Title
Measures of asthma control and quality of life: longitudinal data provide practical insights into their relative usefulness in different research contexts

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Abbreviations
HRQOL = health related quality of life
AQLQ-M = Marks' asthma quality of life questionnaire
SF-36 = SF-36 health survey
PCS = physical components summary (SF-36 scale)
MCS = mental components summary (SF-36 scale)
SABA = short-acting beta agonist
ICS = inhaled corticosteroids
LABA = long-acting beta agonist
NSW = New South Wales

Abstract

*Purpose***:** To further our understanding of relationships between asthma control and health-related quality of life (HRQOL) and provide insights into the relative usefulness of various measures in different research contexts. We present a conceptual model and test it with longitudinal survey data.

*Methods***:** Participants recruited via population sampling and hospital emergency departments completed questionnaires every six months for up to three years. Measures included: sleep disturbance, use of short-acting beta agonists (SABA), activity limitation, urgent medical visits, hospital use, Marks' asthma quality of life questionnaire (AQLQ-M) and the SF-36 health survey. Correlation analysis and multilevel models tested predictions from the conceptual model.

*Results***:** 213 people with asthma aged 16-75 years provided 967 observations. Correlations between asthma control and asthma-specific HRQOL were stronger than those between asthma control and generic HRQOL. The asthma control variables explained 54%-58% of the variance in asthma-specific HRQOL and 8-25% of the variance in generic HRQOL. Activity limitation was the main contributor to between-person variation, while sleep disturbance and SABA use were the main contributors to within-person variation.

*Conclusions***:** Sleep disturbance and SABA use may be most useful in evaluating treatment effectiveness, while activity limitation may be better when monitoring the impact of asthma in populations.

Introduction

The impact of asthma on health-related quality of life (HRQOL) is influenced by the severity of the disease and the degree to which it is controlled. While asthma severity is not directly measurable, it can be inferred from the amount and type of treatment required to maintain asthma control and the observed level of control [1-3]. Observable indicators of asthma control include the frequency and severity of daytime and night-time symptoms, the extent of activity limitation due to asthma, the level of lung function, and the frequency with which short-acting bronchodilator (or "reliever") medication is required [4-6]. Similarly, HRQOL is not directly measurable, but can be inferred from self-report of symptoms and their impact on patients' ability to function physically, socially and emotionally. A number of HRQOL questionnaires are available; some measure the specific impact of asthma (disease-specific instruments) while others address the impact of health impairment generally (generic instruments) [7, 8].

There is some evidence about the relationship between HRQOL and asthma control. Vollmer et al [9] found that perceived asthma control, activity limitation due to asthma, night waking due to asthma and overuse of reliever medication were all correlated with asthma-specific HRQOL, and all except reliever overuse correlated with generic HRQOL. Katz et al found that the number of life activities affected by asthma and the individual's perceived control of asthma explained variations in asthma-specific HRQOL, cross-sectionally and longitudinally [10, 11]. Chen et al [12] found that the number of asthma control problems at baseline was a significant predictor of asthma-specific and generic HRQOL 12 months later, after adjusting for other covariates at baseline (lung function, severity, demographic characteristics and co-morbidity). Change in control from baseline to 12 months was also a significant predictor of asthma-specific but not generic HRQOL, after adjusting for baseline control [12]. However, the relationship is complex. There is evidence that the relation between asthma control and HRQOL is altered by effective treatment [13]. Further, factor analysis on questions from commonly used measures of severity, control and HRQOL suggests that these questionnaires measure separate but related domains for generic HRQOL, asthma-specific HRQOL and asthma control, but do not clearly identify discrete domains for control and severity [5].

The aim of this paper is to generate hypotheses from a conceptual model of the relationships between various aspects of asthma control and HRQOL, to test them in a cohort with asthma of varying severity, and to discuss the implications in terms of which constructs might provide the best outcome measures for monitoring the effect of treatment and for evaluating new interventions.

Conceptual model

Asthma control and HRQOL are part of a dynamic system involving the individual, their environment and their treatment (Figure 1). Innate asthma severity is likely to remain relatively stable or change only slowly over a person's life-time [14]. Environmental factors, such as exposure to viral infections [15], allergens [16] or both [17], may cause acute exacerbations or periods of poor asthma control. Treatment aims to ameliorate the manifestations of both the chronic state and acute exacerbations. The degree to which treatment is effective determines the level of asthma control, which in turn determines the amount of treatment required. When this feedback system works well it minimizes the frequency and intensity of symptoms and titrates the medication requirement to the

appropriate level. When asthma is well controlled, asthma symptoms are maintained at the lowest levels possible and the impact of asthma on HRQOL is minimised. Poor function of the feedback system equates to poor disease management, which results in poor control of asthma and/or over- or under-treatment. These effects flow on to physical, emotional and social functioning. Because an individual's experience of illness and perception of its impact is subjective, the self-report of symptoms and HRQOL is influenced by personality traits and ability to adapt and cope [18]. Other factors such as co-morbidities and life events also influence quality of life and hence dilute the relative impact of asthma on generic HRQOL.

This conceptual model suggests a series of *a priori* expectations:

- Asthma control should have a more direct impact on asthma-specific HRQOL measures than on generic measures. Thus we expect correlations between asthma control and asthma-specific HRQOL to be stronger than correlations between asthma control and generic HRQOL.
- Similarly, we expect asthma-specific HRQOL measures to be more sensitive than generic measures to changes in asthma control; thus correlations between change in asthma control and change in asthma-specific HRQOL should be stronger than correlations between change in asthma control and change in generic HRQOL.
- While we expect asthma treatment will have a beneficial effect on asthma control and asthma-specific HRQOL, we also expect that the measured benefit in an observational cohort study will be attenuated or possibly reversed by the feedback effect of control and HRQOL on treatment. Since it is unclear what the sum of these counter expectations is, we expect these associations to be weak and their direction unpredictable.
- Enduring features of individuals, such as innate asthma severity and personality traits, will lead to differences among individuals in asthma-specific and generic HRQOL that persist over time. Thus we expect that variations in longitudinal HRQOL data will be dominated by differences between individuals in their average levels of HRQOL (between person variance) rather than fluctuations individuals experience over time around their own average levels of HRQOL (within person variance).
- We expect that individual characteristics, such as age and gender, will explain some of the between person variance in HRQOL.
- We expect that asthma control variables will explain a significant amount of within person variance in HRQOL and some between person variance.

Methods

Recruitment and sample

Subjects were participating in a longitudinal study of the economic burden of asthma in New South Wales (NSW), Australia, which commenced in 2002 [19]. The study used two sampling frames: 1) a random community sample stratified by age, gender and area of residence (22% response); and 2) the emergency department databases at three tertiary hospitals (9% response). Ethical approval was granted by the ethics committees at the University of Sydney (Approval 01/08/39), the University of Technology Sydney (Approval 2006-88) and the ethics committees at the hospital recruitment sites. Written consent was provided by adult participants and the parent or guardian of participants aged less than 18 years at recruitment. HRQOL data were collected only when participants were aged 16 years or older. Thus the results reported in this paper are from that subset of the economic study aged 16 at recruitment or turning 16 during the study.

Data collection and timeframes for self-report measures
All data reported in this paper were collected by postal survey at six-monthly intervals for three years. The survey booklet contained 106 questions over 26 pages. The first section, about health perceptions, included two standardized questionnaires (see measures of HRQOL below), each with a timeframe of the last 4 weeks. The remaining sections contained questions devised specifically for this survey about the costs and difficulties associated with medications and health care for asthma and activities at home/work affected by asthma. The time frames for these (either the last 4 weeks or the past six months) were determined by the methods and objectives of the main economic study.

Measures of asthma control and treatment
Asthma control was measured with five variables: sleep disturbance due to asthma, use of inhaled short-acting beta agonist (SABA) medication, activity limitation due to asthma, urgent medical visits, and hospital use (Table 1). The timeframe for these measures was the last four weeks except for activity limitation and hospital use which referred to the past six months. Hospital use and days away from work/study/regular activities (one component of activity limitations) were expected to be relatively rare events and so were asked over the longer period. The other items contributing to activity limitation also referred to six months for consistency. Six questions about the use of inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) medication were used to categorise respondents into three groups: 1) regular users of combined ICS and LABA; 2) regular users of ICS alone; or 3) no preventive therapy. Regular use was defined as used every day or most days (in the last 4 weeks).

Measures of HRQOL
Asthma-specific HRQOL was measured with Marks' Asthma Quality of Life Questionnaire (AQLQ-M) [20], which contains 20 items covering social activity limitations, mood and some practical and existential concerns. We used the total scale as a comprehensive measure of asthma-specific HRQOL and the five-item breathing problems sub-scale as a measure of troublesome asthma-related symptoms. These scales have a range of 0-4; higher scores reflect greater impact of asthma. Generic HRQOL was measured with the Physical Components Summary (PCS) and Mental Components Summary (MCS) scales from the SF-36 Health Survey version 1 [21]. These were calculated as per the user manual [22] using Australian population norms and scoring weights [23]. These scales are normalised to a population mean of 50 and standard deviation of 10; higher scores reflect better HRQOL.

Statistical analysis
Statistical analyses used SAS software version 9.1 [24]. The relative size of associations between asthma control and disease-specific versus generic HRQOL were tested with Spearman correlation coefficients among baseline measures. Spearman correlation coefficients were also used to determine the association between change in HRQOL and change in asthma control. The prediction from the conceptual model was that this association would be stronger for asthma-specific than for generic HRQOL measures, and that this would demonstrate that the former were more sensitive to change in control than the latter. For this analysis, change scores were calculated as follows. The two time-points when each individual's SABA use was at the minimum and maximum levels were identified. Change scores were calculated for all measures of asthma control and HRQOL as the difference between those two time points. SABA use was chosen because it had a relatively even distribution across its range and therefore yielded a larger range of change scores than the other control measures, which were more skewed. Each individual's maximum change score for each control and HRQOL measure was also calculated. The significance of differences

between correlation coefficients was assessed by comparison of their 95% confidence intervals [25], although we note that this is only an approximate test of statistical significance because the assumption of independence of correlation coefficients does not hold in this context.

Multi-level models[26], estimated in SAS Proc Mixed,[24] were used to examine HRQOL patterns over time [27]; specifically, the relative size of within and between person variation, the explanatory power of asthma control and personal characteristics, and whether the relationships between asthma control and HRQOL varied among individuals. Measurement occasion (level 1) was nested within individuals (level 2), HRQOL was the outcome variable, and explanatory variables included asthma control, socio-demographic variables (age, gender, area of residence), recruitment source and smoking status. Excepting hospital use, each asthma control variable was centred on its overall mean.

Each of the four HRQOL scales was analysed separately with the following models:

1. a person-specific random intercept and no explanatory variables;
2. a random intercept and five explanatory variables: age, gender, residential area (capital city or regional NSW), smoking status (current smoker or not), recruitment source (community or hospital), entered as level 2 (person level) effects;
3. five models adding each of the five asthma control variables one at a time to the model at 2 above as level 1 (time varying) effects;
4. each of the five models at 3 above with a person-specific random slope for the asthma control variable;
5. the model at 2 above with all five of the asthma control variables added at once, including a random slope where this was indicated by the models at 4 (the likelihood ratio test was used to compare models with different random effects and select the model of best fit as the final model);
6. the final model from 5 with treatment entered as two dummy variables (level 1 effects) for combined ICS and LABA and for ICS alone.

See the appendix for the detailed model specification.

The proportion of total variance due to between-person variance was calculated from estimates of between and within person variance in Model 1 above [26, p19]. The proportion of between and within person variance explained by asthma control and personal variables was calculated from corresponding variance estimates in the models at Step 5 relative to Model 1 above [28].

Results

The sample comprised 213 people with asthma aged 16 to 75 years who completed one or more HRQOL assessments during the study (Table 2). At baseline, the majority reported few problems with asthma control. However, some individuals showed evidence of poor asthma control, with 15% reporting an asthma attack requiring a medical visit in the previous four weeks, 15% reporting hospital use in the previous six months, and some high scores on all asthma control measures. Baseline AQLQ-M mean scores were close to 1, representing a mild effect of asthma on HRQOL on average, with some individuals experiencing moderate to very severe effects. The baseline mean SF-36 summary scales were about 5 points below the population mean of 50, with a wide range of scores reflecting considerable variation in physical and mental health among individuals. The absolute maximum changes in asthma

control and HRQOL were relatively small, in general, although some individuals experienced moderate to large changes in control and HRQOL.

The 213 participants contributed a total of 967 observations, with a maximum follow-up of three years. Attrition of approximately 10% occurred at each of the six assessments. In total, 124 (58%) respondents completed all scheduled surveys. Compared with these subjects, the 89 subjects who missed at least one survey were younger (mean age at recruitment: 39 versus 49 years, $p<0.0001$) and had more sleep disturbance (on average 1.3 nights/week in the last four weeks versus 0.9, $p=0.006$).

At baseline, the five asthma control variables were more highly correlated with the asthma-specific HRQOL measures (AQLQ-M) than with the generic measures (SF-36) and about half of these correlations were significantly higher (Table 3). Change in sleep disturbance, SABA use and activity limitation were more highly correlated with change in the asthma-specific HRQOL measures than with change in the generic measures and about half of these correlations were significantly higher. Change in urgent medical visits and hospital use were not highly correlated with change in any of the HRQOL measures ($r=0.02$-0.24, Table 3).

Most of the variability in the longitudinal HRQOL data was due to between rather than within person differences (Table 4). When the asthma control variables were individually entered into the multi-level models of AQLQ-M total, AQLQ-M breathing and PCS, the best fit was achieved with a random slope for all asthma control variables except hospital use. This indicated significant variation among individuals in the rate at which HRQOL changed with these control variables. Not all control variables retained significant random slopes when the five asthma control variables were entered together. The effect of treatment was not significant and explained no additional variance in any of the four HRQOL scales. The final models are presented in Table 4.

Socio-demographic factors, smoking status, recruitment source and the asthma control variables together explained more than 70% of the total variance in the asthma-specific HRQOL scales, 50% in the PCS but only 16% in the MCS. Most of the variation in asthma-specific HRQOL was attributable to the asthma control variables which together explained 54-58% of the total variance and more than half of the between and within person variation (Figure 2). This was not the case for generic HRQOL where socio-demographic characteristics, smoking status and recruitment source accounted for much of the explainable variation between people. The asthma control variables together explained 25% of the total variance in the PCS, less than 20% of the within person variation and almost 30% of the between person variation (Figure 2). The asthma control variables explained only 8% of the total variance in the MCS.

Activity limitations, SABA use and sleep disturbance contributed most toward explaining variation between people in the AQLQ-M breathing scores, individually accounting for 30-50% of between person variance (Figure 3). Sleep disturbance and SABA use contributed most toward explaining the fluctuations individuals experienced over time, each individually accounting for about 40% of within person variance in the AQLQ-M breathing scores (Figure 3). The pattern was similar for the AQLQ-M total scores (Figure 4), except that the proportion of the variance explained was slightly smaller. A similar pattern was also seen for the PCS, with a much smaller proportion of the variance explained (Figure 5). Similarly for the MCS, but with an even smaller proportion of variance explained. Two of our measures of asthma control (hospital use and urgent medical visits) showed very little variation (0 at all

time-points for more than 70% of the sample) and so explained very little between or within person variation in any of the HRQOL scales.

Discussion

These findings generally support the hypotheses arising from our conceptual model. The observed correlations and the results from the multilevel models support the propositions that asthma control has a more direct impact on asthma-specific HRQOL measures than on generic measures and that asthma-specific measures of HRQOL are more sensitive than generic measures to changes in asthma control. This is consistent with previous evidence that disease-specific HRQOL measures are more responsive to changes in HRQOL than are generic HRQOL measures [29].

The asthma control variables explained very little of the variation in mental aspects of generic HRQOL, more of the variation in physical aspects of generic HRQOL, and over half of the variance in asthma-specific HRQOL, both between and within individuals. Activity limitations, sleep disturbance and SABA use were the main contributors to this. It is perhaps not surprising that urgent medical visits and hospital use had the least explanatory power, given that they had the least variability of the control measures in our data. Further, they are arguably byproducts rather than dimensions of poor control.

We had expected an unpredictable and probably weak association between treatment and HRQOL in this cohort because of the feedback loop between asthma control and treatment intensity. The finding that, after adjusting for asthma control and socio-demographic factors, reported use of inhaled corticosteroids or combined therapy was not related to HRQOL, is consistent with this prediction.

Our findings are consistent with several other reports on the relation between measures of asthma control and HRQOL. In Katz et al's cohort, activity limitation due to asthma explained 32% of the variance in asthma-specific HRQOL (measured with Marks' AQLQ-M) at baseline and 20% in change over 18 months [11]. In the same cohort, perceived control of asthma explained 15% of the variance in asthma-specific HRQOL at baseline and 15% in change over 3 years, while it explained less than 10% of the variance in generic HRQOL (measured with the SF-36) [10]. Chen et al [12] found that the number of asthma control problems at baseline and change one year later explained 27% of the variance in asthma-specific HRQOL (Juniper's AQLQ) and 7% of the variance in generic HRQOL (Euroqol-5D). Vollmer et al[9] found that the report of normal activities missed due to asthma was a significant predictor of both asthma-specific and generic HRQOL (measured with Juniper's AQLQ and the SF-36, respectively). However, unlike our study, Vollmer et al[9] found reliever overuse was not associated with the SF-36 PCS. Moy et al found that SABA use predicted asthma-specific HRQOL (measured with Juniper's AQLQ) in patients with mild asthma but not in patients with moderate to severe asthma [13]. We have added a further dimension to the evidence from these studies by using multilevel models to show that the relationship between asthma control and HRQOL varies significantly among individuals.

Historically, asthma-specific HRQOL instruments such as Juniper's AQLQ and Marks' AQLQ-M were developed before measures control, which emerged as the focus of health care shifted to asthma management and control, as reflected in initiatives such as the Global Initiative for Asthma [30]. Our study was designed before these measures emerged.

Contemporary measurement of control includes objective measures (ie, pulmonary function tests) and subjective measures (ie, symptoms, quality of life) [31]. Asthma symptoms and activity limitation are included in most measures of asthma control and HRQOL. The resultant overlap is an obvious source of the correlation between measures of control and HRQOL observed in this and other studies [5, 9-13]. It is worth considering the extent to which our and other results merely reflect this overlap, as opposed to more interactive relationships. In our study, the greatest overlap was between asthma-specific HRQOL and our survey's additional measure of activity limitation (Table 1). In the AQLQ-M, eight of the 20 questions relate more or less directly to limitations due to asthma in various aspects of life. This no doubt explains why these two measures were so strongly correlated in our data (Table 3). Further, the longer timeframe for our activity limitation measure ('the last 6 months') may account for it explaining more of the between person variance than the within person variance in the AQLQ-M scores (based on 'the last 4 weeks'). The AQLQ-M also contains a question about sleep ('unable to sleep at night'), but as it is only one of 20 items in the total AQLQ-M score, it is unlikely to have had much influence on the degree of correlation with our control measure (number of nights sleep disturbed). Results for the control measure based on use of short-acting beta-agonists were not affected at all by overlap of content with HRQOL. It is noteworthy that the correlations for this control variable were comparable with those the sleep-control variable (Table 3).

Identifying the aspects of asthma control that explain variations in HRQOL may assist in targeting interventions to improve HRQOL. For example, interventions aimed at reducing sleep disturbance in asthma may be worth pursuing. Understanding these relationships may also inform the choice of endpoints for clinical trials. If measures of asthma control are more efficient for detecting treatment effects than are HRQOL measures (ie, more responsive), and are known to be correlated with them, then it would make sense to use measures of control as endpoints even when the ultimate goal of treatment is to optimise HRQOL. This is a useful direction for further investigation under standardised conditions where systematic treatment effects are expected and measures of both asthma control and HRQOL have been used.

Our study has some potential limitations. Our recruitment strategy and low response rates mean that we may not have captured a representative sample of people with asthma in NSW. However, it is unlikely that the factors associated with non-response influenced the relationships between control and HRQOL. Sample attrition occurred, but we found few differences between those who completed all assessment points and those who did not. We did not measure all the aspects of asthma treatment and impact in our theoretical model. In particular, we did not measure all indicators of asthma control, such as daytime symptoms and level of lung function. Furthermore, we did not use a composite measure of asthma control; Bateman et al [32] found that, in patients with uncontrolled asthma, individual measures of asthma control varied in their speed of response to treatment and the proportion achieving control on individual measures was higher than on all measures suggesting that the use of individual measures may overestimate control.

The conceptual model and empirical results presented here provide some practical insights into the relationships between measures of HRQOL and asthma control, and their usefulness in different research contexts. The measures of asthma control used in this and other studies are often single items that have clear clinical interpretations and relevance. This makes them much easier to interpret than multi-item HRQOL measures[33]. So while the ultimate aim of asthma management is to optimise HRQOL, it may be more practical in some circumstances to measure asthma control. The finding that sleep disturbance due to asthma and SABA use

explain much of the within-person variation in asthma-specific HRQOL suggests that these particular measures of asthma control are likely to be most useful in evaluating treatment effectiveness. Since activity limitation explains much of the between person variation in HRQOL that is not explained by personal characteristics it may be a better measure of asthma control when monitoring the impact of asthma in populations.

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Appendix

Each of the four HRQOL scales was analysed, separately, in the following sequence:

Step 1. A random intercept model:

$$y_{ij} = a + u_i + e_{ij} \qquad \text{Model 1}$$

for i=1 to n participants on j=1 to 6 occasions (the 6 x 6-monthly timepoints of the 3 year survey period), where y_{ij} is the QOL score for patient i on the jth occasion, α is the population mean QOL score (intercept), u_i is a random effect giving the deviation of the average QOL score of the ith patient from the population mean, and e_{ij} gives the deviation of y_{ij} from the average QOL score of the ith patient.

In this model and all subsequent models, the u_i and e_{ij} are assumed to be independent and normally distributed, with mean zero, between-patient variance Φ^2_u and within-patient variance is Φ^2_e. Thus:

$$u_i \sim N(0, \Phi^2_u),\ e_{ij} \sim N(0, \Phi^2_e)$$

The covariance matrix for the e_{ij} was modelled as unstructured (no constraints) at this stage.

Step 2. Five explanatory variables were added simultaneously to Model 1. These were: age, gender, residential area (capital city or regional NSW), smoking status (current smoker or not), recruitment source (community or hospital):

$$y_{ij} = a + \sum_{k=1}^{5} \beta_k x_{ki} + u_i + e_{ij} \qquad \text{Model 2}$$

where x_{ki} are the observed levels of k=1 to 5 recruitment and socio-demographic variables for the ith participant. These variables are called 'person level' or 'level 2' effects, and there is only one value of x_{ki} for each participant, as measured at baseline. β_k is the regression parameter (slope) for the kth socio-demographic variable.

Step 3. The five asthma control variables were then added one at a time to Model 2:

$$y_{ij} = a + \gamma_l z_{ijl} + \sum_{k=1}^{5} \beta_k x_{ki} + u_i + e_{ij}$$

where z_{ijl} is the observed level of the lth asthma control variable for participant i at time j. These variables are called 'time varying' or 'level 1' effects, and there was one value of z_{ijl} for each time each participant completed a survey. Each asthma control variable was centred on its overall mean, except hospital use. γ_l is the regression parameter (slope) for the lth asthma control variable.

Step 4. For each of the five asthma control variable models at Step 3, a person-specific random slope was added:

$$y_{ij} = a + \gamma_l z_{ijl} + \sum_{k=1}^{5} \beta_k x_{ki} + u_i + v_{il} + e_{ij}$$

where v_{il} is a subject-specific effect giving the deviation of the ith subject-specific slope from the population slope, γ_l, for the lth asthma control variable. The v_{il} were assumed to be normally distributed, with mean zero, $v_{il} \sim N(0, \Phi^2_v)$, and to be independent of the u_i and the

e_{ij}. The likelihood ratio test was used to compare each model with the corresponding model at Step 3 to determine whether the random slope improved model fit.

Step 5. The model at 2 above with all five of the asthma control variables added at once, including a random slope where this was indicated at Step 4. The likelihood ratio test was used to compare models with different random effects and select the model of best fit as the final model:

$$y_{ij} = a + \sum_{l=1}^{5} \gamma_l z_{ijl} + \sum_{k=1}^{5} \beta_k x_{ki} + u_i + \sum_{l=1}^{L} v_{li} + e_{ij}$$

where v_{1i} ,...,v_{Li} were retained if they improved the model fit. The covariance matrix for the e_{ij} was constrained to a variance components structure (zeros in the off-diagonals) at this stage because the large number of random effects lead to convergence problems with other covariance structures. The likelihood ratio test was used again at Step 5 to determine if all random slopes retained in the five separate models at Step 4 continued to contribute to the single model at Step 5; the model of best fit here was then the final model from Step 5.

Step 6. Treatment was entered as a time-varying (level 1) effect to the final 'best-fit' model determined in Step 5. Treatment was entered as two dummy variables: ICS plus LABA (combined); ICS alone.

$$y_{ij} = a + \sum_{l=1}^{5} \gamma_l z_{ijl} + \sum_{k=1}^{5} \beta_k x_{ki} + \beta_6 ICSLABA_i + \beta_7 ICS_i + u_i + \sum_{l=1}^{L} v_{li} + e_{ij}$$

Since neither treatment effect was statistically significant for any of the four HRQOL scales, the final model was the best fit from Step 5.

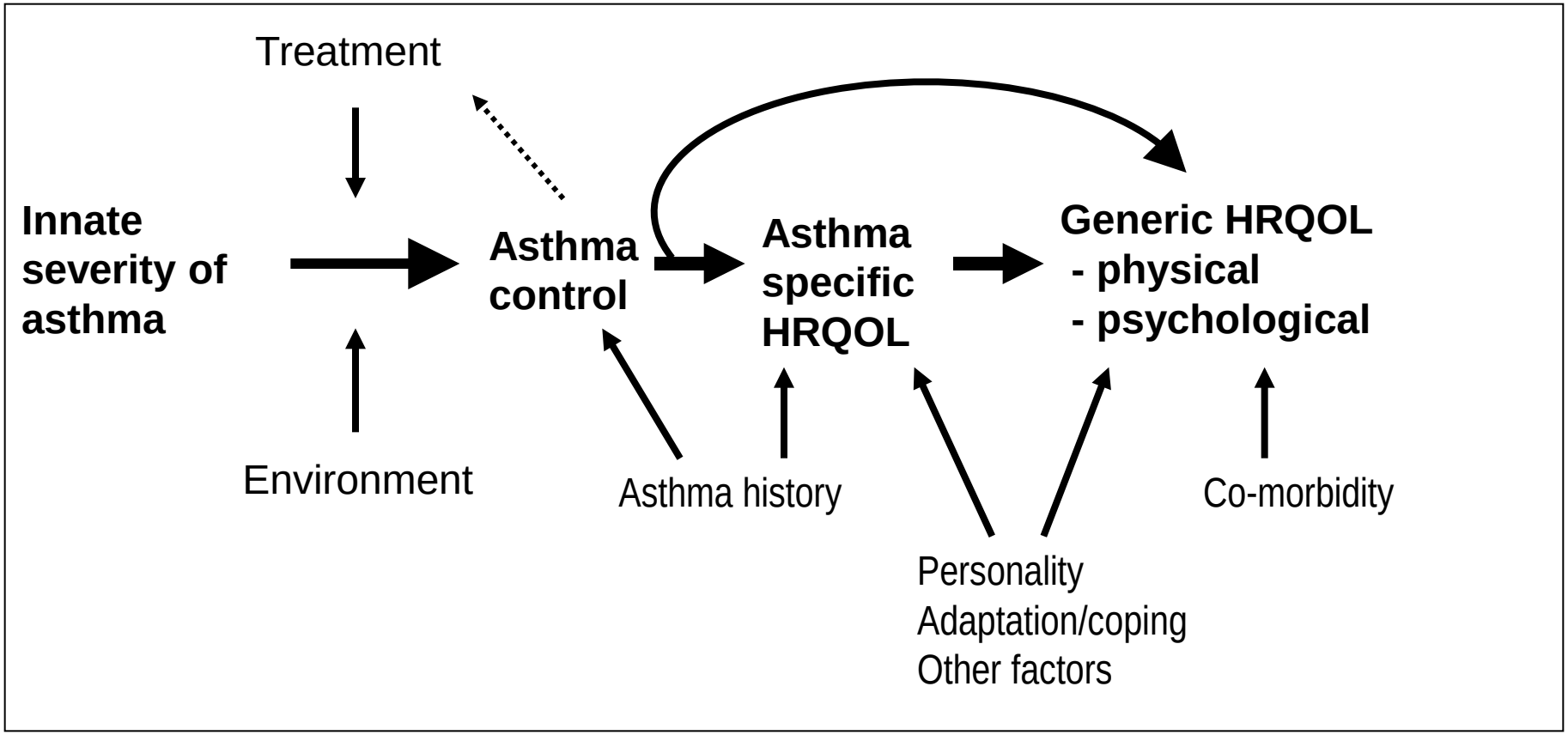

Figure 1: Expected relationship between asthma and HRQOL

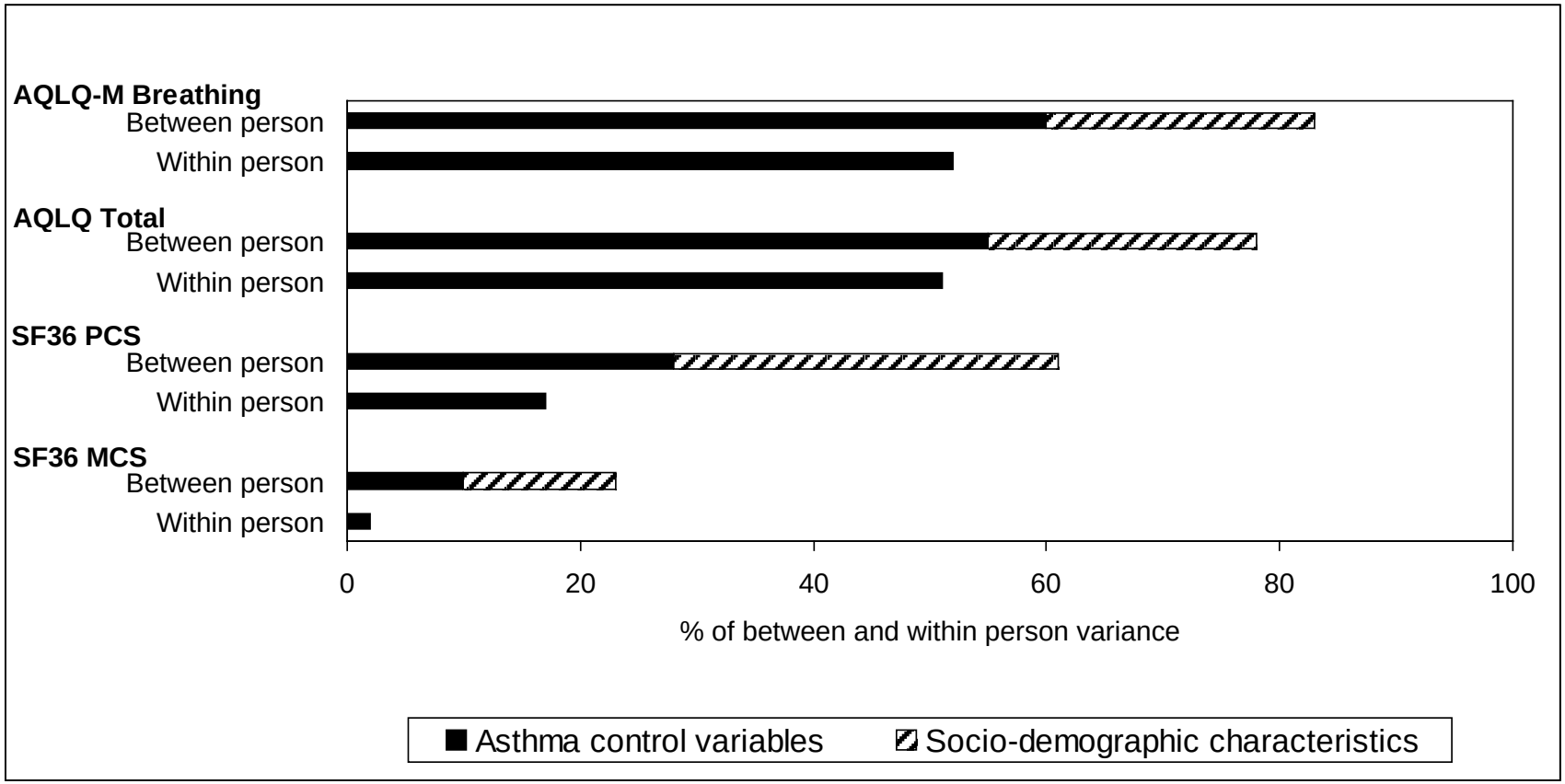

Figure 2: Between and within person variance in HRQOL explained by socio-demographic and asthma control variables

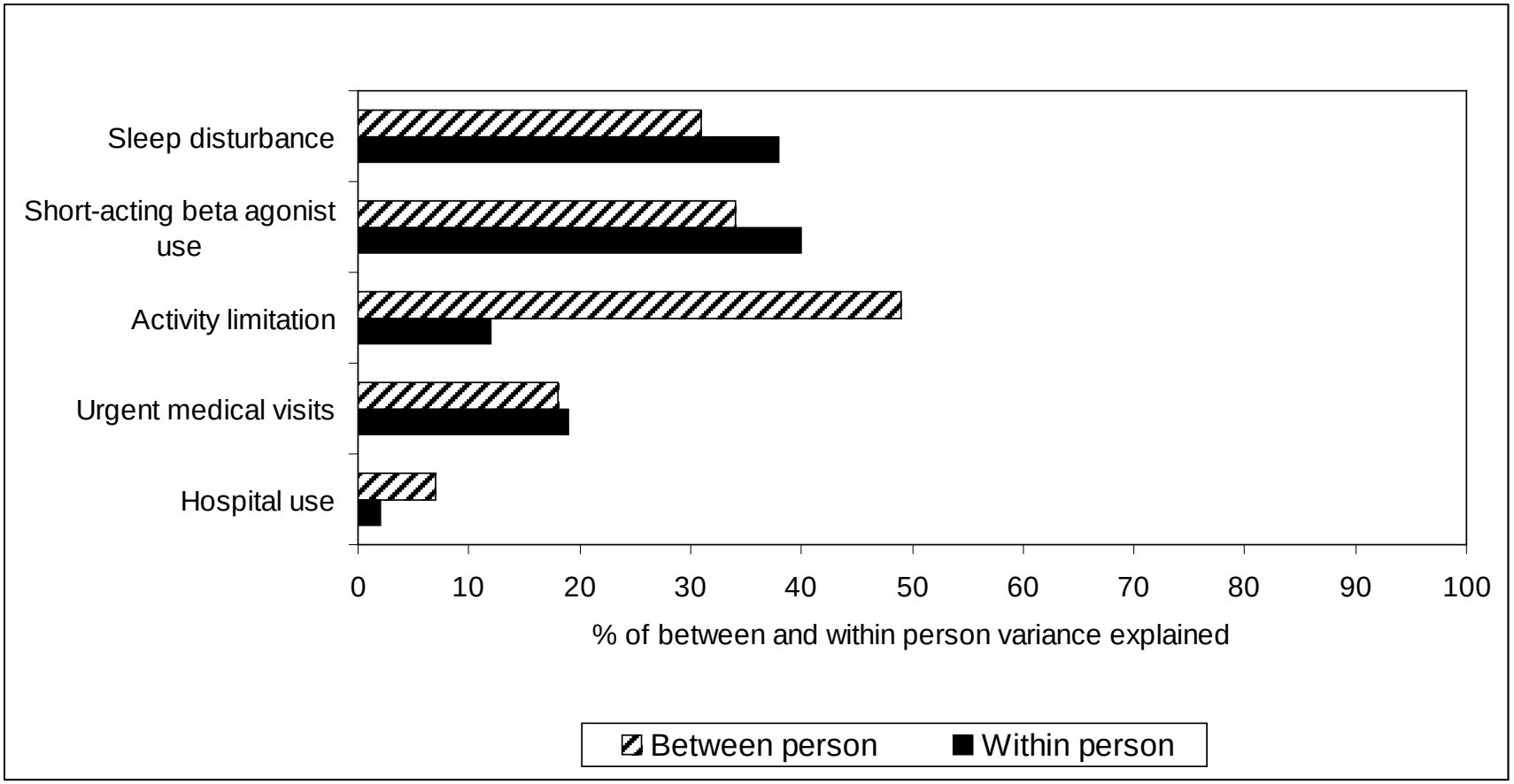

Figure 3: Between and within person variance in AQLQ-M Breathing Problems score explained by five measures of asthma control

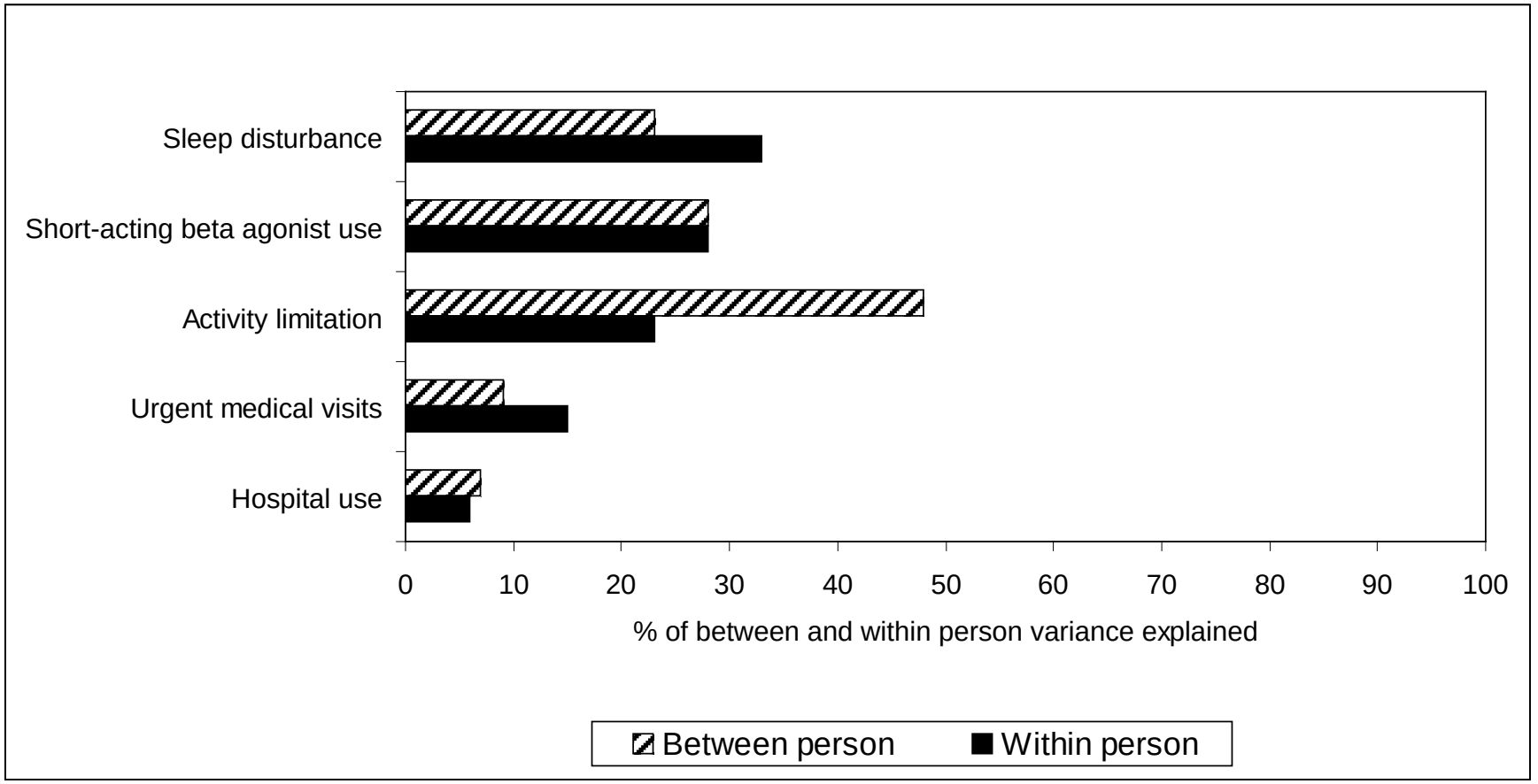

Figure 4: Between and within person variance in AQLQ Total score explained by five measures of asthma control

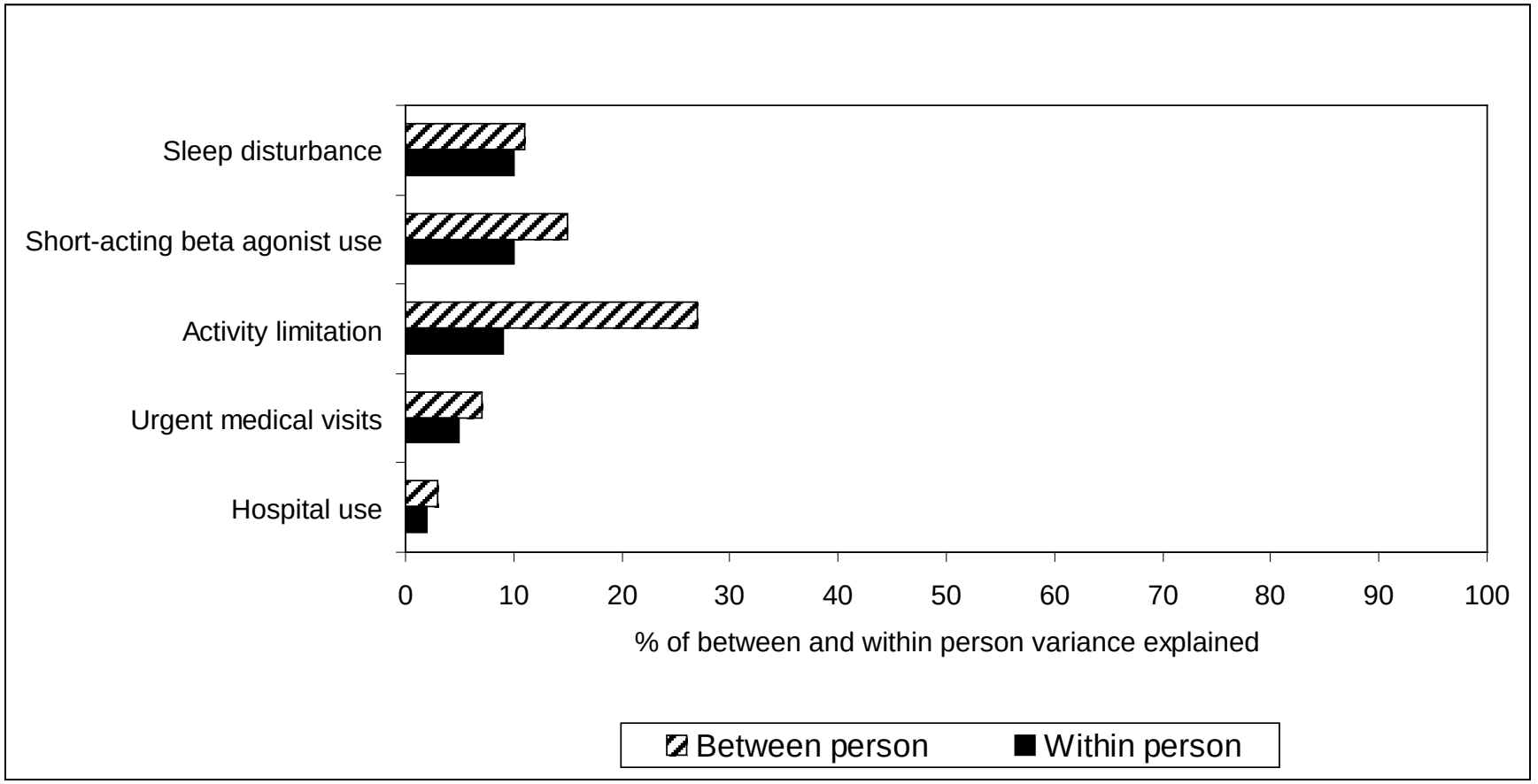

Figure 5: Between and within person variance in SF36 Physical Components Summary score explained by five measures of asthma control

Table 1**:** Measures of asthma control

Aspect	Timeframe	How this aspect was measured or coded
Sleep disturbance due to asthma	last four weeks	average number of nights per week
Use of inhaled short-acting beta agonist (SABA) medication	last four weeks	daily average number of times used (number of days used in the last four weeks x number of times used on those days/28 days)
Activity limitation due to asthma	last six months	Mean of three questions, with range 0-4 (higher scores reflect more limitations): Q1. To what extent did your asthma interfere with your ability to take part in sporting and other strenuous activities? Q2. To what extent did your asthma interfere with your ability to work, study or manage your day-to-day activities? Q1 & Q2 codes: 0 (not at all), 1 (a little bit), 2 (moderately), 3 (quite a lot), 4 (extremely). Q3. How many days did you take off work/study/other regular activities because of asthma? Codes: 0 (0 days), 1 (1-7 days), 2 (8-14 days), 3 (15-28 days), 4 (>28 days).
Urgent medical visits	last four weeks	number of asthma attacks requiring a visit to a doctor or hospital
Hospital use	past six months	Asthma-related hospital admissions or emergency department visits. Codes: 1 (any admissions or emergency visits) or 0 (none)

Table 2: Characteristics of the sample and distributions of the asthma control, treatment and HRQOL measures

		Baseline[a] (n=213)		Absolute Maximum Change[b] (n=189)	
	Percent	Mean (sd)	Median (range)	Mean (sd)	Median (range)
Personal characteristics					
Age at first HRQOL assessment (years)		44.8 (18.2)	44 (16-75)		
Male	45				
Current smoker	15				
Capital city resident	53				
Hospital recruitment	19				
Asthma control					
Sleep disturbance (nights/week last 4wks)		1.07 (1.79)	0 (0-7)	1.71 (1.97)	1 (0-7)
Short-acting beta agonist use (times/day last 4wks)		1.55 (1.61)	0.88 (0-5)	1.43 (1.38)	1.13 (0-5)
Activity limitation (0-4, last 6mths)[a]		0.95 (0.96)	0.67 (0-4)	0.91 (0.75)	0.33 (0-4)
Urgent medical visits (last 4wks)		0.34 (1.17)	0 (0-12)	0.69 (1.38)	0 (0-9)
Hospital use (last 6mths) [c]	15				
Asthma treatment (most/all days)					
Inhaled corticosteroids & long-acting beta agonists	42				
Inhaled corticosteroids alone	20				
Asthma Quality of Life Questionnaire-Marks					
Breathing problems (scale range 0-4) [d]		1.08 (0.88)	0.80 (0-4)	0.93 (0.73)	0.80 (0-3.8)
Total (scale range 0-4) [d]		1.03 (0.82)	0.75 (0-3.8)	0.76 (0.52)	0.55 (0-2.9)
SF-36 Health Survey					
Physical Components Summary[e]		44.5 (11.4)	47 (14-69)	12.1 (7.4)	11 (0-40)
Mental Components Summary[e]		45.1 (12.4)	48 (8-68)	15.2 (9.6)	14 (0-55)

a. Since respondents who turned 16 during the study joined the HRQOL cohort at that age, baseline is defined as the first survey in which HRQOL was assessed.
b. The maximum minus the minimum score for each of the 189 respondents who completed at least two assessments.
c. Hospital use = any hospital admission or Emergency Department attendance for asthma
d. Higher score indicates more limitations/problems; 0 = “Not at all”, 4 = “very severely”.
e. Higher score indicates better quality of life; score normalised to a population mean of 50 and standard deviation of 10.

Table 3: Correlations[a] between asthma control and HRQOL measures for baseline and change scores[b]

	Sleep disturbance	SABA	Activity limitation	Urgent medical visits	Hospital Use[c]
Correlation at baseline (n=213)					
AQLQ-M Breathing	0.57	0.62	0.66	0.45	0.35
AQLQ-M Total	0.54	0.55	0.74	0.42	0.38
SF-36 Physical	-0.27	-0.41	-0.56	-0.30	-0.26
SF-36 Mental	-0.25	-0.18	-0.35	-0.19	-0.15
Correlation of change scores (n=189)					
AQLQ-M Breathing	0.43	0.43	0.36	0.24	0.17
AQLQ-M Total	0.39	0.38	0.57	0.16	0.17
SF-36 Physical	-0.05	-0.06	-0.16	-0.17	-0.23
SF-36 Mental	-0.13	-0.09	-0.23	-0.05	-0.02

a. Spearman rank correlations. The correlations for the SF-36 scales are negative because on these scales a higher score reflects better HRQOL, while on the AQLQ-M scales a higher score reflects greater impact of asthma (worse HRQOL), and for all the asthma control measures, a higher score reflects worse control. Confidence intervals ranged from +/-0.08 to +/- 0.14, with larger correlation coefficients having smaller confidence intervals.

b. Change scores based on the two time-points when each individual's SABA use was at the minimum and maximum levels.

c. Hospital use = any hospital admission or Emergency Department attendance for asthma

Table 4: Multi-level model results: proportion of total variance due to between-person variance[a] and predictors of HRQOL from final best-fit models[b-e] (coefficients with 95% confidence intervals)

Effect	AQLQ-M Breathing[b]	AQLQ-M Total[c]	SF36-PCS[d]	SF36-MCS[e]
Proportion of total variance due to between-person variance	71%	82%	74%	64%
Intercept[f]	0.90 (0.71, 1.09)	0.89 (0.70, 1.07)	54.1 (50.9, 57.4)	42.6 (38.2, 46. 9)
Asthma control[g]				
Sleep disturbance[h]	0.16 (0.12, 0.19)	0.10 (0.07, 0.13)	-0.37 (-0.84, 0.10)	-0.42 (-0.90, 0.06)
SABA use[h]	0.18 (0.14, 0.22)	0.12 (0.09, 0.15)	-1.1 (-1.5, -0.6)	-0.04 (-0.6, 0.6)
Activity Limitation[h]	0.24 (0.19, 0.30)	0.27 (0.22, 0.33)	-2.7 (-3.7, -1.7)	-2.6 (-3.6, -1.6)
Urgent medical visits[h]	0.12 (0.05, 0.19)	0.05 (0.0004, 0.09)	-0.47 (-1.06, 0.12)	-0.42 (-1.16, 0.33)
Hospital use[i]	-0.005 (-0.13, 0.12)	-0.02 (-0.12, 0.08)	-1.8 (-3.7, 0.1)	1.0 (-1.5, 3.4)
Personal characteristics[g]				
Age (10 years)	0.045 (0.013, 0.078)	0.026 (-0.0074, 0.058)	-2.4 (-3.0, -1.9)	0.33 (-0.42, 1.11)
Male	-0.12 (-0.24, 0.001)	-0.10 (-0.22, 0.02)	4.3 (2.3, 6.4)	1.3 (-1.4, 4.0)
Current smoker	0.26 (0.12, 0.39)	0.28 (0.17, 0.40)	-0.80 (-2.95, 1.35)	-3.5 (-6.3, -0.7)
Sydney resident	-0.01 (-0.13, 0.10)	-0.04 (-0.15, 0.08)	-0.94 (-2.94, 1.06)	2.3 (-0.4, 4.9)
Hospital recruitment	0.11 (-0.05, 0.27)	0.26 (0.10, 0.42)	-2.2 (-5.0, 0.51)	-3.7 (-7.3, -0.1)
Random parameters (variance)				
Intercept	0.10 (0.07, 0.14)	0.13 (0.094, 0.173)	39.3 (28.8, 49.9)	76.3 (58.6, 94.1)
Sleep disturbance	0.015 (0.005, 0.025)	0.010 (0.003,0.016)	1.3 (-0.15, 2.7)	
SABA use	0.018 (0.007, 0.029)	0.007 (0.001, 0.013)		
Activity Limitation			8.4 (0.88, 15.9)	
Urgent medical visits	0.024 (-0.001, 0.049)	0.007 (-0.002, 0.015)		
Residual	0.12 (0.11, 0.14)	0.063 (0.055, 0.071)	28.6 (25.3, 31.9)	54.8 (49.3, 60.4)

a. Random intercept models without independent variables were used to calculate proportion of total variance due to between-person variance
b. Random intercept model with random slopes for sleep disturbance, SABA use and urgent medical visits.
c. Random intercept model with random slopes for sleep disturbance, SABA use, urgent medical visits and activity limitation.
d. Random intercept model with random slopes for sleep disturbance and activity limitation.
e. Random intercept model.
f. The intercept represents the overall mean HRQOL score when the four mean-centred asthma control variables are at the overall mean level and the remaining explanatory variables are zero.
g. The coefficients represent the amount of change expected in the HRQOL scale for each unit change in the independent variable.
h. Mean centred variable.
i. Hospital use = any hospital admission or Emergency Department attendance for asthma