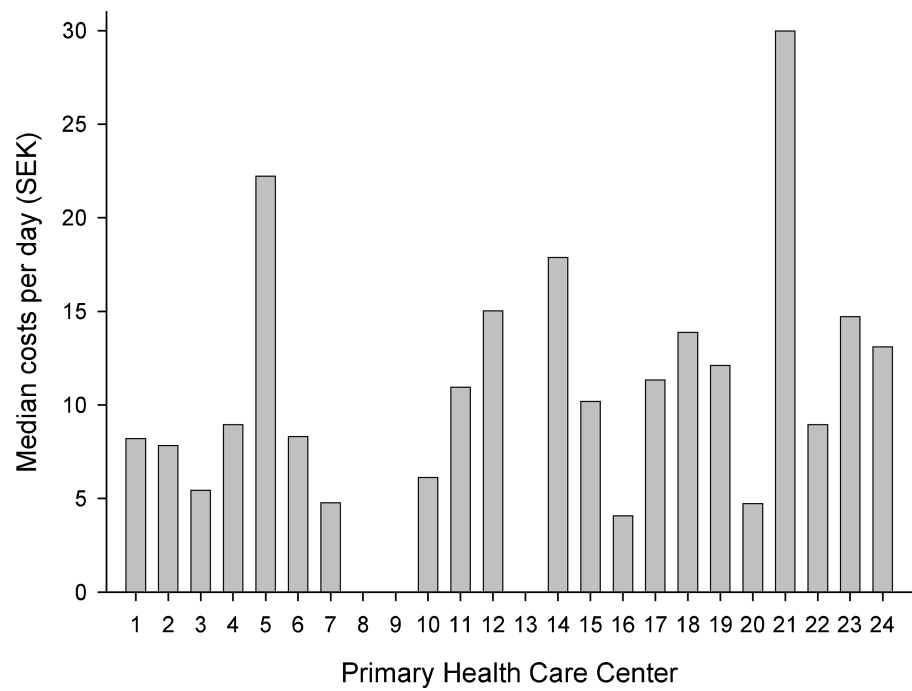


FIGURE 3.—Total cost of asthma medication per day per PHCC (Primary Health Care Center), median. 3 PHCCs failed to include patients who could be evaluated.

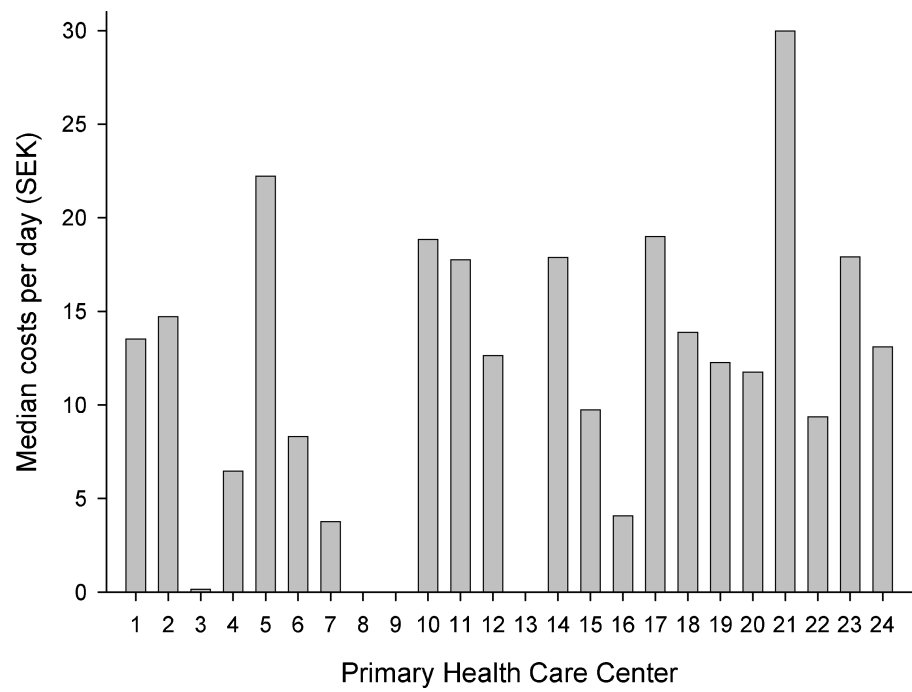


FIGURE 4.—Total cost of asthma medication per day per asthma severity within step 4 (severe asthma).

will lead to classification of the disease as moderate to severe despite few symptoms. Under these circumstances, a subdivision of severe asthma into different levels would improve the classification. Data are nevertheless representative of patients seeking care. The recruitment of PHCCs was voluntary, which could influence the result, in the sense that centers willing to participate may differ from those not willing to participate.

### CONCLUSION

The final model showed that 23% of the observed variation in pharmaceutical costs of asthma in primary care could be explained by asthma severity, disease-specific quality of life, and clinical practice. The strongest correlation in the material was found between pharmaceutical costs, asthma severity, disease-specific quality of life, and clinical practice. We expected to find a strong positive correlation between pharmaceutical costs and generic quality of life, and pharmaceutical costs and lung function, but in contrast, we found only weak inverse correlations. Another somewhat puzzling finding was the large variation in costs between the PHCCs regardless of asthma severity. This finding could be addressed in future studies.

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