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Characterizing persistent disturbing behavior using longitudinal and multivariate techniques

Jan Serroyen[a,b], Liesbeth Bruckers[b], Geert Rogiers[c] and Geert Molenberghs[b,d*]

[a] *Department of Methodology and Statistics, University of Maastricht, Maastricht, The Netherlands;* [b] *Interuniversity Center for Biostatistics and statistical Bioinformatics, Hasselt University, Diepenbeek, Belgium;* [c] *Psychiatric Hospital Sancta Maria, Sint-Truiden, Belgium;* [d] *Interuniversity Center for Biostatistics and statistical Bioinformatics, Katholieke Universiteit Leuven, Leuven, Belgium*

(*Received*)

Persistent disturbing behavior (PDB) refers to a chronic condition in therapy-resistant psychiatric patients. Since these patients are highly unstable and difficult to maintain in their natural living environment and even in hospital wards, it is important to properly characterize this group. Previous studies in the Belgian province of Limburg indicated that the size of this group was larger than anticipated. Here, using a score calculated from longitudinal psychiatric registration data in 611 patients, we characterize the difference between PDB patients and a set of control patients. These differences are studied both at a given point in time, using discriminant analysis, as well as in terms of the evolution of the score over time, using longitudinal data analysis methods. Further, using clustering techniques, the group of PDB patients is split into two subgroups, characterized in terms of a number of ordinal scores. Such findings are useful from a scientific as well as from an organizational point of view.

Keywords: cluster analysis; discriminant analysis; longitudinal data; multivariate methods; psychiatry

1. Introduction

Mental health care institutions in Belgium are confronted with a group of chronically therapy resistant patients. This group is problematic in the sense that no scientific definitions nor theory exists. Furthermore, there is no legislative framework in place. These patients cannot be treated satisfactorily with the latest knowledge of therapy and medication. Their behavior is disturbing in the sense that living together in their natural environment, or even in a hospital ward, is extremely difficult. Since their disease systems are unstable, and given that their behavior is persistent over

*Corresponding author. Email: geert.molenberghs@uhasselt.be

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time, intensive supervision over 24 hours is required. This condition is referred to as *persistent disturbing behavior* (PDB).

The current Belgian health care system is clearly not accommodating to this group. Indeed, from the two residential settings, psychiatric hospitals and psychiatric nursing homes, the former are defined as non-residential institutions for intensive specialist care. As the PDB group needs a prolonged stay in such a setting, a psychiatric hospital is not the optimal environment. In addition, a 1996 law states that a psychiatric nursing home is intended for patients with stabilized chronic psychiatric conditions. Although the law does not specify the meaning of stabilized condition, it is generally understood that PDB patients are not stable. We, therefore, have to conclude that mental health care does not explicitly accommodate the PDB group.

The PDB group raises four important questions. First, how can it be distinguished from related but different groups, such as patients with acute or short-term disturbing behavior. Second, since a clear definition is emerging only now, the size of the PDB group is unclear. Third, it is conceivable that the PDB group consists of a number of subgroups that can be usefully distinguished between. Finally, it is not clear where such patients should be based, even though this will in all likelihood neither be the ambulatory setting nor sheltered living. Further, psychiatric wards of general hospitals are intended for acute problems while PDB patients are clearly a chronic group.

To rectify this situation, legislative work is necessary. Before this can be done, one first needs to properly define the PDB group and undertake a quantitative analysis, formulating an answer to the aforementioned questions.

Since there is no generally accepted definition, we will use the following working definition. To be classified as PDB, a patient has to be subject to socially inadequate behavior, that is persistent and treatment resistant, disruptive for the patient's environment, and confronting the therapeutic team with unrealistic demands. The inadequate behavior can take one or several of many different forms such as multiple forms of aggression (directed to oneself or to others), sexually uninhibited behavior, agitation, loss of decorum, and suicidal behavior.

In 1998 a cross-sectional pilot study was set up in the psychiatric hospitals and the psychiatric nursing homes in the Belgian province of Limburg to (1) estimate the size of the PDB group and (2) explore factors to discriminate between PDB and non-PDB patients [2]. Although these results are very useful, there are a number of residual issues. First, due to its cross-sectional nature, the focus is on disturbance rather than on persistence. Second, the working definition presented earlier did not exist at the time. Third, the group of patients shown for study was chosen for comparison with a non-PDB control group rather than for representativeness. This design implies that, although conclusions regarding differences between PDB and non-PDB patients, and conclusions pertaining to subgroups within the PDB group can be drawn with confidence, caution is necessary when making inferences about the magnitude of the PDB group. For the latter goal, the study should be seen as being of a pilot type. Nevertheless, it is important to know whether the group is sufficiently large so as to warrant specific components of care. Should one want to draw more refined conclusions, then a follow-up study, less prone to selection bias, would be in place.

By making use of longitudinal psychiatric registry data, we sshow how the persistence aspect of the group can be studied and how insight into the PDB patients can be enhanced further. Furthermore, we present the results of a cluster analysis, to initiate identification of subgroups within the PDB group.

The data on which our analyses are based are presented in Section 2, with methodology (longitudinal data analysis, discriminant analysis, and cluster analysis) reviewed in Section 3. Section 4 presents our findings. Precisely, after reviewing and expanding upon the cross-sectional discriminant analysis, the data are analyzed using longitudinal methodology, whereas cluster analysis provides further insight. These findings are used in Section 5 to formulate a perspective on the patient population with PDB.

2. The data

For every patient admitted to a residential psychiatric care setting in Belgium specific data are registered. This registration system was made mandatory in 1996 for psychiatric hospitals and in 1998 for the psychiatric nursing homes by the federal Ministry of Public Health and is called *minimal psychiatric data* (MPD). The entire set of data is extensive, organized in a number of modules. A major source for the MPD instrument, but not the only one, is the so-called *Diagnostic and Statistical Manual of Mental Disorders*, known as DSM. The items, relevant for our purposes, are concisely listed in Table 1.

Our data set, previously used by Bruckers *et al.* [2], contains information on 611 patients from the province of Limburg about more than 200 psychiatric, physical, and sociological characteristics. The variables in this data set are mostly of a categorical or ordinal type, although some continuous variables are present as well. The four key continuous variables are the PDB score, which will be discussed in more detail in Section 4.1, with mean 0.62 and standard deviation 1.97, age (mean 47.48 and standard deviation 15.60), duration (mean 3365.71 and standard deviation 3143.43), and *global assessment of functioning* (GAF) score (mean 32.28 and standard deviation 80.00). The GAF scale, is a numeric scale (1–100) used by mental health clinicians and doctors to rate the social, occupational, and psychological functioning of adults. Incidentally, the GAF scale constitutes the fifth axis of the DSM-IV psychiatric classification system. It is considered a potential explanatory variable in all subsequent analyses.

To provide the reader with a perspective on the data, individual profiles of 20 randomly selected subjects are presented in Figure 1. The average profiles and the group-specific empirical variance functions are displayed in Figure 2. Obviously, not all patients are observed at all times. An overview of the number of measurements available, for each of the eight occasions and within

Table 1. Logistic regression analysis results, separately for psychiatric hospitals and psychiatric nursing homes.

Item	Hospitals	Nursing homes
Psychiatric signs and symptoms		
Auto-aggressive actions	5.62 (1.93; 16.42)	3.52 (1.61; 7.72)
Aggression against people	1.87 (1.21; 2.88)	
Aggression against objects		3.17 (1.26; 7.99)
Anti-social attitude		1.92 (1.05; 3.50)
Intensified supervision		
Suicide danger	1.39 (1.19; 1.63)	
Separation/isolation		3.34 (1.12; 9.95)
Patient functioning		
Appearance	1.60 (1.18; 2.17)	
Respect for others	1.49 (1.03; 2.16)	1.81 (1.16; 2.82)
Socially unacceptable behavior		2.02 (1.27; 3.19)
Age	0.97 (0.95; 0.99)	
Gender	6.10 (2.89; 12.90)	
Primary diagnosis at admission		
Mental retardation		0.43 (0.19; 0.97)
DDAC[a]	0.22 (0.06; 0.87)	
Schizophrenia	1.75 (0.95; 3.21)	
V-codes	0.10 (0.01; 0.92)	

[a] Delirium, Dementia, Amnestic, and Cognitive disorders.

Odds ratios [95% confidence intervals] are reported. All items are coded such that an odds ratio greater than 1 corresponds to a less desirable score. The non-PDB group is the reference group.

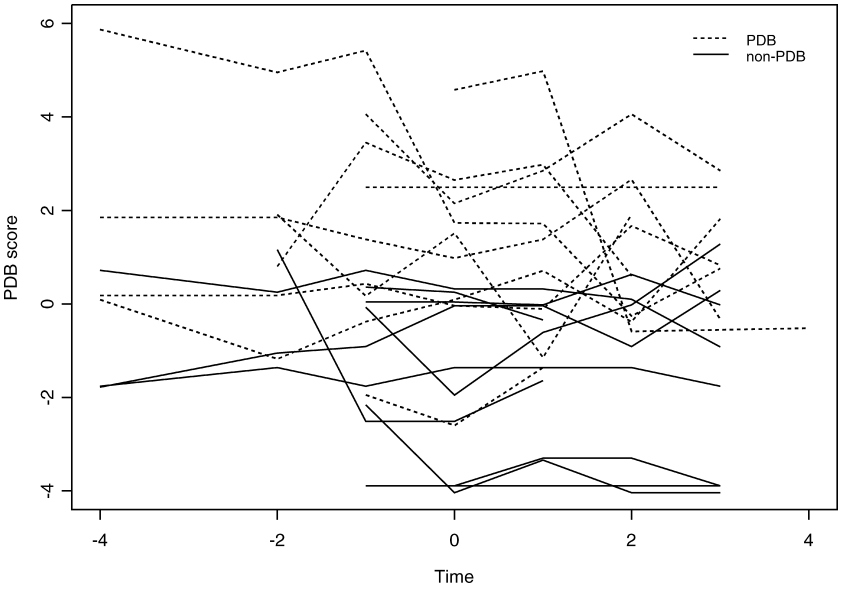

Figure 1. Random sample of individual PDB score profiles for 10 PDB and 10 non-PDB patients.

Table 2. Number of measurements available per measurement occasion, PDB group, and sector.

Group	Sector	Measurement year (semester)								Range of number of measurements
		96(2)	97(2)	98(1)	98(2)	99(1)	99(2)	00(1)	00(2)	
Non-PDB	Hospitals	128	180	197	202	183	158	116	115	1–8
PDB	Hospitals	47	112	122	125	120	102	50	86	2–8
Non-PDB	Homes			214	20	211	202	189	186	2–6
PDB	Homes			64	64	63	52	50	48	2–6
Total		175	292	597	611	577	514	405	435	

each of the four PDB status by psychiatric sector combinations, is given in Table 2. In addition, the range of measurements per patient is displayed.

3. Methodology

Information available in the MPD registration system was used to construct a discriminant function. Data registered in the second part of 1998 were used to develop this function. The items which make up the discriminant score have been recorded twice annually since 1996. After 2000, the legal registration framework changed, whence it is wise to restrict attention to the 1996–2000 interval. Thus, the score was calculated at the other registration occasions as well, thus producing a longitudinal profile per patient. We employed linear mixed models to study the evolution of the mean discriminant function, for the PDB and non-PDB groups. Also, the length of stay contains very valuable information to investigate the persistence dimension. PDB patients cannot be discharged from the institution, since, due to their behavior, they are incapable of properly functioning in society.

A linear mixed-effects model takes the form [8,12]

$$\boldsymbol{Y}_i = X_i\boldsymbol{\beta} + Z_i\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i, \tag{1}$$

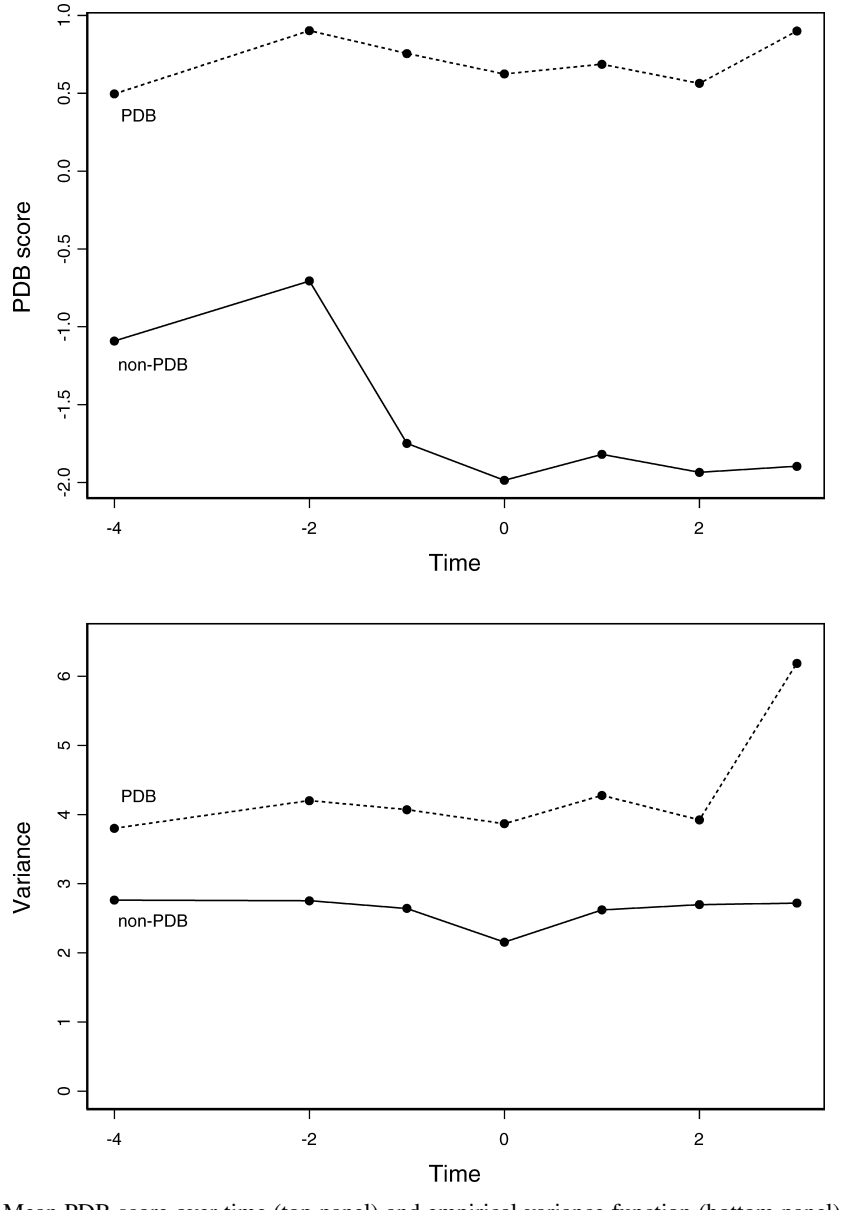

Figure 2. Mean PDB score over time (top panel) and empirical variance function (bottom panel) for PDB and non-PDB group.

where $\boldsymbol{Y}_i$ is the n_i dimensional response vector for patient i, containing the PDB scores at the different moments, $1 \leq i \leq N$, N is the number of patients, X_i and Z_i are $(n_i \times p)$ and $(n_i \times q)$ dimensional matrices of known covariates, respectively, $\boldsymbol{\beta}$ is the p dimensional vector containing the fixed effects, $\boldsymbol{b}_i \sim N(\mathbf{0}, D)$ is the q dimensional vector containing the random effects, and $\boldsymbol{\varepsilon}_i \sim N(\mathbf{0}, \Sigma_i)$ is a n_i dimensional vector of residual components, combining measurement error and serial correlation. In some cases, it is useful to apply further modeling to Σ_i. For example, one may want to model the residual correlations within Σ_i explicitly as a function of the time lag between two measurement occasions. Furthermore, also the variances, i.e., the diagonal elements of Σ_i, may be subject to further modeling. A popular structure is the so-called power-of-mean

function, where the variance is proportional to a certain power of the population mean value for a particular subject, i.e., $\Sigma_i = \sigma^2 |x_i' \beta|^\theta$. Inference is conveniently based on the distribution for the response $\boldsymbol{Y}_i$. We use restricted maximum likelihood for parameter estimation. More details can be found in [12].

When the focus is on distinguishing between PDB and non-PDB patients, discriminant analysis in an obvious tool. Practically, two samples, one of which is of PDB type while the other consists of control patients, can then be classified based on a set of potential predictors. Linear and logistic discriminant analysis are the more popular versions of the technique; the ones considered here [3–5,7,11].

When we further want to explore whether the PDB patient group can be divided further into subgroups, without definite knowledge about group definition or even the number of groups, cluster analysis techniques can be employed. Johnson and Wichern [7] presented a wide variety of methods. We will use a so-called non-hierarchical method, the so-called K-means method. One then partitions the subjects in K initial clusters or chooses K initial centroids. Next, the subjects are re-assigned to the cluster with the closest centroid, whereafter the centroids are computed again. This process is repeated until convergence. We obviously need a distance function, and prefer the use of Gower's distance measure [6], since it can handle all outcome types, i.e., asymmetric nominal, ordinal, interval, and ratio variables. The Gower's dissimilarity coefficient is defined as

$$d(\boldsymbol{y}_1, \boldsymbol{y}_2) = 1 - \frac{\sum_{j=1}^{n} w_j \, \delta^j_{y_1, y_2} \, d^j_{y_1, y_2}}{\sum_{j=1}^{n} w_j \, \delta^j_{y_1, y_2}},$$

where $\boldsymbol{y}_i$ $(i = 1, 2)$ is the vector of measurements on subject i, n the number of measurements, and y_{ij} the jth measurement on subject i. Further, w_j represents the weight for the jth variable and $w_j = 0$ when either y_{1j} or y_{2j} is missing. For symmetrically nominal, ordinal, interval, and ratio variables, $\delta^j_{y_1, y_2} = 1$, whereas for asymmetric nominal variables $\delta^j_{y_1, y_2} = 0$ if both y_{1j} and y_{2j} are absent and 1 otherwise. Finally, for nominal and asymmetric nominal variables, $d^j_{y_1, y_2} = 1$, if $y_{1j} = y_{2j}$, and 0 otherwise. For ordinal, interval, and ratio variables, $d^j_{y_1, y_2} = 1 - |y_{1j} - y_{2j}|$. In case of ordinal variables, the data are replaced by their corresponding rank scores. The hierarchical Ward's minimum variance method [13] was adopted as clustering algorithm. In Ward's minimum-variance method, the distance between two clusters is the ANOVA sum of squares between the two clusters added up over all variables. At each generation, the within-cluster sum of squares is minimized over all partitions obtainable by merging two clusters from the previous generation.

4. Application to the data

We first undertake a cross-sectional study and thereafter switch to longitudinal and multivariate methods.

4.1 *A cross-sectional PDB score*

As mentioned in the introduction, a cross-sectional pilot study was undertaken in both the psychiatric hospitals and the psychiatric nursing homes in the province of Limburg to obtain a rough estimate of the size of the PDB group and to determine factors that can usefully distinguish between PDB and non-PDB patients. We briefly report on the results reported in Bruckers *et al.* [2], and supplemented them with additional analyses. The cross-sectional analysis focuses on the 'disturbance' aspect, while the next section brings in the longitudinal 'persistence' dimension too.

In November 1998, a number of wards were screened for PDB behavior, by an interdisciplinary team, and classified by expert opinion as PDB when the team judged that living together with

patients is hard and that they needed continuous supervision. The persistence dimension was approached by restricting attention to patients residing in chronic-patient wards within psychiatric hospitals or in psychiatric nursing homes. This is relevant, since patients residing in one of these wards in general already have had an intensive therapy in an acute ward and, in case of a psychiatric nursing home, also a long stay in a chronic ward.

Based on the screening, supplemented with data from the so-called MPD Registry, a discriminant function was developed, producing the probability of dealing with a PDB patient, based on discriminatory MPD items. When this probability exceeds a threshold value we classify the patient as PDB. The function turned out to have good discriminative power. The screening status and the classification status agree for about 80% of the screened patients. Further details of this study are reported in Bruckers *et al.* [2].

The functional form of the discriminant function for the patients admitted in a psychiatric hospital, relevant for all further analyses in this article, takes the form

$$\begin{aligned}\text{PDB}_{ij} = &-4.81 + 1.73 \cdot \text{Aggr.A}_{ij} + 0.62 \cdot \text{Aggr.P}_{ij} + 0.33 \cdot \text{Suicid}_{ij} + 0.47 \cdot \text{Appear}_{ij} \\ &+ 0.40 \cdot \text{Respect}_{ij} - 0.03 \cdot \text{Age}_i + 1.81 \cdot \text{Gender}_i - 1.50 \cdot \text{DDAC}_i \\ &+ 0.56 \cdot \text{Schizo}_i - 2.32 \cdot \text{Resid}_i + \varepsilon_{ij}, \end{aligned} \tag{2}$$

where 'Aggr.A' stands for aggression toward oneself (auto-aggression; measured on a three-point ordinal scale: absent, present but of secondary importance, present and directly contributing to intake), 'Aggr.P' for aggression against people (same scale), 'Suicid' for suicide danger (measured on a six-point ordinal scale, ranging from absent to occurrence on almost a daily basis), 'Appear' for appearance (scored on a four-point ordinal scale: absent, somewhat, clearly present, severely present), 'Respect' for respect for others (same scale), 'Age' for age in 1998, 'DDAC' for the diagnostic class Delirium, Dementia, Amnestic, and Cognitive disorders (absent/present), 'Schizo' for the diagnostic class schizophrenia (absent/present), 'Resid' for the residual diagnostic class (so-called V-codes), and ε_{ij} is the residual error term. The functional form for patients in psychiatric nursing homes

$$\begin{aligned}\text{PDB}_{ij} = &-6.39 + 1.26 \cdot \text{Aggr.A}_{ij} + 1.15 \cdot \text{Aggr.O}_{ij} + 0.65 \cdot \text{Asoc}_{ij} + 1.21 \cdot \text{Separ}_{ij} \\ &+ 0.70 \cdot \text{Social}_{ij} + 0.59 \cdot \text{Respect}_{ij} - 0.85 \cdot \text{Retar}_i + \varepsilon_{ij}, \end{aligned}$$

with the same abbreviations as in Equation (2) and in addition 'Aggr.O' standing for aggression against objects, 'Asoc' for anti-social attitude, 'Separ' for need for separation or isolation, 'Social' for socially unacceptable behavior, and 'Retar' for the diagnostic class mental retardation.

The use of cross-sectional information for a longitudinal goal may seem inherently contradictory, but has the advantage of allowing for early classification, perhaps even at intake. We conducted a sensitivity analysis for the fact that a cross-sectional discrimination is done with a view on longitudinal characteristics, we repeated the exercise, for one earlier follow-up occasion, 1998 (first semester), as well as for a later one, the first semester of 1999. The so-obtained results, encompassing three moments in time, are graphically represented in Figure 3, by way of point estimates and confidence intervals for each of the coefficients, for each one of the two sectors, and for each of the three moments in time. Although there is some variation, as one could expect, the results are relatively stable, confirming that it is sensible to classify patients based on a single moment in time, even though the psychiatric condition clearly has got a longitudinal component.

A very important conclusion from Bruckers *et al.* [2] was that, following such a discriminant rule, 35.5% of the patient population in a psychiatric hospital might belong to the PDB group, with a similar figure (32.1%) for the psychiatric nursing homes. Of course, these findings have to be taken with some caution, for two reasons. First, the longitudinal nature is ignored. Second,

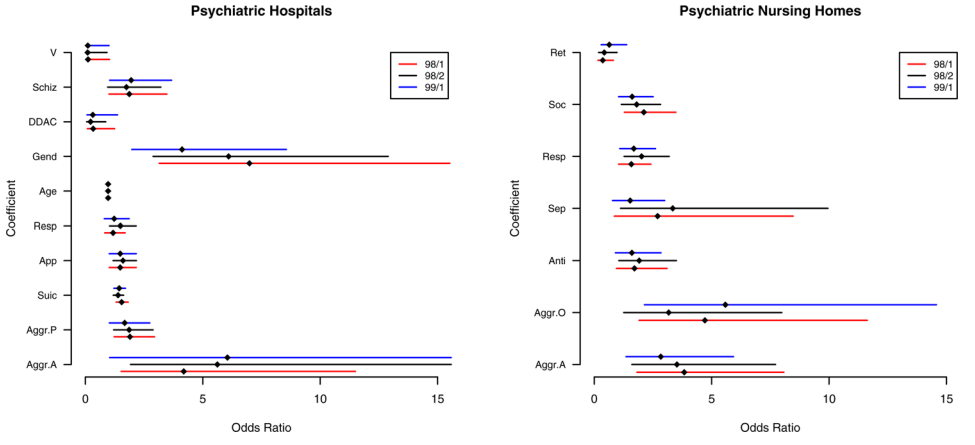

Figure 3. Sensitivity analysis for the odds ratios, originally determined in 1998 (second semester), by re-estimating the parameters from both 1998 (first semester) and 1999 (first semester). For each effect, listed in Table 1, the odds ratios and their confidence intervals are presented, for each of the three moments and time and for each of the two sectors.

there are problems inherent to the set of data in view of this goal. Therefore, as a consequence of the results derived in Bruckers *et al.* [2] as well as in this article, a new study has been designed, with the sole purpose of refining the discrimination between PDB and non-PDB patients on the one hand, and of discerning subgroups within the PDB patients on the other hand. In this respect, it is important to note that the concept of PDB, even though the group is large, is as such relatively novel and has not received a lot of scientific interest as of yet. This new study also has got a qualitative part, primarily geared at refining the very definition of PDB.

Finally, even though the discriminant function appears to be rather stable when applied to differing moments in time, the focus remains more on the disturbance aspect than on the persistence component. Using longitudinal methods, we can do more justice to the latter, as well.

4.2 *Longitudinal analysis*

The question arises, of course, whether or not the group considered to be PDB in 1998 indeed was chronic in their disturbing behavior. The fact that these patients are staying at long-stay wards only indicates that we are dealing with chronic disease statuses, not necessarily that the disturbing behavior is persistent. As stated before, it would be possible that the patient was going through an acute phase of disturbing behavior, something hard to disentangle based on information localized in time. This suggests the use of longitudinal methods.

We will apply the same definition of the PDB score is assumed across time, for reasons of consistency. This is practically most relevant and can be defended at least over a relatively short time span, as is the case here. However, when the time span increases and/or when other internal or external factors, such as the legal framework, would change, a careful assessment of the score's optimality across time would be in place. In principle, more complex models, such as dynamic longitudinal models, could be envisaged. However, such an approach would be essentially descriptive in nature, hard to use in practice, and less robust to idiosyncracies of the dataset. To build a model that adequately describes the evolution of the value of the discriminant function over time we need to consider appropriate mean, variance, and covariance models. It is essential to perform an exploratory data analysis. As shown in Figures 1 and 2, the mean profiles for the discriminant function for the PDB and non-PDB groups are different and a non-linear structure

emerges for the non-PDB group. The individual profiles follow more or less the same pattern. The figure with the individual profiles clearly shows substantial between and within variability. A key feature of the individual profiles is a vertical shift. This suggests the presence of a random intercept.

The variance functions for the PDB and non-PDB groups (Figure 2) display variance heterogeneity in the data. The variance is not constant over time. Moreover, the variability in the PDB group is larger than the variability in the non-PDB group.

To select a final model, describing the evolution of the discriminant function over time, we proceeded as follows. Verbeke and Molenberghs [12] suggest selecting a variance–covariance structure based on the most complex mean structure one is prepared to consider. After selecting such a structure, the mean model can be simplified. A model including the PDB grouping indicator, time, quadratic time, and pairwise interaction effects with PDB grouping was used as the most complex mean structure. **Q2**

The cross-sectional analysis, based on logistic regression (Table 1) already indicated that the important predictors for patients from psychiatric hospitals are rather different from that of patients from psychiatric nursing homes. Therefore, it was decided to build separate models for both types of institutions.

The variance model was selected starting from the preliminary model including three PDB group-specific random effects: an intercept, a linear, and a quadratic time slope. The 3×3 covariance matrix D for the random effects of each group was assumed to be unstructured. For the psychiatric hospitals, the residual error matrix was modeled using a group specific power-of-mean structure, allowing for the inclusion of covariates in the variance structure. For the psychiatric nursing homes, on the other hand, a group-specific Gaussian serial correlation structure provided the best fit.

The random-effect structures of both models were simplified considering hierarchically ordered models. The significance of the effects was tested using likelihood ratio test statistics. The p-values were calculated using appropriate mixtures of χ^2 distributions as reference distribution [12, p. 69–72]. The quadratic random slope was not significant at the 5% level of significance for both models and, therefore, removed from the models. However, the random intercept and linear random slope were kept in both models. These random effects and the residual matrix structures as discussed in the previous paragraph were found to be PDB group-specific.

Finally, the mean model was reduced, using the covariance structure that was just selected. For both models the mean structure for the PDB group could be simplified to a linearly increasing function with a common slope for PDB and non-PDB patients.

The reduced final model for psychiatric hospitals can be written as

$$\begin{aligned}\text{PDB-score}_{ij} &= \beta_0 + \beta_1\,\text{PDB}_i + \beta_2 t_{ij} \\ &\quad + (b_{1i} + b_{2i}t_{ij})\,\text{PDB}_i + (b_{3i} + b_{4i}t_{ij})\,\text{non-PDB}_i + \varepsilon_{ij},\end{aligned} \tag{3}$$

where β_0 is the fixed-effects intercept, β_1 the fixed effect of the PDB group versus the non-PDB group, and β_2 the fixed effects slope over time. The parameters b_{1i} and b_{3i} are the random intercept terms for the PDB and non-PDB groups, respectively. The subject-specific slopes are denoted by b_{2i} for the PDB group, b_{4i} for the non-PDB group, respectively, and ε_{ij} is the residual error term. The random effects have covariance matrix

$$D = \begin{pmatrix} d_{11} & d_{12} & 0 & 0 \\ d_{21} & d_{22} & 0 & 0 \\ 0 & 0 & d_{33} & d_{34} \\ 0 & 0 & d_{43} & d_{44} \end{pmatrix},$$

where the upper block refers to the PDB group and the lower block to the non-PDB group.

Table 3. Parameter estimates (standard errors) for the final linear mixed-effects model for psychiatric hospitals, using restricted maximum likelihood (the model is fitted to the log-transformed PDB score as well).

Effect	Parameter	Estimate (standard errors)	
		Score	Log(score+7)
Mean structure			
Intercept	β_0	−1.36 (0.10)	1.70 (0.02)
PDB effect	β_1	2.08 (0.17)	0.32 (0.03)
Time effect	β_2	−0.10 (0.02)	−0.02 (0.003)
Random-effects variance components			
Intercept (PDB)	d_{11}	2.32 (0.32)	0.05 (0.01)
Intercept (non-PDB)	d_{33}	1.96 (0.21)	0.11 (0.01)
Time (PDB)	d_{22}	0.05 (0.01)	0.001 (0.0002)
Time (non-PDB)	d_{44}	0.02 (0.01)	0.002 (0.0004)
Covariance (PDB)	d_{12}	−0.05 (0.05)	−0.001 (0.001)
Covariance (non-PDB)	d_{34}	0.09 (0.03)	0.01 (0.002)
Residual variance structure			
Power (PDB)	θ_1	0.35 (0.16)	2.19 (1.02)
Power (non-PDB)	θ_2	−1.13 (0.26)	4.29 (1.31)
Residual variance	σ^2	1.12 (0.08)	0.003 (0.002)

Parameter estimates of the model for the psychiatric hospital patients are given in Table 3, whereas Table 4 contains the results for the psychiatric nursing homes. The intercept is chosen to represent the mean value for the second part of 1998. The standard errors accompanying the variance components in Tables 2 and 3 should be interpreted with caution, for reasons reviewed

Table 4. Parameter estimates (standard errors) for the final linear mixed-effects model for psychiatric nursing homes, using restricted maximum likelihood (the model is fitted to the log-transformed PDB score as well).

Effect	Parameter	Estimate (standard errors)	
		Score	Log(score + 7)
Mean structure			
Intercept	β_0	−2.23 (0.08)	1.52 (0.02)
PDB effect	β_1	2.92 (0.27)	0.47 (0.04)
Time effect	β_2	0.03 (0.02)	0.004 (0.004)
Random effects variance components			
Intercept (PDB)	d_{11}	3.74 (0.79)	0.07 (0.01)
Intercept (non-PDB)	d_{33}	1.22 (0.18)	0.05 (0.01)
Time (PDB)	d_{22}	0.00 (–)	0.00 (–)
Time (non-PDB)	d_{44}	0.01 (0.02)	0.0002 (0.001)
Covariance (PDB)	d_{12}	0.07 (0.13)	0.0001 (0.003)
Covariance (non-PDB)	d_{34}	0.07 (0.03)	0.002 (0.001)
Serial structure			
Variance (PDB)	τ_1^2	1.58 (0.22)	0.02 (0.004)
Variance (non-PDB)	τ_2^2	0.14 (0.12)	0.01 (0.01)
Rate of Gaussian decrease (PDB)	$\frac{1}{\rho_1^2}$	0.26 (5.32)	0.00 (–)
Rate of Gaussian decrease (non-PDB)	$\frac{1}{\rho_2^2}$	1.63 (1.48)	2.41 (1.13)
Measurement error variance	(σ^2)	0.65 (0.08)	0.02 (0.002)

in [12]. As Figure 2 already suggested, the mean value of the discriminant function for the PDB group is significantly higher than the mean value of the non-PDB group. For 1998 this is not a surprise since the function was constructed using these data. The difference between the two groups is maximal around the end of 1998 and the beginning of 1999. For the non-PDB group we note a steep decrease between 1997 and 1998. This is probably due to the effect of a successful treatment to alter the behavior of the patients. This effect is less pronounced in the PDB group, which agrees with the definition of therapy-resistant patients.

Apart from an analysis using the raw PDB score as dependent variable, additional analyses were done, for both sectors, based on the log-transformed score. Parameter estimates (standard errors) are to be found in the final columns of Tables 3 and 4, respectively. The score is augmented by seven prior to taking logarithms, so as to avoid negative arguments of the logarithmic function. Although parameters between these sensitivity analyses and the original ones are not directly comparable, it is important to observe that inferences made about the PDB effect would not qualitatively change when switching from the direct to the logarithmic version of the analysis.

The PDB-score profile over time is stable in the PDB group than in the non-PDB group. Also, the variance–covariance structure contains information on the persistence dimension of the patient group under investigation. For both models it is clear that, when comparing the variance of the random intercept with the measurement error and in case of the psychiatric nursing homes with the variance of the serial component, patient-specific characteristics are important. Thus, some patients intrinsically have high values while others intrinsically have low values. The variance of the random intercepts is larger in the PDB group than in the non-PDB group, whereas the variances for the random slopes are comparable. Furthermore, note that the variance of the serial component for the PDB group (Table 4) is much larger than its counterpart for the non-PDB group. This was already observed in the exploratory data analysis. Interestingly, the rate of Gaussian decrease is much larger in the non-PDB group than in the PDB group. This indicates that stronger serial correlation exists between PDB scores in PDB patients compared with non-PDB patients in psychiatric nursing homes.

When entertaining a complex longitudinal model, it is imperative to ascertain whether its fit is of decent quality. Verbeke and Molenberghs [12] discuss a variety of model assessment techniques. We fitted a model with (1) an unstructured rather than a smooth parametric mean function and (2) a general unstructured and a heterogeneous Toeplitz covariance structure (details not reported). Both of these models failed to provide a significant improvement of the model entertained here, thus contributing to the confidence in the model and the conclusions based there upon. This in itself is not surprising, because the model building exercise undertaken already started from rather a complex model, corroborating that our model reduction exercise had led to an adequate model.

Let us also inspect the fitted correlations deriving from the estimated marginal variance-covariance matrix $V_i = Z_i D Z_i' + \Sigma_i$. This matrix is presented in Table 5 for the psychiatric hospitals. Table 6 contains the results for the psychiatric nursing homes. Considering Table 5, we clearly observe that the correlations between time points close in time is stronger for PDB patients than for non-PDB patients in psychiatric hospitals. Precisely, the PDB patients exhibit a slower decay with time lag, coupled with a time-independent correlation structures, whereas for the non-PDB patients the correlation decays faster with time, and is further a function of the actual times at which the measurements are taken. This can be explained as follows. The non-PDB patients exhibit an unstable phase, with relatively high average scores, but lower correlation. Afterward, they tend to stabilize, leading to a lower score on average, that does not vary a lot, and hence exhibits a higher correlation. The PDB patients on the other hand, are chronic in their behavior, with, on an average, a severe score. It is, therefore, unsurprising to find the correlation dependent on time lag but not on the actual measurement times.

It seems logical to consider a direct comparison between the observed and fitted correlation structure, but unfortunately this is less than straightforward for two main reasons. First, linear

Table 5. Estimated correlation matrix for PDB and non-PDB patients in psychiatric hospitals.

	Time	−4	−2	−1	0	1	2	3	4
PDB	−4	1.0000	0.7250	0.6911	0.6454	0.5881	0.5208	0.4467	0.3698
	−2	0.7250	1.0000	0.7115	0.6883	0.6538	0.6087	0.5552	0.4965
	−1	0.6911	0.7115	1.0000	0.7016	0.6810	0.6495	0.6088	0.5616
	0	0.6454	0.6883	0.7016	1.0000	0.7009	0.6845	0.6581	0.6239
	1	0.5881	0.6538	0.6810	0.7009	1.0000	0.7109	0.6998	0.6797
	2	0.5208	0.6087	0.6495	0.6845	0.7109	1.0000	0.7313	0.7258
	3	0.4467	0.5552	0.6088	0.6581	0.6998	0.7313	1.0000	0.7604
	4	0.3698	0.4965	0.5616	0.6239	0.6797	0.7258	0.7604	1.0000
Non-PDB	−4	1.0000	0.5885	0.5894	0.5855	0.5776	0.5666	0.5533	0.5385
	−2	0.5885	1.0000	0.6492	0.6577	0.6612	0.6603	0.6560	0.6491
	−1	0.5894	0.6492	1.0000	0.6845	0.6935	0.6977	0.6979	0.6950
	0	0.5855	0.6577	0.6845	1.0000	0.7191	0.7282	0.7328	0.7338
	1	0.5776	0.6612	0.6935	0.7191	1.0000	0.7521	0.7608	0.7656
	2	0.5666	0.6603	0.6977	0.7282	0.7521	1.0000	0.7826	0.7908
	3	0.5533	0.6560	0.6979	0.7328	0.7608	0.7826	1.0000	0.8101
	4	0.5385	0.6491	0.6950	0.7338	0.7656	0.7908	0.8101	1.0000

Table 6. Estimated correlation matrix for PDB and non-PDB patients in psychiatric nursing homes.

	Time	−1	0	1	2	3	4
PDB	−1	1.0000	0.6220	0.6266	0.6311	0.6356	0.6400
	0	0.6220	1.0000	0.6307	0.6351	0.6394	0.6437
	1	0.6266	0.6307	1.0000	0.6391	0.6432	0.6474
	2	0.6311	0.6351	0.6391	1.0000	0.6470	0.6510
	3	0.6356	0.6394	0.6432	0.6470	1.0000	0.6547
	4	0.6400	0.6437	0.6474	0.6510	0.6547	1.0000
Non-PDB	−1	1.0000	0.6410	0.6143	0.6053	0.6048	0.6042
	0	0.6410	1.0000	0.6664	0.6432	0.6366	0.6377
	1	0.6143	0.6664	1.0000	0.6922	0.6720	0.6671
	2	0.6053	0.6432	0.6922	1.0000	0.7175	0.6998
	3	0.6048	0.6366	0.6720	0.7175	1.0000	0.7416
	4	0.6042	0.6377	0.6671	0.6998	0.7416	1.0000

mixed models involve three parts: (a) the fixed-effects structure; (b) the random effects; (c) the residual or serial correlation. Calculating the empirically observed correlations so as to take this layered structure into account is not without ambiguity. Even the definition of residuals, needed to calculate empirical correlations, in such a hierarchical context is a topic of some controversy. Second, data are incomplete since not all patients have a score available for all times. Unless the missing data mechanism is missing completely at random [9], observed and expected features do not have to agree in the same way as they would if data were complete, even for a well fitting model.

In summary, a longitudinal analysis refines the perspective and enhances understanding of the PDB group, by simultaneously studying the disturbance and persistence characteristics. The analysis suggests that the group is substantial in size. Of course, given the selection of the data in the pilot study, this conclusion should be treated with caution. The aforementioned follow-up study will enable us to refine the conclusion. Nevertheless, in the meantime, it is of interest to explore whether the contingent of PDB patients can usefully be subdivided into meaningful subgroups, which could then be treated in tailor-made, high quality, wards.

4.3 *Cluster analysis*

To further explore the group of PDB patients, we can perform a cluster analysis to suggest possible relevant therapeutic or organizational subgroups.

As stated in Section 3, Gower's distance measure was chosen since it can handle all outcome types, i.e., (asymmetric) nominal, ordinal, interval, and ratio variables. The hierarchical Ward's minimum-variance method was applied and two clusters retained. Since the clearest separation between these two clusters can be found in the ordinal variables, a frequency table of these variables by cluster is presented in Table 7. Cluster #1 appears to consist of PDB patients with higher scores on the ordinal variables compared with Cluster #2, indicating that these patients show more pathological behavior. The χ^2 tests underscore highly significant differences in the distribution of scores between the two clusters. Further, it appears that the mean PDB score for the first cluster (0.78) is higher than for the second one (0.47). Nevertheless, this has to be judged against the background of large variability, the standard deviations being 1.80 and 2.11, respectively.

The identification of two clusters requires careful qualification and a number of comments are in place. First, cluster analysis is a pragmatic, exploratory method. It is, therefore, hard to fully formally establish that the number of clusters is equal to two, rather than three or more, or, perhaps only a single one. Therefore, our results should be taken as a mere indication that there is some room for entertaining the concept of more severe *versus* less severe PDB patients. Second, even then, one might argue it is likely for severity of PDB, as well as for other characteristics, to vary continuously across patients, rather than in a dichotomous fashion. Even then, considering a dichotomized version can be pragmatically helpful, with a view on efficiently organizing care. Arguably, these features need further study and the currently conducted follow-up study is well suited for this goal.

5. Perspective and concluding remarks

Based on the discriminant analysis and longitudinal model building, the PDB score is rather different between the PDB and non-PDB groups. This is true for the mean profiles, the variance, and correlation structure. Comparing PDB with non-PDB patients, the score is influenced by a

Table 7. Frequency table of the ordinal variables by cluster.

		Score								
Variable	Cluster	1	2	3	4	5	Total	χ^2	df	p-value
Mobility	1	36	4	40	6	5	91	43.81	4	<0.0001
	2	82	4	12	0	0	98			
Recognition of persons	1	7	32	33	9	10	91	119.56	4	<0.0001
	2	85	8	4	1	0	98			
Notion of time	1	11	20	25	4	31	91	119.42	4	<0.0001
	2	88	8	0	0	2	98			
Initiative	1	7	17	23	44		91	50.91	3	<0.0001
	2	21	39	34	4		98			
Social	1	0	12	22	57		91	29.34	3	<0.0001
	2	10	37	18	33		98			
Respect	1	2	15	24	50		91	42.37	3	<0.0001
	2	8	36	43	11		98			
Conflicts	1	3	31	23	34		91	23.09	3	<0.0001
	2	13	38	37	10		98			

different set of covariates, and for the effects in common, the magnitude of the effects is different. Also note that the different types of institutions are associated with different sets of covariates. Turning to variability, it is the largest in the PDB group. This implies relatively more heterogeneity among such patients, opening perspectives for further subdivision. This can be done using cluster analysis, where discrete groups are found, or rather by considering a patient's relative position on the PDB score's scale, in case a more continuously oriented ranking is preferred.

The modeling strategy entertained here is definitely more complex than a simple analysis, such as a time-point-specific one or one where the repeated measures are erroneously treated as independent. However, such simple analyses are subject to concern. First, treating correlated measurements as if they were independent generally results in major biases; depending on which effect is being estimated (time-independent versus time-varying, average effect versus evolution parameter, etc.), such biases can take different signs. Also, less-than-easy-to-handle multiple comparison issues may arise. Furthermore, the strategy entertained here is much more flexible when data are unbalanced, be it due to missingness or for other reasons. These points are amply treated in [9,12]. Assessment of the model's fit, for example, using a super-model as is done here, helps build confidence that the model is well fitting and hence ensuing inferences reliable. Should doubt remain, then a so-called robust, sandwich-estimator-based version of the linear mixed model [12] can be entertained.

From a practical point of view, the more complex modeling strategy comes with several advantages. First, by the very nature of the PDB condition, a cross-sectional analysis can meaningfully be done only for the disturbance but not for the persistence component. For the latter, the time component needs to be brought into the model. Second, given this, a proper longitudinal analysis is necessary to avoid the issues described in the previous paragraph. Second, even for a number of seemingly cross-sectional questions, such as estimating the size of the PDB group, a proper longitudinal analysis is advisable. In the reverse case, the size of the group can be overestimated because it would essentially be based on the severity of the disturbance component, while ignoring the more subtle differences between genuine PDB patients and patients with highly disturbing but acute behavior. Admittedly, the size-estimation-issue is a delicate one and we return to it in what follows.

Regarding the correlation structure, let us first turn to psychiatric hospitals. The correlation structure is subtly different between both groups. The PDB group is roughly of a first-order autoregressive type, showing relatively large correlations between adjacent measurements (around 0.75), which decreases with increasing time lag, dropping to about 0.35. Thus, the PDB group exhibits a chronic behavior from the beginning, with fluctuations happening in the long run rather than immediately. The non-PDB group correlation structure is closer to compound symmetry, amended by the fact that the correlations increase toward later times. This may suggest that there is an unstable, acute phase at the beginning of the study.

Turning to psychiatric nursing homes, the picture emerging from the estimated correlation structures is different. Both are relatively close to compound-symmetry, with a common correlation around 0.65. This is plausible from a field work point of view, because these patients are almost by definition of a chronic type.

Through the longitudinal analysis, we already established the rather heterogeneous nature of the PDB group, with a relative stability of the score within a patient. The longitudinal analysis does not allow to easily define subgroups within the PDB group, but the aforementioned heterogeneity encourages further exploration. By means of cluster analysis, we were able to suggest the presence of two clusters, characterized on the basis of the ordinal variables mobility, recognition of persons, notion of time, initiative, socially unacceptable behavior, respect for others, and conflicts. Classical contingency table analysis confirmed a significant difference between the two clusters on each of these variables. A significant difference was not found on the continuous variables.

In conclusion, the PDB patients are numerous, differ considerably from the control patients, in the sense that they exhibit a higher score. The group is also heterogeneous allowing one to further

subdivide the group in clusters, based on the ordinal components of the score. Obviously, this opens perspectives for further therapeutic and/or organizational refinement. Most importantly, not only is there a need for specialized treatment entities, but also further sub-specialization between such entities is to be recommended.

Some caution is needed, though. Arguably, the data behind this experiment are less useful to estimate the size of the PDB group. Indeed, they have to be considered as a pilot, predominantly intended to study the difference between PDB and non-PDB patients on the one hand, and to explore the existence of subgroups within the PDB segment on the other hand. Currently, a purposefully designed study is being undertaken so as to allow for measuring up the size of the PDB group. As a consequence, results pertaining to size estimation have to be treated as preliminary at best. This notwithstanding, it has been deduced by Bruckers *et al.* [2] that the subgroup is likely much larger commonly assumed.

Further work will be directed toward refining the clustering of PDB patients by means of methods that take the longitudinal structure of the profiles into account. This might, for example, be achieved by means of latent class models [10].

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