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Examining the Heterogeneity and Cost Effectiveness of a Complex Intervention by Segmentation of Patients with Chronic Obstructive Pulmonary Disease

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A B S T R A C T

Objectives: To examine the heterogeneity in cost-effectiveness analyses of patient-tailored complex interventions. **Methods:** Latent class analysis (LCA) was performed on data from a randomized controlled trial evaluating a patient-tailored case management strategy for patients suffering from chronic obstructive pulmonary disease (COPD). LCA was conducted on detailed process variables representing service variation in the intervention group. Features of the identified latent classes were compared for consistency with baseline demographic, clinical, and economic characteristics for each class. Classes for the control group, corresponding to the identified latent classes for the intervention group, were identified using multinomial logistic regression. Cost-utility analyses were then conducted at the class level, and uncertainty surrounding the point estimates was assessed by probabilistic sensitivity analysis. **Results:** The LCA identified three distinct classes: the psychologically care class, the extensive COPD care class, and the limited COPD care class. Patient baseline characteristics were in line with the features identified in the LCA. Evaluation of cost-effectiveness revealed highly disparate results, and case

management for only the extensive COPD care class appeared cost-effective with an incremental cost-effectiveness ratio of £26,986 per quality-adjusted life-year gained using the threshold value set by the National Institute of Health and Care Excellence. **Conclusions:** Findings indicate that researchers evaluating patient-tailored complex interventions need to address both supply-side variation and demand-side heterogeneity to link findings with outcome. The article specifically proposes the use of LCA because it is believed to have the potential to enable more appropriate targeting of complex care strategies.

Keywords: case management, chronic obstructive pulmonary disease, complex interventions, economic evaluation, heterogeneity, latent class analysis, variability.

Introduction

Health economic evaluation of complex interventions is still in its infancy and needs to be developed further [1,2]. This article is a contribution to this development.

Health economists evaluating complex interventions are faced with a number of challenges, because complex interventions often 1) consist of multiple components that act both on their own and in conjunction with each other, 2) are provided to a group of patients with different unobservable preferences and needs, and 3) are studied in pragmatic trials in which the provided health care typically varies over time and in patients and providers in contrast to protocol-driven trials (e.g., drug-trials).

A standard health economic evaluation treats patients as a homogeneous group, and the effects and costs of alternatives are

calculated and presented as average point estimates for the group with a given uncertainty. Nevertheless, applying such an approach for interventions containing heterogenic groups of patients might lead to wrongful decisions of funding; for example, an intervention reimbursed on the basis of its average cost-effectiveness for the total population may not be cost-effective for a subgroup of these patients. Health economists taking patient heterogeneity into account typically stratify their analyses according to traditional subgrouping methods. In such analyses patient heterogeneity is assessed using either prespecified subgroups or subgroups identified post hoc on the basis of observable patient characteristics associated with outcome [3,4]. Such subgrouping methods are problematic though, when evaluating complex interventions entailing multiple components and unobservable patient heterogeneity, because they do not address

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the actual differences in patient treatment pathways. Although efforts have been made to guide those evaluating complex interventions, practical advice on how to evaluate and report on patient heterogeneity is described in less detail [1,2,5]. Hence, previous studies of patient heterogeneity in complex interventions have solely focused on reporting differences in frequencies or duration [6,7].

In this article, we propose a new method for analyzing heterogeneity in a randomized controlled trial (RCT) of a complex intervention in health care. We will consider the case with a single provider of health care services delivering a multicomponent intervention to a single group of patients. Context and implementation issues are not included although these issues could probably also be taken into account. The sources of complexity under these circumstances can then be reduced to

1. different types of care (i.e., the different components that the intervention consists of);
2. different levels of intensity of treatment (i.e., the different combinations of components that the individual patient may receive and how much);
3. a selection process, postrandomization, into different types and intensity of treatment (i.e., the selection of the "package" or patient pathway for the individual patient). This selection process is likely to be driven by patients' needs and preferences (probably unobservable to the analyst and the decision maker) as well as case manager preferences.

Given these treatment features, heterogeneity in treatment efficacy and costs may arise from

1. the type of care: one component of the care may be more cost-effective in itself than other components, regardless of patients' characteristics;
2. the level of intensity of care (i.e., the number of treatment components provided and how much may drive efficacy and costs regardless of the type of care);
3. the selection on returns: patients may respond better to some type/intensity of treatment because of unobservable health characteristics, preferences, or needs and may select themselves (or are selected by the health care provider) accordingly.

For simplicity, we will use the term "demand-side heterogeneity" to describe observable and unobservable patient characteristics associated with heterogeneity in costs and efficacy of treatment. The term "supply-side variation" will be used to describe the different types of care and different levels of intensity of care provided to the patients.

As an alternative method to identify subgroups within a heterogeneous sample/patient group, latent class analysis (LCA) has been performed in this study. The method has been widely applied in marketing research, in which it is used to classify consumers into underlying segments with the purpose of maximizing within-segment homogeneity and between-segment heterogeneity according to similarities in response patterns [8]. In LCA, unobserved latent variables are inferred from observed measures usually on the basis of individual responses from multivariate categorical data [9]. In the field of health economics, LCA has previously been used to examine unobserved patterns in demand for, access to, and utilization of health care [10–13], and to quantify patient preferences for treatment [14,15]. Nevertheless, to our knowledge, the use of LCA in the field of health economic evaluation is yet to be explored.

In this article, we propose the use of LCA not as a segmentation tool based on traditional customer/patient differences, but as a tool for identifying patterns of interaction between supply-side variation and demand-side heterogeneity in the evaluation of complex interventions. The method is illustrated using data from a complex RCT of case management for patients suffering from chronic obstructive pulmonary disease (COPD) [16,17]. The intervention contained both supply-side variation and demand-side heterogeneity, because the patients could receive different types of care and at varying intensities in response to each individual's needs and preferences for care. The process of care selection was conducted after randomization, and care was continuously adjusted throughout the trial on the basis of changing health status and patient preferences. This article focuses on demonstrating the use of LCA as a tool for investigating service variation and patient heterogeneity in cost-effectiveness analyses of complex interventions. The purpose of the study was specifically to 1) identify latent classes on the basis of different patterns of service provision in the case management of COPD, 2) examine the heterogeneity of patient characteristics of the identified classes, and 3) estimate cost-effectiveness at the class level.

Methods

The RCT was conducted in a large Danish municipality from 2012 to 2014. The study had an intervention period of 12 months and included 150 patients with COPD. Patients were eligible for participation if they had been referred by their general practitioner or by hospital respiratory specialists for pulmonary rehabilitation at the local rehabilitation center in 2011. The patients were randomly assigned to either an intervention group or a control group. A thorough description of the study design can be found elsewhere [16].

Control

Patients in the control group received usual care as according to most recent evidence-based guidelines [18]. In the intervention period, the control group had no contact with the case manager.

Intervention

Patients assigned to the intervention group received community-based case management in addition to usual care, and the program was delivered by an experienced COPD nurse. The case manager was not supposed to take over the role and responsibility of other health care providers but to serve as an advisor and support person. The focus of the intervention was to develop and support the autonomy and self-care of the patients so that the patients would be better equipped to handle their disease. The case manager used motivational dialogue and positive performance feedback in her work.

The intervention consisted of a total of eight components. All patients were provided with the knowledge of COPD, its associated consequences, and advice on the incorporation of physical activities in daily life. In addition, the patients were educated in how to manage exacerbations; they were trained in correct inhalation and coughing techniques, and they received an introduction on why, when, and how to take their COPD medication correctly. Advice on proper diet was provided, and smokers received support for smoking cessation. The case manager prepared the patients for appointments with other health professionals through formulation of issues and questions to address, and she provided general counseling and support throughout the intervention. Tailored care plans were formulated together with each patient on the basis of what was relevant for the individual, and the health status and needs of each patient were continuously monitored through regular telephone calls and face-to-face meetings. The multicomponent nature of the

intervention created a heterogeneous utilization pattern among participants. This was a reflection of both demand (i.e., individual characteristics of participants) and supply (in the sense that various services were available).

Measures

During the study, a large amount of data was collected, which included measures of effects, costs, and use of particular services and type of support from the case manager.

Effects

Both groups filled out questionnaires at baseline and after 12 months of participation. The following questionnaires were included: the generic questionnaires the three-level EuroQol five-dimensional questionnaire (EQ-5D-3L), the 12-item short-form health survey (SF-12), and the Patient Activation Measure (PAM-13) as well as the disease-specific questionnaire St George's Respiratory Questionnaire (SGRQ). The questionnaire that was filled out at baseline covered the patients' demographic, disease-specific, and psychosocial status.

Costs

Costs were gathered alongside the RCT from the perspective of the health care sector. The included costs were direct disease-related costs in the primary health care sector (general practitioner contacts), the secondary health care sector (inpatient and outpatient hospital treatment), cost of community care (home assistance and household cleaning, home nurse care, training, and temporary stay at nursing home), costs for prescription medication, and intervention costs (case manager salary, cost for coaching course, and cost for driving in case of home visits and overhead). Valuation of the case manager salary reflected the time spent per patient, whereas fixed costs for the intervention were evenly distributed among intervention patients. All but intervention costs were drawn from Danish registers by using the patients' unique identification numbers. Costs related to trial execution were not included in the analysis because they were considered one-time costs. A thorough description of the valuation of the applied costs and the change in resource use over the course of treatment is given elsewhere [17].

Utilization of services

Besides an introduction to the disease and advice on incorporation of physical activities in daily life, which all patients received, the case manager systematically registered the components that were addressed for each patient during the intervention while the RCT was carried out. The components and associated rates provided for the patients during the trial are presented in Table 1. Each component could be addressed more than once during the intervention; that is, patients could, for instance, receive psychological support several times during the intervention period; nevertheless, data on this were not registered during the trial.

Statistical Analysis

Latent class analysis

Because the case management that was provided differed according to patient needs and preferences, LCA was used to identify whether there existed subgroups of patients in the intervention group on the basis of eight registered measures of utilized services. LCA is a latent variable model in which both the latent variable and the observed variables for each latent class are categorical [9]. In LCA, two types of parameters are estimated: 1) latent class prevalence and 2) probabilities of individuals'

Table 1 – Overview of the components of the case management intervention and associated rates provided for the patients.

Intervention component	Rate
Instructions on how to prevent, detect, and deal with acute exacerbations	53%
Assessment of pharmacological treatment of COPD	66%
Provision of dietary advice for underweight/overweight patients	66%
Advice on smoking cessation/reduction	32%
Preparation of appointments with other health personnel	54%
Involvement of caregivers in the care plan	16%
Support for psychological problematics (e.g., anxiety, identity, and relations)	51%
Support for social problematics (e.g., economy, work situation, and housing)	12%

Note. The table lists the components provided for the patients during the intervention.
COPD, chronic obstructive pulmonary disease.

responses on each observed variable for each latent class. The latter forms the basis for interpretation and labeling of the latent classes. LCA should ideally result in the identification of a set of homogeneous classes.

With the number of latent classes initially being unknown, a series of LCA models holding an increasing number of classes were fitted to the data. To determine the optimal number of classes, the bootstrapped likelihood ratio test (BLRT) was used to test the null hypothesis of the current number of classes against an alternative with one additional class [19]. A fundamental assumption of LCA is that conditional on the latent variable, the observed variables should be statistically unrelated to or independent from each other [9]. To assess whether this assumption was in fact met, the bivariate residuals were obtained. A bivariate residual higher than 1.96 indicates significance, meaning that the assumption of conditional independence is not met. A precise description of the model specification can be found in the Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.08.001. In LCA it is not uncommon to identify several models that fit data adequately. The final model selection should be based on parsimony of the latent class model as well as on interpretability of the latent classes [9]. Therefore, in addition to the model-fit statistics, the theoretical meanings of the identified classes were considered. After the selection of the best-fitting model, baseline demographic, clinical, and economic characteristics for each latent class were identified using descriptive statistics such as the Student t test for continuous variables and χ^2 tests for categorical data. This was done to examine whether the characteristics were in line with the labeling of the latent classes.

Mplus version 7 (Muthén & Muthén, Los Angeles, California) and Stata version 13 (StataCorp LLC, College Station, Texas) were used for the calculations.

Cost-effectiveness analysis

To examine the cost-effectiveness at the class level, classes similar to the latent classes identified in the intervention group needed to be identified for patients in the original control group. There is no agreement in the literature on the procedure for generating a control group for cost-effectiveness analysis of heterogeneous groups. Here, this was achieved by using multinomial logistic regression (MLR), which predicts the probabilities

of different possible outcomes of a categorically distributed dependent variable (here, class affiliation), given a set of independent variables. The model was controlled for all the baseline variables the case manager knew of in her work with the intervention group, which included age, sex, educational status, employment status, smoking status, pack-years of cigarette smoking [20], modified Medical Research Council dyspnea scale, COPD airflow limitation according to guidelines [18], number of comorbidities, baseline utility obtained by the EQ-5D-3L (total score and the five dimensions), and baseline scores for the SGRQ and PAM-13. Patients were assigned to the class with the highest probability for affiliation.

Cost-effectiveness was examined by using cost-utility analyses (CUAs), and incremental cost-effectiveness ratios (ICERs) were calculated for each class. Quality-adjusted life-years (QALYs) were calculated by linear interpolation of utility scores obtained from the EQ-5D-3L between baseline and after 12 months. Patients dying during the follow-up period received an EQ-5D-3L index score equal to the health state for death. Incremental estimates of QALYs and costs were obtained using a seemingly unrelated regression model [21], in which QALYs were adjusted for baseline health-related quality of life (HRQOL) and cost outcomes were adjusted for baseline total cost [22,23]. Uncertainty surrounding the point estimates of mean costs and effects was assessed by probabilistic sensitivity analysis (PSA) by drawing 10,000 trial simulations from a normal distribution. The Cholesky decomposition was applied to obtain correlated draws. The results from the sensitivity analyses were presented at cost-effectiveness thresholds of £20,000 to £30,000, and jointly illustrated in a cost-effectiveness scatterplot.

Results

Randomization allocated 74 patients to usual care and 76 patients to the case management intervention. During the study period six patients died, of which two died shortly after randomization and before receiving any case management. These two intervention patients were excluded from further analysis to enhance precision of the CUA estimates [24]. An additional five patients were lost to follow-up during the study period. Missing data were present in 2% to 4% of the cases. Before assessing the cost-effectiveness, missing data were estimated according to guidelines by using multiple imputations assuming data were missing at random [25,26].

Model Selection

On the basis of the BLRT calculated for two-class to five-class models, we decided on a three-class model. Neither of the estimated models had issues with the assumption of conditional independence as evidenced from Table 2. The probabilities for class allocation ranged between 85% and 100%, with most probabilities ranging between 99% and 100%.

Characteristics of the Classes

Latent class analysis

An overview of the three classes is presented in Table 3. Class 1 was the smallest class and contained 12% of the intervention patients. The class was labeled the "psychologically care" class because there was a 100% conditional probability that patients in this class had received psychological support and support for preparation of appointments with other health personnel during the intervention. This class also had the highest probability of having received social support and involvement of caregivers compared with the other two classes. Nevertheless, the probability of having received advice on COPD exacerbation prevention was 0. Class 2 contained 46% of the intervention patients and was

No. of classes	BLRT	Bivariate residuals >1.96
Two	0.0001	0
Three	0.6667	0
Four	0.1923	0
Five	0.6667	0

Table 2 – Fit statistics for the Latent Class Analyses.

BLRT, bootstrapped likelihood ratio test.

labeled the "extensive COPD care" class because patients in this class had especially high probabilities of having received the COPD-specific components of the intervention. Hence, there was a 100% conditional probability that patients in class 2 had received COPD exacerbation prevention and almost 100% conditional probability that the patients had their COPD pharmacological treatment assessed. Class 3 consisted of 42% of the intervention patients. The class was labeled the "limited COPD care" class because this class was characterized by patients having low probabilities for any of the eight components.

Descriptive statistics

Upon formation of the LCA, the demographic, clinical, and economic characteristics for each class were examined, the data of which are presented in Table 4. The psychologically care class primarily consisted of females and most of the patients had a bachelor's or master's degree. The patients were all nonsmokers, had the lowest rate of pack-years of cigarette smoking, and presented with equally grouped stages of COPD. In the year before inclusion in the study, no COPD-related hospital admissions were registered for this class, and the patients received less COPD medicine compared with patients in the other classes. The psychologically care class had the lowest total health care cost in the year before inclusion, which was primarily due to no hospital admission costs during the previous year. The main cost driver was the use of community care. The low EQ-5D-3L and SF-12 scores showed that the psychologically care class contained highly vulnerable patients. This held against the low use of COPD medicine, and the moderate SGRQ score indicated that something other than COPD might contribute to the patient's state of health. Although it could be speculated whether the patients suffered more from, for example, depression, no data were registered that could clarify it.

The extensive COPD care class contained a slight over-representation of males and most of the patients had no education or were lower educated. The class had the highest rate of current smokers and smoking pack-years and presented with a worse mean modified Medical Research Council score than did the other two classes. More than 70% of the patients in the extensive COPD care class had severe or very severe COPD, and the class did not contain any patients with mild COPD. The class presented with the lowest EQ-5D score and SGRQ scores for all parameters, and scored additionally low for the SF-12 questionnaire. The class received markedly more medicine than did the other classes, and it presented with the highest mean total health care cost. The baseline characteristics for the class supported the findings from the LCA, because this class appeared to consist of patients with more progressive COPD than did patients from the other classes.

The limited COPD care class contained slightly more females, and, similar to the extensive COPD care class, most of the patients had no education or were lower educated. The limited COPD care class predominantly consisted of patients with moderate COPD (61%), and the class presented with considerably better scores for EQ-5D-3L, SF-12, and SGRQ than did the other classes, indicating better HRQOL and a lower burden of COPD.

Table 3 – Overview of classes.

Class and prevalence (%)	Components of case management							
	Disease-specific components				Psychosocial components			
	COPD exacerbation prevention	COPD pharmacological treatment	Smoking cessation support	Nutritional guidance	Preparation of appointments	Involvement of caregivers	Psychological support	Social support
Psychologically care class (0.12)	0	0.47	0	0.95	1	0.22	1	0.22
Extensive COPD care class (0.46)	1	0.93	0.42	0.59	0.66	0.20	0.62	0.14
Limited COPD care class (0.42)	0.15	0.43	0.31	0.67	0.28	0.11	0.26	0.08
All (1.00)	0.66	0.53	0.32	0.66	0.54	0.16	0.51	0.12

Note. Entries show conditional probabilities of addressing the topic (columns) given class membership (rows).
COPD, chronic obstructive pulmonary disease.

The number of general practitioner visits and the use of community care were lower for patients in the limited COPD care class, although a smaller proportion of patients experienced hospital admissions.

Cost-Effectiveness of the Classes

Using MLR for construction of control groups with a reasonably good result, three subgroups were identified in the control group presenting with similar baseline characteristics as the classes in the intervention group. The MLR resulted in a 100% match for the intervention group, meaning that the regression model identified the same class affiliation for the intervention group as did the LCA. The identification of three subgroups in the control group using MLR was believed to be justifiable.

The CUAs resulted in three distinct results, which are presented in Table 5. The psychologically care class had an incremental mean total cost of £972 (95% confidence interval [CI] –808 to 2750) per patient for case management. In addition, the case-managed group had an incremental loss of –0.0387 QALY/patient (95% CI –0.1455 to 0.0681), which altogether resulted in an ICER of –£25,085/QALY. The PSA revealed that the trial simulations were scattered in the northwest and northeast quadrants primarily, with most being scattered in the northwest quadrant, indicating case management being dominated by usual care (see Fig. 1). The probability of case management being cost-effective for the psychologically care class was as low as 10% to 12% at cost-effectiveness thresholds of £20,000 to £30,000/QALY. The form of case management that was applied was therefore not deemed cost-effective. Nevertheless, the result should be interpreted with great caution given the very small sample size for this class.

The extensive COPD care class had an incremental mean total cost of £1652 (95% CI –2725 to 6029) per patient for the case-managed group. Case management resulted in a significant QALY gain of 0.0612 (95% CI 0.0219 to 0.1006) per patient. With an ICER of £26,986/QALY gained, which is in between the threshold set by the National Institute of Health and Care Excellence, the case management that was applied for the extensive COPD care class was cost-effective. Most of the trial simulations were scattered in the northeast quadrant of the cost-effectiveness scatterplot, which indicated the intervention being more effective but also more costly than usual care. The PSA revealed large uncertainty in the cost-effectiveness estimate with a probability of 43% to 53% for the intervention being cost-effective at thresholds of £20,000 to £30,000/QALY.

The limited COPD care class had a decreased incremental total cost of –£471 (95% CI –1712 to 770) and an incremental QALY of –0.0556 (95% CI –0.1192 to 0.0080) for the case-managed group. This resulted in an ICER of £8470/QALY. The cost-effectiveness scatterplot primarily contained trial simulations in the southwest and northwest quadrants, with most of them being scattered in the southwest quadrant, indicating case management being both less expensive and less effective than usual care. Although being cost-saving, it appears to be at the expense of the patients' HRQOL if the applied form of case management was to be implemented for this patient group. The probability of the case management intervention being cost-effective at thresholds of £20,000 to £30,000/QALY was decreasing with probabilities of 24-15%.

Because the classes consisted of different groups of patients receiving different components of case management, the cost-effectiveness results should be interpreted separately.

Discussion

LCA is an emerging method in the evaluation of patient heterogeneity in health research [27–31]. This study is the first to apply the method to analyze the interaction between service provision variability and patient heterogeneity in cost-effectiveness analyses of complex interventions. First, LCA revealed variability in the case management service that was provided during the trial for each patient, because three distinct classes were detected. We named these the psychologically care class, the extensive COPD care class, and the limited COPD care class. Second, observable baseline patient characteristics were examined across the classes, and the characteristics were generally in line with the class-specific features identified in the LCA. Third, highly disparate cost-effectiveness estimates were revealed for the three classes as well as probability of cost-effectiveness.

Interventions tailored to patient needs and preferences and with active involvement of the patient are increasingly popular. Such complex interventions introduce various confounding variables that need to be taken into account in an evaluation. Researchers, however, typically treat variation and heterogeneity as noise that should be actively suppressed to establish the efficacy of tests or procedures. When doing so, one risks giving patients treatments that do not help or denying patients treatments that would. In addition, research is often based on, presented as, and funded using average point estimates.

Table 4 – Descriptive statistics for all treated patients by class.

Patients' characteristic	Class 1 (n = 9)	Class 2 (n = 37)	Class 3 (n = 28)	Total (N = 74)
Baseline demographic characteristics				
Age (y), mean ± SD	66.95 ± 9.67	68.79 8.62	69.86 7.94	68.97 ± 8.43
Sex, male, n (%)	3 (33.33)	21 (56.76)	12 (42.86)	36 (48.65)
Living alone, n (%)	4 (44.44)	11 (29.73)	13 (46.43)	28 (37.84)
Employed, n (%)	2 (22.22)	5 (13.51)	4 (14.29)	11 (14.86)
Educational level, n (%)				
No education	2 (22.22)	15 (40.54)	14 (50.00)	31 (41.89)
Vocational education or academy profession degree	1 (11.11)	19 (51.35)	7 (25.00)	27 (36.49)
Bachelor's and/or master's degree	6 (66.67)	3 (8.11)	7 (25.00)	16 (21.62)
Baseline clinical measures				
Comorbidities, n (%)				
Diabetes	–	4 (10.81)	3 (10.71)	7 (9.46)
Heart disease	6 (66.67)	21 (56.76)	19 (67.86)	46 (62.16)
Osteoporosis	2 (22.22)	7 (18.92)	5 (17.86)	14 (18.92)
Cancer	2 (22.22)	5 (13.51)	6 (21.43)	13 (17.57)
Current smoker, n (%)	–	13 (35.14)	8 (28.57)	21 (28.37)
Pack-year, mean ± SD	21.65 ± 17.40	45.91 ± 18.42	33.31 ± 19.18	38.19 ± 20.24
mMRC, mean ± SD	1.88 ± 1.05	2.24 ± 0.72	1.75 ± 0.65	2.01 ± 0.77
Airflow limitation, n (%)				
Mild ($FEV_1 \geq 80\%$)	2 (22.22)	–	1 (3.57)	3 (4.05)
Moderate (FEV_1, 50%–79%)	2 (22.22)	11 (29.73)	17 (60.71)	30 (40.54)
Severe (FEV_1, 30%–49%)	3 (33.33)	19 (51.35)	7 (25.00)	29 (39.19)
Very severe (FEV_1, < 30%)	2 (22.22)	7 (18.92)	3 (10.71)	12 (16.22)
SGRQ, mean ± SD				
Symptoms score	44.47 ± 32.01	57.66 ± 13.74	43.69 ± 22.44	50.77 ± 20.97
Activity score	57.49 ± 29.38	71.11 ± 19.17	49.03 ± 22.05	61.10 ± 23.75
Impact score	33.57 ± 25.40	37.43 ± 20.86	21.31 ± 17.68	30.86 ± 21.41
Total score	42.70 ± 26.79	51.18 ± 16.87	33.42 ± 17.68	43.43 ± 20.09
PAM-13, mean ± SD	60.68 ± 13.00	59.07 ± 11.92	60.42 ± 13.37	59.78 ± 12.46
EQ-5D, mean ± SD	0.71 ± 0.22	0.68 ± 0.24	0.89 ± 0.14	0.75 ± 0.22
SF-12, mean ± SD				
Physical score	31.78 ± 13.98	34.29 ± 8.90	41.78 ± 10.51	36.68 ± 10.80
Mental score	51.57 ± 15.73	50.74 ± 12.50	58.18 ± 8.63	53.53 ± 12.07
Resource use 1 y before inclusion				
Primary care (GP consultations)				
Mean ± SD	8.33 ± 7.19	10.51 ± 8.17	9.25 ± 7.67	9.77 ± 7.81
Median (25%–75%)	8 (2–12)	8 (6–12)	7 (5–11)	8 (5–12)
Secondary care				
COPD admissions				
Mean ± SD	–	0.43 ± 0.90	0.39 ± 1.52	0.36 ± 1.13
Median (25%–75%)	–	0 (0–0)	0 (0–0)	0 (0–0)
COPD outpatient visits				
Mean ± SD	1.00 ± 2.00	0.68 ± 1.08	0.21 ± 0.69	0.54 ± 1.13
Median (25%–75%)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)
Packages of prescribed COPD medicine				
Mean ± SD	15.89 ± 14.25	32.98 ± 18.29	18.64 ± 17.80	25.45 ± 19.02
Median (25%–75%)	13 (5–20)	30 (20–38)	20 (2–26)	24 (13–33)
Hours of community care				
Mean ± SD	59.06 ± 102.29	47.81 ± 123.65	26.02 ± 85.65	40.93 ± 107.47
Median (25%–75%)	0 (0–60)	0 (0–36)	0 (0–2)	0 (0–35)
Costs (£) 1 y before inclusion				
Primary care, mean ± SD	508 ± 315	709 ± 508	831 ± 1226	731 ± 839
Secondary care, mean ± SD	316 ± 646	1432 ± 2648	1225 ± 4441	1218 ± 3305
COPD medicine, mean ± SD	607 ± 606	1047 ± 475	665 ± 573	849 ± 559
Community care, mean ± SD	1039 ± 1788	830 ± 2137	461 ± 1516	716 ± 1870
Total cost, mean ± SD	2469 ± 2113	4019 ± 4080	3182 ± 7295	3514 ± 5356

Note. Non-normally distributed variables are listed with both mean and median. SGRQ scores go from 0 (better health status) to 100 (worse health status). PAM-13 scores are divided into four levels of activation: level 1, starting to take a role (score ≤47.0); level 2, building knowledge and confidence (score 47.1–55.1); level 3, taking action (score 55.2–67.0); and level 4, maintaining behaviors (score ≥67.1). SF-12 scores go from 0 (worse health status) to 100 (better health status).

COPD, chronic obstructive pulmonary disease; EQ-5D-3L, three-level version of the EuroQol five-dimensional questionnaire; FEV_1, forced expiratory volume in 1 minute; GP, general practitioner; mMRC, modified Medical Research Council; PAM-13, Patient Activation Measure; SF-12, 12-item short-form health survey; SGRQ, St George's Respiratory Questionnaire.

Table 5 – Cost-effectiveness results at class level.

| Class	Incremental cost (£) (95% CI)	Incremental QALY (95% CI)	ICER (£/QALY)	Cost-effectiveness plane (%/quadrant)				Probability of being cost-effective at thresholds of £20,000–£30,000/QALY
				NW	NE	SE	SW	
Psychological care	972 (−808 to 2752)	−0.0387 (−0.1455 to 0.0681)	−25,085	0.66	0.21	0.03	0.10	10%–12%
Extensive COPD care	1652 (−2725 to 6029)	0.0612 (0.0219 to 0.1006)*	26,986	0.00	0.76	0.24	0.00	43%–53%
Limited COPD care	−471 (−1712 to 770)	−0.0556 (−0.1192 to 0.0080)	8470	0.22	0.01	0.03	0.74	24%–15%

CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICER, incremental cost-effectiveness ratio; NE, northeast quadrant (more cost and more effect); NW, northwest quadrant (more cost and less effect); QALY, quality-adjusted life-year; SE, southeast quadrant (less cost and more effect); SW, southwest quadrant (less cost and less effect).

* Significant difference (P < 0.05).

Previously, the cost-effectiveness of our study of case management was evaluated in the group as a whole in accordance with current practice, and when adjusting for the same covariates as in the present article, the intervention resulted in an ICER of £52,961/QALY gained [17]. The findings in this study, however, indicate that "the average patient" does not exist, which illustrates the need for this to be addressed in an evaluation of complex interventions. Albeit the result was associated with high uncertainty, it appears that case management might be cost-effective for the extensive COPD care class with an ICER of £26,986/QALY gained assuming a threshold value of £30,000. Hence, ignoring the interaction between variation in service provision and patient heterogeneity, when this is in fact present, could be costly both in monetary terms and in health gain.

Current health economic guidelines address patient heterogeneity by using different stratified analyses [3,4,32]. As described earlier, traditional regression-based techniques for subgrouping patients post hoc identify subgroups on the basis of the patient characteristics associated with outcome; nevertheless, findings from such analyses can be obscured when both supply-side variation and demand-side heterogeneity are present, as was the case in our analysis. The impact on cost-effectiveness of using a traditional approach for subgroup analysis has been assessed as part of a sensitivity analysis, and the results are presented in the Supplemental Materials. Two subgroup analyses have been conducted. The first analysis addressed supply-side variability, because subgroups were formed on the basis of treatment intensity (number of components received). This analysis did not demonstrate a correlation between treatment intensity and cost-effectiveness. Demand-side heterogeneity was addressed in the second analysis, because subgroups were formed on the basis of severity of airflow limitation according to the classification provided by the Global Initiative for Chronic Obstructive Lung Disease [33]. This analysis demonstrated that case management was a dominant strategy when compared with usual care in patients with severe airflow limitation, because it was cost-saving at an additional QALY gain. Case management would not be considered a cost-effective strategy in patients with COPD with mild/moderate and very severe airflow limitation. Although this is an interesting finding, the analysis does not reveal anything about what was (and what should be) supplied for patients with COPD with severe airflow limitation to obtain this outcome, just as the analysis does not take potential unobservable patient heterogeneity into account.

Contrary to the traditional approach for subgroup analysis, LCA provides an opportunity to address supply-side variation and unobservable demand-side heterogeneity simultaneously. LCA is not driven by associations with an outcome but instead uses a mixture of distributions to identify latent data structures. A strength of LCA is that it, as opposed to traditional methods, provides an overview of the latent patterns of heterogeneity that
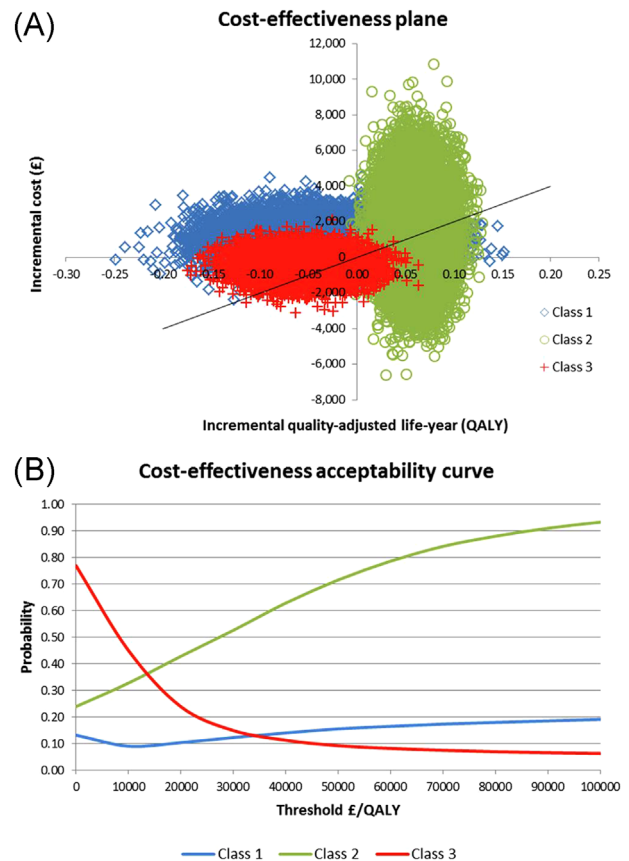
Fig. 1 – The cost-effectiveness plane (A) and the cost-effectiveness acceptability curve (B) at the class level. *Note.* Part (A) illustrates the cost-effectiveness scatterplot of case management vs. usual care with 10,000 simulations of incremental costs and QALYs for each class. The cost-effectiveness threshold of £20,000 is illustrated by the black line running through (0.0) in the scatterplot. For the extensive COPD class, 43% of the simulations fall under the threshold line, indicating that case management is a cost-effective strategy compared with usual care in 43% of the simulations. For the psychologically care class and the limited COPD care class, only 10% and 24% of the simulations, respectively, fall under the threshold line. Part (B) illustrates the probability of case management being cost-effective at different cost-effectiveness thresholds as compared with usual care at the class level. COPD, chronic obstructive pulmonary disease; QALY, quality-adjusted life-year.

is present within a sample, which can later be studied against a range of outcomes [32]. LCA helped to identify the treatment pattern that provided the best balance between considering all patients to belong to the same group and considering all existing treatment patterns to be a relevant subgroup on their own. All patients being in one subgroup would have meant that the provided case management originated from one underlying distribution with scores from 0 to 8 (from no case management components to all case management components). This would have implied that it was not important how many and which components of case management the individual patient received. Instead, LCA enabled us to identify treatment patterns in the data that best explained the latent data structure.

A three-class model was chosen as the optimal number of classes on the basis of the BLRT as well as on the interpretability of the model. Nevertheless, to assess the sensitivity of the cost-effectiveness results to the definition of classes, a sensitivity analysis had been conducted using a two-class and a four-class model. The results hereof are presented in the Supplemental Materials. The extensive COPD care class was likewise identified in the two-class model and presented with a similar cost-effective result as in the three-class model, which supports the finding on cost-effectiveness for this subgroup. The four-class model, however, did not result in the identification of distinctive and meaningful subgroups.

When conducting research on complex interventions, much thought needs to be given to proper evaluation already at the design phase of the intervention. From the perspective of economic evaluation, it is important to determine the mechanisms of a complex intervention that may influence both outcomes and costs. We emphasize strongly that, in addition to traditional baseline and follow-up measures on patient characteristics, effects, and costs, appropriate process data on service utilization need to be collected. Such process measures should at a minimum reflect which patients received which components of the intervention. Without doing so it becomes difficult, if not impossible, to examine what is actually done under the heading of "the intervention" and link it with outcome. In addition, measures on dosage of the intervention, such as amount, frequency, and duration, could be considered collected, although the potential gain of such detailed recording should be balanced against the associated use of resources.

As with any research, this study also had limitations. Keeping the total sample size in mind, there is a risk that small but meaningful subgroups have gone undetected. As a consequence, the findings are merely hypothesis-generating and should be validated in future research. The findings from the LCA rely on the case manager's ability to correctly identify the best treatment protocol for each patient. It cannot be precluded whether the patients would have benefited further from receiving more or all components of the intervention. Nevertheless, the fact that the same features identified in the LCA could be observed in the baseline characteristics supports her skills as a case manager. In addition, only one case manager was affiliated with the trial, and presently it cannot be ruled out whether other classes would have formed if the intervention had been provided by another case manager. The use of LCA in health care decision making is not straightforward because of a number of potential issues. Because LCA is more exploratory in nature than subgroups identified using associations with a clinical outcome, it can lead to subgroups that are difficult to interpret [32]. Future studies should therefore examine whether other demographic, clinical, or behavioral factors can more readily distinguish between the classes and link findings with outcome. The LCA disentangled patient heterogeneity in respect of process measures on received case management components. Whether the same latent classes would have been identified if the analysis had been conducted using other process measures (e.g., treatment intensity) remains to be examined. The process measures were obviously not registered for the control group patients. Instead, counterfactuals for each latent class were estimated by MLR using observable patient baseline characteristics. The patients' baseline characteristics for each counterfactual revealed overall consistency with the patients' baseline characteristics identified for the corresponding latent classes in the intervention group. It is believed that the estimated counterfactuals are justifiable. Nevertheless, because falsely estimated counterfactuals can substantially impact on estimations of cost-effectiveness, it should be examined in future research whether there are other more appropriate methodologies for generating control groups in the analysis of heterogeneity.

We believe that our proposed method provides a means to uncover some of the complexity of complex interventions, because it can provide a deeper understanding of what works for whom. It is conceivable that it can be applied both to full-scale RCTs and for pretesting in pilot trials, with the latter of the two informing researchers about potential classes and their intervention contents to be tested in subsequent RCTs. In time, it may serve as a tool to enable more appropriate targeting of complex care strategies to those patients expected to show the strongest response. Nevertheless, the proposed method calls for further research to determine its applicability in economic evaluation, and, in particular, its usefulness for health care decision making.

Conclusions

By using LCA on process measures of service utilization, three subgroups of COPD patients with significant differences in patient characteristics and estimates of cost-effectiveness were identified. This illustrates the importance of investigating patterns of interaction between supply-side variation and demand-side heterogeneity when evaluating complex interventions targeted to individual patient needs, preferences, and health behaviors. In this context, we propose the use of LCA and recommend that further research be conducted in the field of economic evaluation of complex interventions.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2017.08.001 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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