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FACULTY OF SCIENCES

Master of Statistics: Biostatistics

Masterproef

Sick leave and presenteeism in Ankylosing Spondylitis patients under treatment with Tumor Necrosis Factor (TNF) inhibitor

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Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

Transnational University Limburg is a unique collaboration of two universities in two countries: the University of Hasselt and Maastricht University.

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Maastricht, 02 Feb 2013

Thien Thi Vinh Nguyen

Abstract

Presenteeism and days of sick leave were considered to be important socioeconomic outcomes in Ankylosing Spondylitis (AS) patients. The objectives of the present study was to investigate (1) the trend of change in presenteeism over two years, and (2) whether presenteeism was a better predictor of sick leave than disease activity (BASDAI) and functional status (BASFI) using longitudinal data analysis.

Seventy-one AS patients with paid jobs from the European Ankylosing Spondylitis Infliximab Cohort (EASIC) study were assessed for disease-related sick leave days, presenteeism and some important clinical outcomes like BASDAI and BASFI over a period of two years. For Objective 1, a linear mixed model (LMM) was used. For Objective 2, Poisson regression, Negative Binomial, Zero-inflated Poisson, Zero-inflated Negative Binomial models were used for modeling the association between sick leave, presenteeism and BASDAI, BASFI.

Presenteeism was not dependent on time, but significant influenced by the interaction between BASDAI and BASFI. The variability of presenteeism between the patients was found significantly larger than that within patients. The probability of zero day of sick leave was associated with only the value of presenteeism at previous time. The odds of having zero day of sick leave decreases by 25% as presenteeism increases by one unit. The number of sick leave days depends on time with quadratic function and also on presenteeism: an increase of one unit in presenteeism yields an increase in the estimated mean for sick leave days by 29%.

In conclusion, presenteeism was found better than BASDAI and BASFI in prediction the probability of getting sick leave and number of sick leave day.

List of Abbreviations

AIC	Akaike information criterion
AS	Ankylosing Spondylitis
ASSERT	Ankylosing Spondylitis Study for Evaluation of Recombinant infliximab Therapy
BASDAI	Bath Anlylosing Spondylitis Disease Activity Index
BASFI	Bath Anlylosing Spondylitis Functional Index
BIC	Bayes information criterion
EASIC	European Ankylosing Spondylitis Infliximab Cohort study
EM	Expectation Maximization
LMM	Linear Mixed Model
LRT	Likelihood ratio test
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple Imputation
ML	Maximum Likelihood
MNAR	Missing not at random
NB	Negative Binomial
NPMLE	Non parametric maximum likelihood estimation
REML	Residual maximum likelihood
VAS	Visual analogue scale
ZINB	Zero-inflated Negative Binomial
ZIP	Zero-inflated Poisson

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1. Introduction

1.1. Background

Ankylosing spondylitis (AS) is the prototype of the spondylarthopathies, a family of chronic inflammatory rheumatic disease with an estimated prevalence of about 0.4% in Europe (Braun et al. 2004, Akkoc and Khan 2005, Muñoz-Fernández et al. 2010). The disease usually starts in the third decade of life, when the professional career is one of the most important social roles in a person's life (Khan 2002). The disease is two to three times more common in men than in women (Listing et al. 2004). Clinical symptoms usually begin with back pain and stiffness in adolescence, and can lead to impaired spinal mobility and/or chest expansion. In addition, fatigue can be a severe problem for patients. Consequently, patients experience difficulties to carry out daily activities, and perform their job. This will lead to not only presenteeism as the act of attending work while sick, but also sick leave defined as absence from work because of sickness in those with paid jobs and eventually withdrawal from paid work.

In AS, symptoms usually have an onset in early adulthood, when people start their career and this contributes to the relevance of worker participation. Notwithstanding, the socioeconomic consequences of AS received only limited attention in the literature before 2000 because of several reasons. On the one hand, the prevalence of AS had been underestimated (Van der Linden et al. 1984). Recent studies showed considerably higher AS prevalence proportions (e.g. 0.86% in German population (Braun et al. 1998) and 1.4% in Norwegian population (Gran et al. 1985)) than the classic estimate (0.08%). On the other hand, the society had not been aware of the fact that there would be introduction of expensive treatments and that the costs of treatments with these drugs may be partially offset by the improvement in the work outcomes.

Recently, socioeconomic consequences of AS has increasingly received attention and become a recognized outcome measure (Elixhauser et al. 1993). The socioeconomic impact of a disease refers to the effect of illness on the ability to perform work. One of the important economic endpoints is labour force participation. The work restrictions not only affect the quality of life and economic status of individual patients but also impose an economic burden on the society (Boonen et al. 2001b).

1.2. Recent study on work outcomes in Ankylosing Spondylitis

There have been several studies on work outcomes in AS in the last decade but most concentrated on employment/work disability and few adjusted employment rates for those in the general population (Boonen et al. 2001c). Boonen (2001a) and Marengo (2008) showed that work disability was remarkably increased in AS patients. With regard to sick

leave, a study showed about 50% of patients annually having episodes of sick leave and sick leave per year in AS was higher than in general population (Boonen et al. 2002). A study on the impact of AS on sick leave, presenteeism and unpaid productivity demonstrated that patients with AS not only had substantial sick leave but also experienced restrictions while being at work and this restriction was associated with limitation in physical functioning (Boonen et al. 2010).

1.3. Problem statements

It is important to understand not only the magnitude of the impact of disease on work outcome but also the factors affecting restrictions in work participation of the patients. Currently, there are no published studies that explore factors contributing to presenteeism and sick leave using longitudinal data analysis. In classic models, factors investigated include age, gender, disease duration, disease activity assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(Garrett et al. 1994) and physical functioning assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) (Calin et al. 1994). These instruments belong to the core outcome measures of AS. In addition to these biomedical factors, contextual factors such as type of work, education, the ability to cope with pain and limitations are also known to play a role. These factors, however, are rarely measured in studies due to a lack of awareness of their importance. To our knowledge no study has been performed to understand sick leave and presenteeism in persons adequately treated with tumour necrosis factor α (TNF-α) inhibitors.

Recently, AS clinicians believe that presenteeism might predict sick leave. Given that presenteeism is closely related to work, presenteeism might better predicts sick leave than BASDAI and BASFI. If this was true, using presenteeism as a tool for detecting patients at risk of sick leave would be much more efficient than using clinical measures.

The objectives of the present study was to investigate in patients with AS that are adequately treated with TNF-α inhibitors (1) the trend of change in presenteeism over two years in relation to work-related, demographic and clinical variables, and (2) whether presenteeism was a better predictor of sick leave than BASDAI and BASFI using longitudinal data analysis.

2. Material and methods

2.1. Data description

Ankylosing Spondylitis Study for Evaluation of Recombinant infliximab Therapy (ASSERT) was one of the few studies reporting results of a randomized, double blind, placebo controlled trial with regard to work outcomes. About 60% of the population was at work at baseline. After 24 weeks there was a substantial improvement in sick leave and presenteeism. In ASSERT, all patients continued on infliximab from week 30 onwards. The

European AS Infliximab Cohort study (EASIC) study followed by ASSERT study provide 2 year follow-up data, continue provides not only clinical measurements but also economic information.

All 145 European AS patients who had completed visit "week 96" in the ASSERT (the last visit week in two year) were invited to participate in a 96 weeks follow up open label study EASIC. Between end of ASSERT and start of EASIC, there was an average period without follow up of 1.3 years.

One hundred and nine patients participated in EASIC study, who were from six European countries: Germany (n=37), The Netherlands (n=27), Belgium (n=27), United Kingdom (n= 10), France (n= 5) and Finland (n=3). All of these patients were treated with infliximab at mean dose of 5 mg/kg of body weight every 6 – 8 weeks.

Basic demographic data (age, gender, weight, height, employment status, type of work) and clinical as well as work-related measurements (BASDAI, BASFI, presenteeism, sick leave days) were collected at baseline and every six months (five time points of study in total). Ninety two percent of patients in the EASIC were followed up until week 96^{th}, with some missing value in specific measurements.

Sick leave in this study was defined as the time off from work (in work days) in the last six months, accounting for temporary inability to perform duties because of AS disease. Presenteeism was determined using a questionnaire to measure the effect of AS on productivity while a patient is at work. Presenteeism score ranges from 0 to 10 with 0 indicating no effect of disease and 10 indicating strong effect on productivity.

The clinical outcomes included BASDAI and BASFI. BASDAI measures severity of disease activity in term of spinal and peripheral joint pain, fatigue, localized tenderness and morning stiffness. BASDAI was determined using a visual analogue scale (VAS) of 0-10 (0: no problem; 10: worst problem). BASFI measured functional capability to cope with daily tasks. Similar to BASDAI, BASFI was determined using a VAS of 0-10 (0: easy; 10: impossible). The questionnaires used to measure BASDAI and BASFI are given in Appendix 1.

2.2. Statistical analysis

2.2.1. Exploratory data analyses

Prior to statistical modeling, data were explored using graphs. For both outcomes, sick leave and presenteeism, individual profile, mean profile and variance profile were plotted to visualize how presenteeism and sick leaves vary over time. The individual profile helps comparison of the between- and within- patient variability. The mean plot is useful for choosing an appropriate fixed-effect structure in statistical modeling. The average trend of square residuals over time in the variance profile indicates whether a constant variance model or serial correlation should be added to the model.

For count data of sick leave, an extra frequency plot was used to determine the extent of excess zeros. In additional, bar graphs were used with the bars representing the proportions of sick leave in different groups of type of work and gender.

2.2.2. Longitudinal study on presenteeism

For this objective, we used a linear mixed model to analyze presenteeism.

The linear mixed model (LMM) introduced by West *et al.* (2006) is represented as:

$$\boldsymbol{Y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{Z}_i\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i$$

where $\boldsymbol{Y}_i$ is the response vector for patient i, $\boldsymbol{X}_i$ is the design matrix for the fixed effects, $\boldsymbol{\beta}$ is the vector of regression coefficients, $\boldsymbol{Z}_i$ is the design matrix for subject-specific effects, $\boldsymbol{b}_i$ is the vector of random effects, and $\boldsymbol{\varepsilon}_i$ is the vector of error components.

In this model, it is assumed that $\boldsymbol{b}_i \sim N(\mathbf{0}, \boldsymbol{D})$ and $\boldsymbol{\varepsilon}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma}_i)$, and $\boldsymbol{b}_i$and $\boldsymbol{\varepsilon}_i$ are independent, where **0** is a zero matrix, $\boldsymbol{D}\ and\ \boldsymbol{\Sigma}_i$ are the variance-covariance matrices.

Once the fixed effects and random effects have been introduced into the model, the remaining variation in the response is due to the residual error $\boldsymbol{\varepsilon}_i$. Many covariance structures for the residuals can be specified. A special class of parametric models for Σ_i is obtained from the splitting $\boldsymbol{\varepsilon}_i$ into a measurement error component $\boldsymbol{\varepsilon}_{i(1)}$ and a serial correlation component $\boldsymbol{\varepsilon}_{i(2)}$. Frequently, $\boldsymbol{\varepsilon}_{i(1)}$ is assumed to be normal distributed with mean 0 and constant variance, $\boldsymbol{\varepsilon}_{i(2)}$ can be follow Gaussian or Exponential functions.

The solution for fixed effects to the mixed model equation is a maximum likelihood (ML) estimate. The likelihood ratio test (LRT) can be used to compare different models with different mean structure but equal covariance structure. The test statistic is calculated by subtracting the -2ML log-likelihood for the full model from that for the nested model. The asymptotic null distribution of the test statistic is the χ^2 with degrees of freedom equal to the difference in the number of fixed-effects parameters.

Covariance parameters in the LMM can be estimated using ML estimation or residual maximum likelihood (REML) estimation. Different models with the same fixed-effects parameters but different sets of covariance parameters can be compared using likelihood ratio test. It should be noticed that REML estimates should be used for both full and nested models in this test. The distribution of test statistic depends on the following two cases:

Case1: If parameters satisfying the null hypothesis do not lie on the boundary, the test statistic is asymptotically distributed as χ^2 with degrees of freedom equal to the difference in the number of covariance parameters in the full and the nested model.

Case2: If parameters satisfying the null hypothesis lie on the boundary, the test statistic is asymptotically distributed as a mixture of two χ^2 distributions (Self and Liang 1987, Stram and Lee 1994, Verbeke and Molenberghs 2009).

2.2.3. Predictors of sick leave

To investigate whether presenteeism can predict sick leave better than clinical measures, we used standard models, and zero-inflated (mixed) models for count data.

2.2.3.1. Standard models

Poisson regression is usually used to model count data assuming Poisson distribution for response variables and the logarithm of their expected value can be modeled by a linear combination of unknown parameters. A Poisson distribution is characterized by two parameters having the same value, the expected value (mean) and the variance. However, this is does not always apply to count data. It is not uncommon that the observed variance of a count variable is greater than the observed mean, which is referred to as overdispersion. In this case, using Poisson regression to model data is not appropriate.

When overdispersion occurs as a consequence of omission of relevant explanatory variables, data can be modeled using Negative Binomial (NB) regression. Like Poisson regression, NB regression also examines relationship between predictors and count dependent variable through log link, but assumes a mixture distribution for count variable. Suppose that $\boldsymbol{Y}_i \sim Poisson\ (\boldsymbol{\lambda}_i)$, but $\boldsymbol{\lambda}_i$ itself is a random variable with a Gamma distribution with mean $E(\boldsymbol{\lambda}_i) = \boldsymbol{\mu}_i$ and the variance $\text{var}(\boldsymbol{\lambda}_i) = \boldsymbol{\mu}_i/k$. Then the unconditional distribution of $\boldsymbol{Y}_i$ is Negative Binomial with the probability density function

$$f(Y_i = y_i) = \frac{\Gamma(y_i + k)}{\Gamma(k) y_i!}\left(\frac{k}{k + \mu_i}\right)^k \left(\frac{\mu_i}{k + \mu_i}\right)^{y_i}$$

This distribution has mean $E(\boldsymbol{Y}_i) = \boldsymbol{\mu}_i$ and variance $\text{Var}(\boldsymbol{Y}_i) = \boldsymbol{\mu}_i(1 + \boldsymbol{\mu}_i k^{-1})$. The k^{-1} is the dispersion parameter. When k^{-1} = 0, the variance and the mean become identical, the NB distribution will reduce to Poisson distribution. When $k^{-1} > 0$, the variance will exceed the mean, the distribution allows for overdispersion. An important characteristic of this distribution is that it accounts only for overdispersion, not for underdispersion (i.e. the variance is smaller than the mean).

2.2.3.2. Zero-inflated models

In some situations where a major source of overdispersion is the preponderance of zero counts in data, the so-called zero-inflated data, data are not accurately modeled. There are considerable literature on modeling zero-inflated count data using the hurdle model (Mullahy 1986) and the zero-inflated count model (Lambert 1992).

The hurdle model is a two-part model for count data. The first part is the model for the binary variable indicating whether the response outcome is zero or positive. Conditional on a positive outcome, the second part of model uses a truncated Poisson distribution or a truncated Negative Binomial (NB) distribution to model the positive variable. Let $\boldsymbol{Y}_i$ denote the observation matrix for subject I (i = 1, ..., n). The probability P($\boldsymbol{Y}_i > 0$) = $1 - \boldsymbol{p}_i$ and P($\boldsymbol{Y}_i = 0$) = $\boldsymbol{p}_i$. A logistic regression model was used for $\boldsymbol{p}_i$ and a log-linear model was used for the mean of the truncated Poisson distribution or truncated Negative Binomial (NB) distribution.

The zero-inflated count model is an alternative for count data with excess zeros. This model assumed that data are from a mixture of a degenerate distribution at zero and an ordinary count distribution, such as a Poisson or Negative Binomial distributions. For example, zero-inflated Poisson (ZIP) model assumed for subject i,

$$\boldsymbol{Y}_i \sim \begin{cases} 0 & with\ probability\ \boldsymbol{p}_i; \\ Poisson\ (\boldsymbol{\lambda}_i) & with\ probability\ 1 - \boldsymbol{p}_i \end{cases}$$

the parameters $\boldsymbol{p}_i$ and $\boldsymbol{\lambda}_i$ are modeled via canonical link GLMs as $\log(\boldsymbol{\lambda}_i) = \mathbf{B}_\mathrm{i}\boldsymbol{\beta}$ and $\mathrm{logit}(\boldsymbol{p}_i) = \mathbf{G}_\mathrm{i}\boldsymbol{\gamma}$ for design matrices $\mathbf{B}_\mathrm{i}$ and $\mathbf{G}_\mathrm{i}$. Although this model consists of two distinct parts, but the components must be fit simultaneously.

The zero-inflated Negative Binomial (ZINB) model replaces the Poisson distribution for count data by Negative Binomial distribution. The difference between ZIP and ZINB models is that overdispersion is not accounted in the ZIP model, but is accounted in the ZINB model. When there is excess zeros and variability in the non-zero outcomes, the ZIP model is less adequate than the ZINB model.

These models can be fitted using maximum likelihood (ML) via the Expectation Maximization (EM) algorithm. Asymptotic variance-covariance matrices for the parameter estimates can be estimated using the inverse Fisher information matrix, and inference can be performed using likelihood ratio tests.

2.2.3.3. Zero-inflated mixed model for repeated measurements of sick leave

The models proposed in section 2.2.3.2 were based on assumption of independence among the responses. In the repeated/longitudinal design, such an assumption is clearly violated. There certainly is a correlation among repeated measures on the same patient. Thus, hurdle (hurdle Poisson, hurdle NB) and zero – inflated count models (ZIP, ZINB) can seriously affect the validity of statistical inference in such a case.

Introducing the random effects into variety of regression model can account for correlated response and multiple sources of variability. Hall (2004) extended the Lambert (1992) zero-inflated count models to handle longitudinal data, adding a random effect to account for the within-subject correlation in the count state. Min and Agresti (2005)

proposed a general case by adding random effects in both two components. If Y_{ij} be the observation j (j=1,..,t_i) for subject i (i = 1,..,n) and let $\boldsymbol{b}_i = (\boldsymbol{b}_{1i}, \boldsymbol{b}_{2i})'$ be random effects designed to account for within-subject correlation. The models for λ_{ij} and p_{ij} are of the forms:

$$\log(\lambda_{ij}) = B_{ij}\boldsymbol{\beta} + \sigma_{1ij}\mathbf{b}_{1i},$$

$$\text{logit}(p_{ij}) = G_{ij}\boldsymbol{\gamma} + \sigma_{2ij}\mathbf{b}_{2i}$$

where $B_{ij,}$ G_{ij} and σ_{1ij}, σ_{2ij} are covariate vectors pertaining to the fixed and the random effects respectively. Further assumption for $\mathbf{b}_{1i}$ and $\mathbf{b}_{2i}$ can be made like jointly normal distributed and possible correlation or even uncorrelated.

ML via EM algorithm can be used to estimate the parameters. For large sample size, the Wald test and confident interval can be performed, but for moderate and small sample, likelihood ratio test was preferred (Lambert 1992).

2.2.4. Information criteria

For model selection, we used the Akaike information criterion (AIC) (Akaike 1973), which is calculated as follows: $AIC = -2 \times \ln(L) + 2p$, where L is the ML or REML of the fitted model and p is the total number of parameters being estimated in the model. AIC provides a way to compare any two models fitted to the same set of observations; i.e., the models do not need to be nested. A smaller value of AIC indicates a better fit of model.

The Bayes information criterion (BIC) is also commonly used to assess the fit of a model. BIC is calculated as: $BIC = -2 \times \ln(L) + p \times \ln(n)$, with n is the total number of observations used in estimation the model. Similar to AIC, model with smaller value of BIC will be preferred in model selection.

2.3. Software

R was used for data exploration and SAS 9.2 for model fitting. The significant level was set at 0.05. Proc MIXED was used to fit the linear mixed model. Proc COUNTREG was used to fit the model to data with assumed Poisson distribution and Negative Binomial distribution. Proc NLMIXED with initial values for parameters set at 0 was used to fit the Hurdle model. Proc NLMIXED was used to fit both ZIP model and ZINB model.

3. Results

3.1. Longitudinal study on presenteeism

3.1.1. Exploratory data analyses for presenteeism

Because presenteeism was defined as the impact of AS on worker productivity, only patients who have paid job were considered in this analysis. Seventy-one patients have paid job in which only 4 patients changed their employment status and the others keep their employment status constant over two years.

3.1.1.1. Baseline characteristics of patients

The baseline characteristics of the EASIC patients who have paid jobs (n = 71) are presented in Table 1. Mean age of these patients is 40 years. Most of them are male (> 80%). The values of BASDAI and BASFI at baseline are lower than 4, indicating that the function and spinal mobility of AS patients at the beginning of study was well controlled by TNF-α inhibitors.

Table 1: The baseline characteristics of EASIC employed patients (n = 71)

	Mean	**Standard deviation**
Age	40.52	9.56
Male gender (%)	86%	
Weight(kg)	80.601	12.571
Height(cm)	175.185	9.335
Fulltime job (%)	83.63%	
BASDAI	3.15	1.70
BASFI	3.50	1.38

3.1.1.2. Individual profile

The individual profile of presenteeism score was given in Figure 1. The differences among the entry time points in different patients were shorter than 3 months (most of them entered the study in June 2006; the last patient entered in September 2006). We observed the substantial variability within and between patients. Only 275 observations were obtained instead of 355 (5 follow-up time points planned for each patient). The missing data occurred due to drop-out of patients as well as intermittent missing measurements within patients.

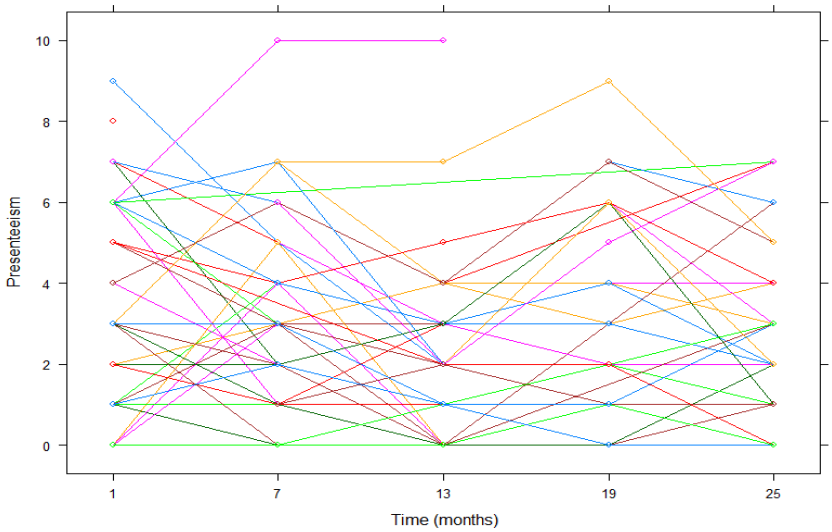


Figure 1: Profile plot of Presenteeism over time

3.1.1.3. The mean structure

The solid line in Figure 2 shows the smoothed average of presenteeism for the whole population at different time points. The average of presenteeism decreased over time since baseline. This implies that the influence of disease on productivity in AS patients at work decreased over time at the population level. This will be explored further in statistical modeling.

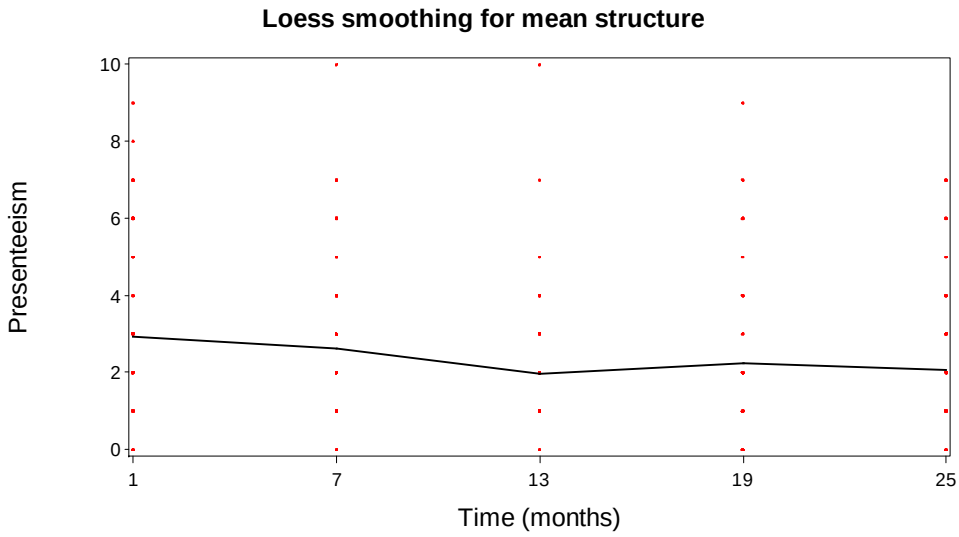


Figure 2: Average evolution of Presenteeism

3.1.1.4. The variance structure

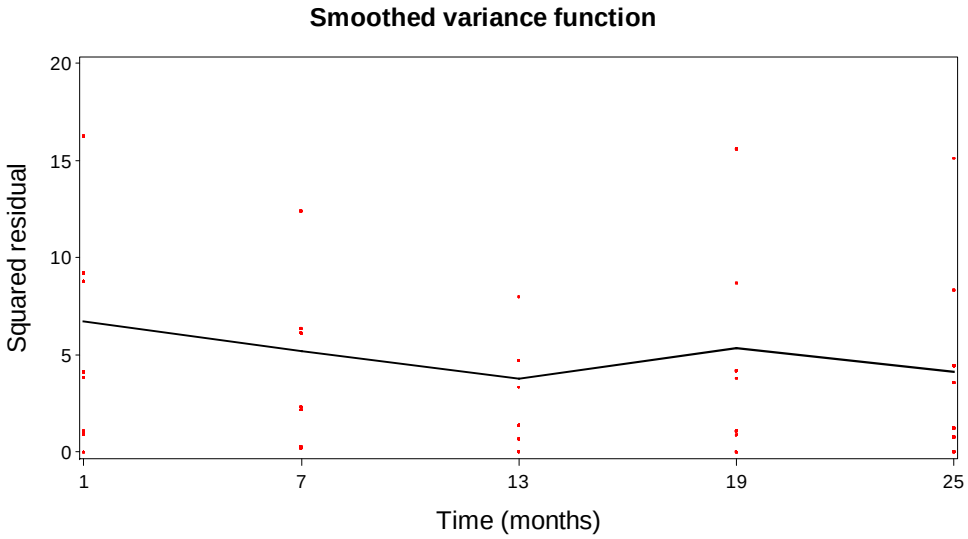


Figure 3: Variance structure of Presenteeism

In addition to the mean structure, the changing of the variance is important to build an appropriate longitudinal model. It depicts the overall evolution of the variance over time. Figure 3 suggests a constant variance function.

3.1.1.5. The plot of Presenteeism with BASDAI and BASFI

BASDAI and BASFI were considered to be very important measurements in AS and are expected in this study to predict the presenteeism of AS patients. The plot that can show us how the value of presenteeism changes with the changing of both BASDAI and BASFI was constructed. Level plot in R is a type of graph used to display a surface in two rather than three dimensions. The level plot uses colour region to present the value of presenteeism, where the more intense color the dots have, the lower values of presenteeism they represent (red = 0; white = 10).

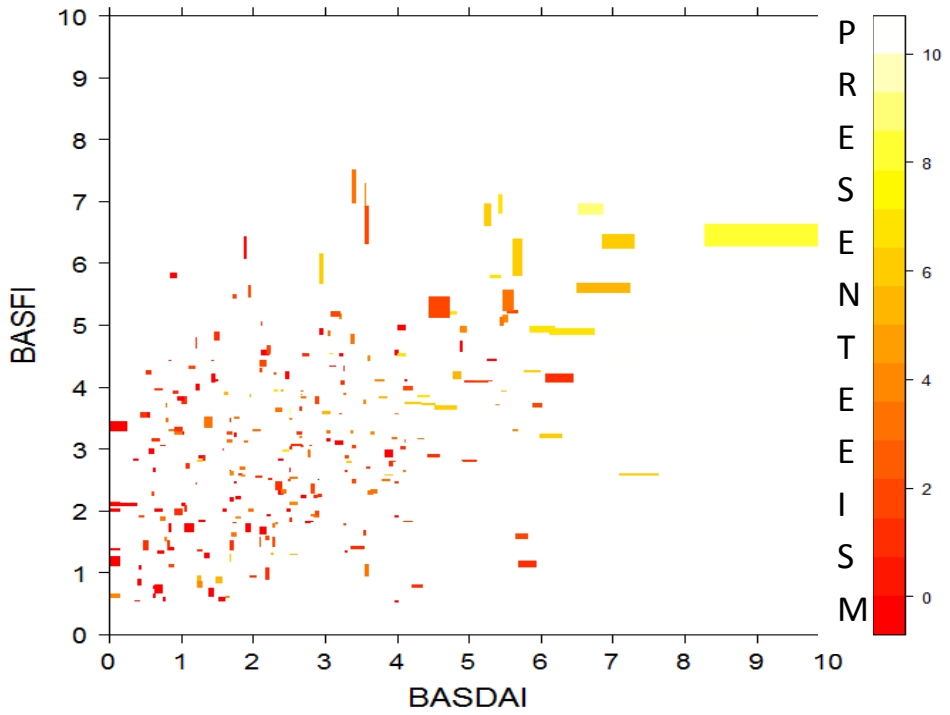


Figure 4: Level plot of Presenteeism versus BASDAI and BASFI

Figure 4 shows that the rate of changing presenteeism as a function of BASDAI is smaller in patients with low values of BASFI than in patients with high values of BASFI. Especially in patients with BASFI < 1, presenteeism decreased with increasing BASDAI. This suggests an interaction effect between BASDAI and BASFI on presenteeism.

3.1.2. Linear mixed model (LMM) for presenteeism

Based on the average trend in the mean structure plot, initially the evolution of Presenteeism was assumed to have a linear time effect. Then the models with quadratic time and cubic time effects were also fitted. The results showed that the quadratic time was significant while the cubic time effect was not significant.

The initial multivariate model was fitted to the data with independent variables including time, time^2, baseline age, gender, BMI index, BASDAI, BASFI, type of work (full/part-time) and the interactions between BMI with time, interactions between BASDAI and BASFI, interaction between BASDAI, BASFI with time and time^2. To see whether the employment status (stable or not stable) had an effect on presenteeism, this variable was introduced to the model. However, we could not estimate the parameter associated with this effect since we had too few observations on the unstable employment status. Thus, the analysis was re-done for those patients who had stable employment status (n= 67). The results from two analyses were very similar. Employment status had no influence on presenteeism and were excluded from the models.

We introduced the random effects into the model to estimate the variability between the patients. The random effect structure included a random intercept and two random slopes for time and time^2 (unstructured type). The value of presenteeism of patient i ($i = 1, \dots, 71$) at time j ($j = 1, .., 5$) was initially modeled as follows:

$$Presenteeism_{ij} = (\beta_0 + \alpha_{0i}) + (\beta_1 + \alpha_{1i}) * time_{ij} + (\beta_2 + \alpha_{2i}) * {time^2}_{ij} + \beta_3 * age_i + \beta_4 * gender_i + \beta_5 * BMI_i + \beta_6 * type_i + \beta_7 * BASDAI_{ij} + \beta_8 * BASFI_{ij} + \beta_9 * time_{ij} * BMI_i + \beta_{10} * time_{ij} * BASDAI_{ij} + \beta_{11} * time_{ij} * BASFI_{ij} + \beta_{12} * {time_{ij}}^2 * BASDAI_{ij} + \beta_{13} * {time_{ij}}^2 * BASFI_{ij} + \beta_{14} * BASDAI_{ij} * BASFI_{ij} + \varepsilon_{ij}$$

where $\beta_0, \dots, \beta_{14}$ are parameters for the fixed effects, $\alpha_{0i}, \alpha_{1i}, \alpha_{2i}$ are parameters for the random effects, and ε_{ij} is the error term, $\varepsilon_{ij} \sim N(0, \boldsymbol{\Sigma})$.

3.1.2.1. Residual covariance structure

The initial model with mean and random effect structures was fitted three times, with varying serial correlation structures. The model with the Exponential serial correlation structure did not converge. The BIC values for model with simple correlation and Gaussian correlation were 1032.5 and 1041.1 respectively. The model with smaller value of BIC was preferred. Thus, model with simple correlation was chosen for further analysis.

3.1.2.2. Reduction of random effects structure

We first tried to reduce the random slope effect for time^2 and then random slope for time. Finally, we test for the need of random intercept. The model selection was based on the likelihood ratio test where the asymptotic null distribution of the test statistic is mixed Chi-square with equal weights of 0.5 (Verbeke and Molenberghs 2009). Table 2 shows the model selection results.

Table 2: Likelihood ratio tests for model comparison of random effects

Model	Random Effects	-2L(REML)	Ref.	Asymptotic Null Distribution	P-value
1	Intercept, time, time^2	1022.0			
2	Intercept, time	1029.3	1	${x^2}_{2,3}$	0.065
3	Intercept	1031.3	2	${x^2}_{1,2}$	0.51
4	-	1102.6	3	${x^2}_{0,1}$	<0.001

The difference in values of -2L(REML) for the models with random intercept and non-random intercept was significant. The covariance structure could not be simplified by removing the random intercept effect.

3.1.2.3. Reduction of mean structure

In order to get a parsimonious model, we applied the backward selection to remove non-significant variables. Likelihood ratio test was used to compare the models. The results for mean structure comparison were shown in Table 3.

Table 3: Likelihood ratio tests for model comparison in mean structure

Model	Mean structure	Parameters	-2L(ML)	Reference model	P-value
1	All	19	939.9		
2	Exclude BMI and interactions	17	940.3	1	0.53
3	Exclude age	16	940.6	2	0.58
4	Exclude sex	14	941.9	3	0.52
5	Exclude time^2, BASFI * time^2 BASDAI * time^2	11	947.6	4	0.12
6	Exclude BASFI * time, BASDAI * time	9	948.8	5	0.54
7	Exclude time	8	951.0	6	0.13
8	Exclude type	6	952.2	7	0.54
9	Exclude BASDAI*BASFI	5	968.4	8	<0.001

Note: Type variable: Type of work (full time/ part time); G^2: Different value in log likelihood

We got the final linear mixed model for presenteeism (model 8) which contained BASDAI, BASFI and the interaction between them as the fixed effects. The parameter estimates for this model were given in Table 4. BASDAI and BASFI were not significant, but the interaction effect between them was highly significant on presenteeism of AS patients.

The estimated variability $var(\alpha_{0i})$ between patient was 2.01, and the estimated variability within patients $var(\varepsilon_{ij})$ was 1.40. This agrees with our observation from the individual profile (Figure 1) in the exploratory data analysis.

Table 4: Parameter estimates for a linear mixed model of presenteeism

Effects	Estimate	SD	t-value	Pr > |t|
Intercept	1.6248	0.4566	3.56	0.0007
BASDAI	-0.0355	0.1433	-0.25	0.8045
BASFI	-0.1532	0.1344	-1.14	0.2557
BASDAI* BASFI	0.1451	0.0355	4.09	<0.0001

In conclusion, the influence of the disease on the productivity depends on the activity of disease (BASDAI) and the limitation in physical function of patients (BASFI). Moreover, the effect of BASDAI on the presenteeism would be different with different values of BASFI. For example, the expected presenteeism of a patient with BASFI = 3 will increase by 0.399 while that with BASFI = 6 will increase by 0.83 with an increase in BASDAI by 1 unit. The observed values and the predicted lines of both cases are shown in Figure 5.

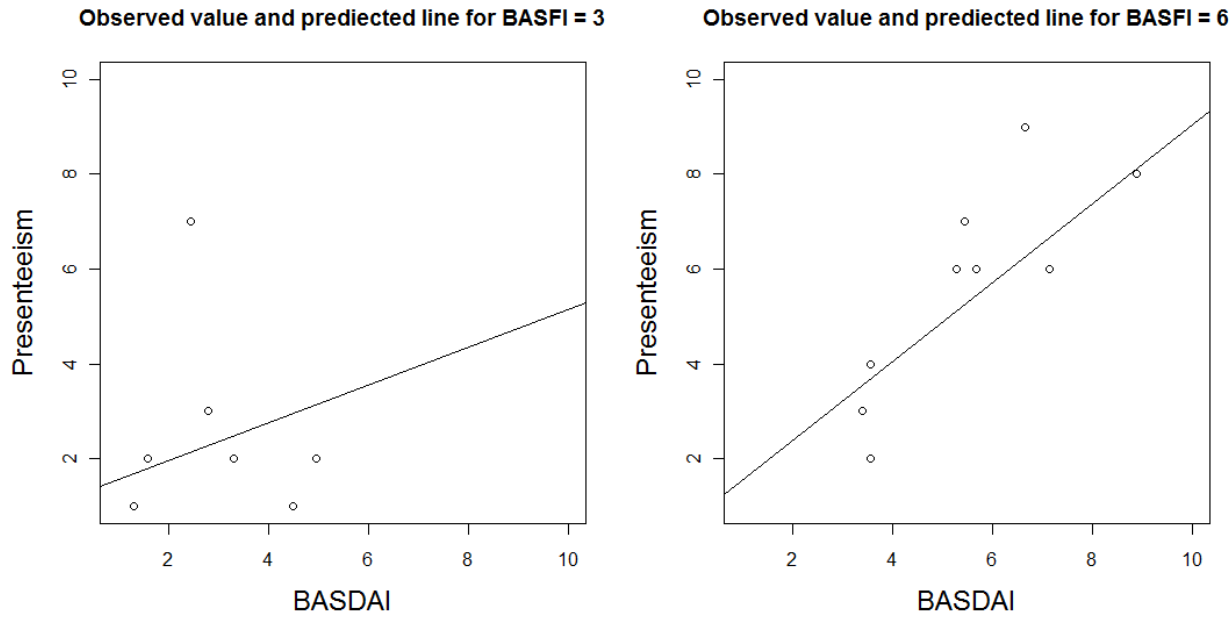


Figure 5: Observed values and predicted line of Presenteeism versus BASDAI

3.1.3. Model diagnostics for LMM of presenteeism

The final model for presenteeism was checked for its assumptions on the residuals as well as for identifying the potential outliers in the data set. To check for the independence, homogeneity and normality of residuals, the scatter plot of studentized residuals against predicted value of presenteeism and the normal quantile-quantile plot (Q-Q plot) were constructed (Figure S1 in Appendix 2).

The scatter plot shows that the residuals are fairly homogeneous across the fitted value, and there are some possible outliers that may warrant further investigation. Figure S1 also suggests that the assumption of normality is valid. This was confirmed by the Shapiro-Wilk test (test statistic = 0.987; p-value = 0.44).

Seven possible outliers were discarded and model was refitted. The parameter estimates for fixed effects were similar to those for the original model (see Table S1 in Appendix 2). This suggests that the outliers do not strongly influence these estimates.

The influence of outliers on covariance parameter estimates was examined by the influence plots (Figure S2 in Appendix 2). Patient with ID number 802005 was found to have a very high value of Cook's distance and a lowest value of CovRatio. When all observations from this patient were removed, the variance for patient effect in the new model decreased from 2. 01 to 1.88. This change was small as we expected.

The distribution of the estimated random intercept effect generated by fitting LMM for presenteeism has limited value to check for normality, because this distribution does not fully reflect the true distribution of the random effect (West et al. 2006).

3.2. Predictors of sick leave

3.2.1. Exploratory data analyses for sick leave

3.2.1.1. Frequency of sick leave days

The same dataset as used in the study on presenteeism was used in this study on sick leave. Only the sick leave days related to AS were counted. Figure 6 presents frequency of sick leave days for AS patients. The minimum and maximum values of sick leave are 0 and 82 days, respectively. The histogram picks at 0 (> 88% of the observations) because most of patients have 0 day of sick leave during two year of study. Forty-six patients (65%) had 0 day of sick leave at all the time points of study. Only 25 patients had at least one day of sick leave during the study.

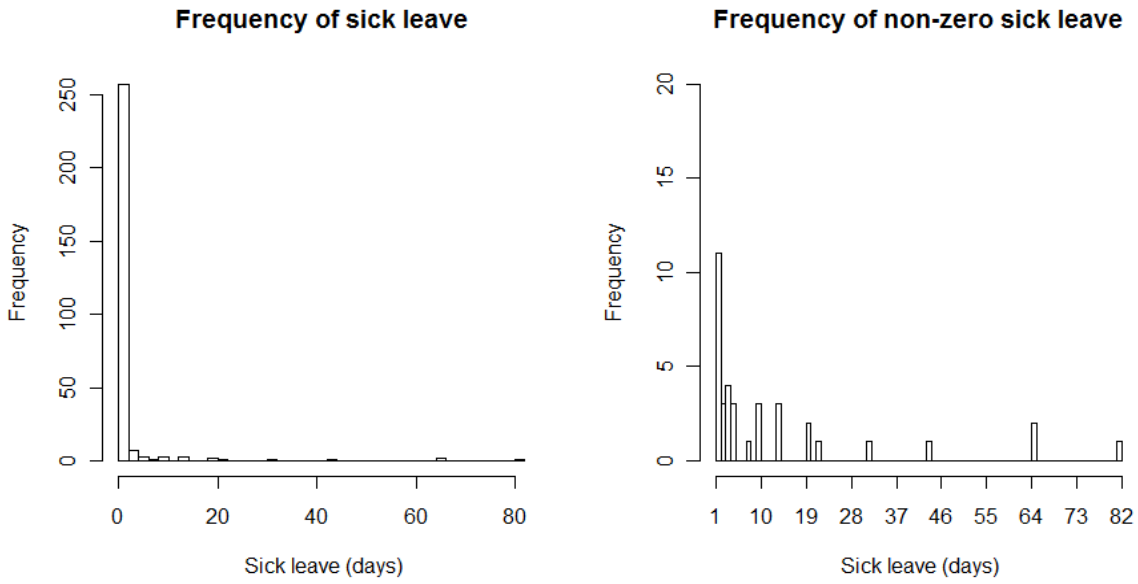


Figure 6: Frequency of sick leave in days

Figure 7 showed the proportion of sick leave in different groups of gender and type of work (full time/part time). There was a high difference in sick leave days between male and female and in overall women seemed to have more days of sick leave than men (Figure 7a). But at month seventh and thirteenth of study, there was no proportion of sick leave for women, while about 10% of male patients had sick leave days.

There was a difference in proportion of sick leave between patients who have full time job and part time job (Figure 7b). At months 1, 7 and 13 patients with full time job had more sick leave days than patients with part time job, but at months 19 and 25 patients with part time job had more sick leave days than patients with full time job.

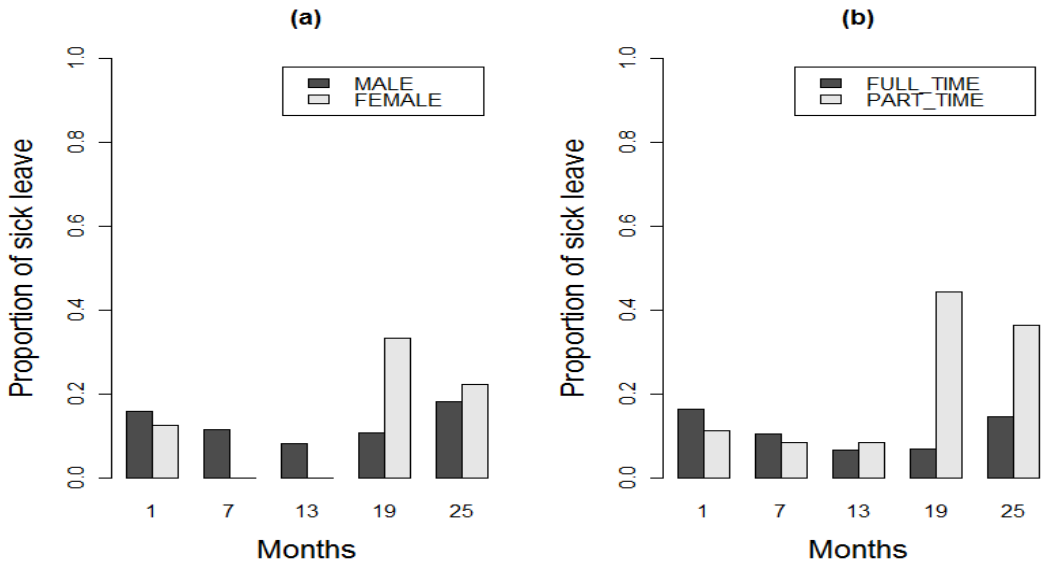


Figure 7: Proportion of sick leave in different groups of gender and type of work

3.2.1.2. Individual profile of sick leave

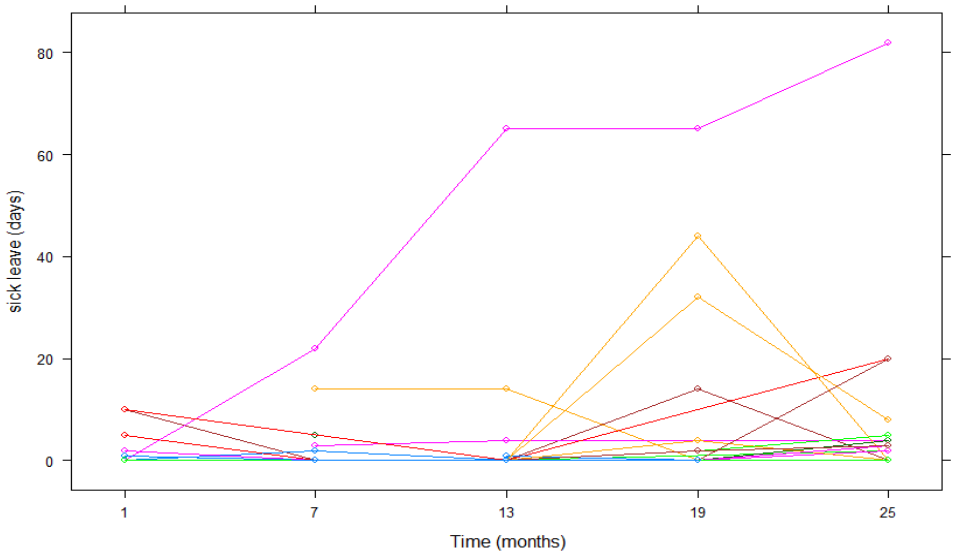


Figure 8: Individual profile plot of sick leave (in days)

Figure 8 shows the trends of changing sick leave days over two year of individual patients in the studied population. One patient had much more sick leaves days than the average values of the population. This patient was found to be work disable and removed from the analysis. Two patients with high numbers of sick leave days at 19 months were found to have physiotherapy at that time with unknown reasons (i.e. whether or not the physiotherapy was performed to treat AS or another disease was unclear). We treated these two patients as outliers in the analysis.

3.2.1.3. Mean structure of sick leave

The mean structures of sick leave days in the analyses with and without including outliers are presented in Figure 9. Mean sick leave days in the data set with outliers at 1, 7, 13, 19 and 25 months were 0.78, 0.44, 0.33, 1.88 and 1.224 respectively. It was not clear which function of time was valid to represent mean sick leave days in Figure 9a and we tried the cubic function for the first analysis. Mean sick leave days in the data set without outliers at 1, 7, 13, 19 and 25 months were 0.81, 0.45, 0.35, 0.44 and 1.125 respectively. Figure 9b suggests a quadratic function of time for numbers of sick leave days.

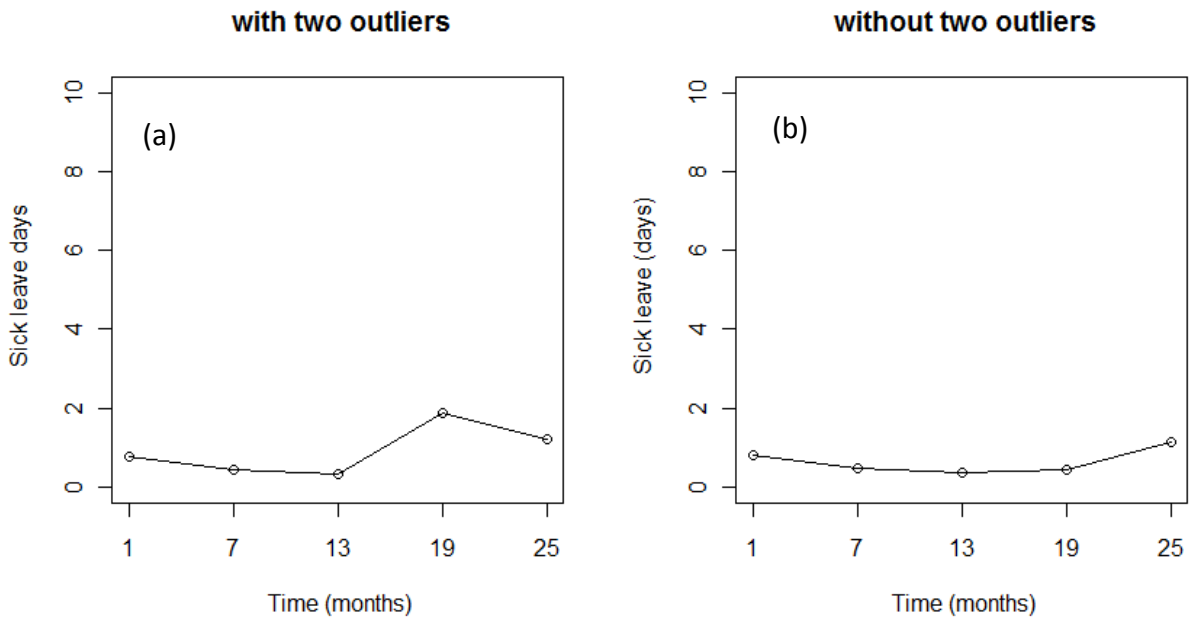


Figure 9: Mean structure plot of sick leave (in days)

3.2.1.4. Variance structure of sick leave

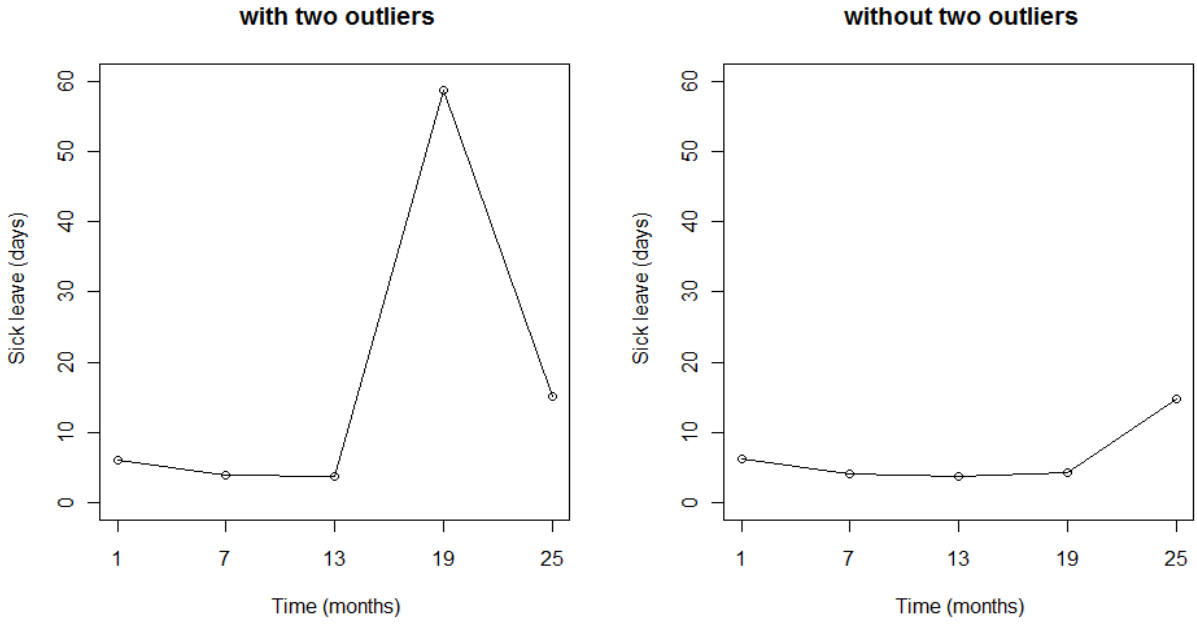


Figure 10: Variance structure plot of sick leave (in days)

The variance structures in the analyses with and without including outliers are presented in Figure 10. In both cases the variances were much larger than the means at all time points. In addition to the plots in Figure 10, the individual profile plot (Figure S3 in Appendix 2) and the plots for means and the variances (Figure S4 in Appendix 2) for non-zero sick leave days suggest overdispersion of the response variable.

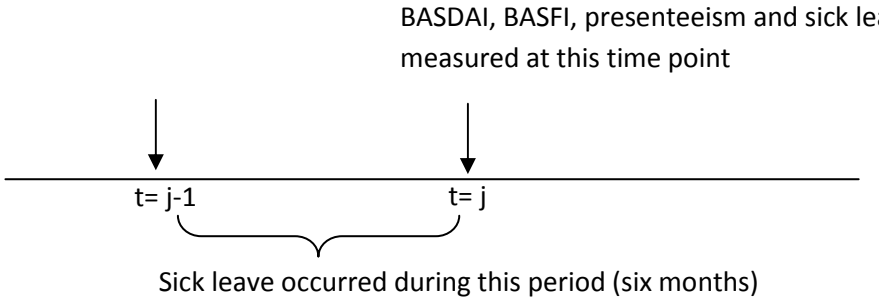
There is high variability of sick leave days over time in both cases (with and without inclusion of the outliers). The outliers appeared to influence the variance structure. Figure 10 suggests that the random components of the models for sick leave days should consist of both intercept and slope(s).

3.2.2. Statistical data analysis

3.2.2.1. Fixed effect models

All the proposed count models for fixed effects in section 2.2.3.1 and 2.2.3.2 (Poisson, Negative Binomial, hurdle models and zero-inflated count models) were fitted for both data sets with and without two outliers.

Based on the results from exploratory data analysis, the selection of a fixed effect model for the number of sick leave days was started with a model containing time, time^2, time^3, gender, baseline age, BASDAI, BASFI, presenteeism and the type of work (part-/full –time). The estimated coefficients for BASDAI, BASFI and presenteeism from the full model appeared to be illogical in opinion of experts in AS because they showed that patients with high values of BASDAI, BASFI and presenteeism had fewer sick leave days. A possible explanation for these illogical estimates was that BASDAI, BASFI and presenteeism were instantaneous measures at a specific time point, while sick leave days at the same time point were a cumulated measure over the period preceding that time point. This suggests that sick leave at a specific time point is mainly influenced by BASDI, BASFI and presenteeism at the previous time point.



Based on this consideration, the models for sick leave days were modified to contain time, time^2, time^3, gender, age (at baseline), BASDAI-lag1, BASFI-lag1, presenteeism-lag1 and the type of work (part-/full –time). Pair-wise interactions between BASDAI-lag1, BASFI-lag1, presenteeism-lag1, age, gender, time, time^2, time^3 were included in the model. All of these interactions were found to have non-significant effects on sick leave days and the corresponding AIC values for models containing these interactions were larger than those for the model without interactions.

The parameter estimates and corresponding p-values obtained from fitting models in two cases (with and without including the outliers) were very similar, indicating that the two outliers did not influence the fixed effects. Therefore, we report only the results for the data set with outliers.

After model selection, the explanatory variables included in the final Poisson and NB models were the same, being time, time^2, gender, BASDAI-lag1, BASFI-lag1 and prensenteeism-lag1. The count parts in the final ZIP and ZINB models consisted of the same explanatory variables as in the Poisson and NB models. The zero-inflation parts in the final ZIP and ZINB models consisted of only presenteeism at the previous time. All of parameter estimates with their corresponding standard errors as well as values of log likelihood and AIC of Poisson, NB, ZIP, ZINB models were given in Table 5. In fitting the Hurdle models, the final Hessian matrix was not positive definite and therefore we could not get the parameter estimates.

Table 5: Parameter estimates of fixed effects models for sick leave days

Parameters	Poisson model estimates (S.E.)	NB model estimates (S.E.)	ZIP model estimates (S.E.)	ZINB model estimates (S.E.)
		Count model		
(Intercept)	-16.825597(1.943013)*	-5.761830(2.924931)*	-5.749319(1.966570)*	-5.116632(2.337947)*
Time	1.433943(0.199032)*	0.234042(0.354171)	0.733821(0.204432)*	0.638079(0.264236)*
$Time^2$	-0.035149(0.005137)*	-0.002710(0.010660)	-0.019750(0.005285)*	-0.016825(0.007357)*
Female	2.363191(0.196953)*	1.460640(0.906695)	1.218479(0.242495)*	0.976033(0.492913)
BASDAI.lag1	-0.218951(0.057200)*	-0.135768(0.355024)	-0.118343(0.072948)	-0.123761(0.218917)
BASFI.lag1	0.362175(0.064430)*	0.075691(0.328396)	0.163371(0.073326)*	0.099757 (0.202117)
Pre.lag1	0.565723(0.039752)*	0.586075(0.211341)*	0.255635(0.040241)*	0.255057(0.089386)*
k^{-1}		15.391899(4.921653)*		0.415784(0.236722)
		Zero-inflation model (logistic part)		
(Intercept)			2.733246(0.629030)*	2.708561(0.46827)*
Pre.lag1			-0.282388(0.102607)*	-0.28777(0.12545)*
	Log likehood = -265.560 AIC = 547.12	Log likehood = -112.158 AIC = 242.32	Log likehood = -120.857 AIC = 261.71	Log likehood = -107.012 AIC = 236.02

*: significant parameter estimates

k^{-1}: overdispersion parameter

The ratio of the deviance of Poisson regression to its degrees of freedom was 2.5118, confirming the overdisperson. Therefore, the NB regression model was used instead, which yielded a log likelihood of -112.158. The likelihood ratio test comparing the NB with the Poisson model was significant (p-value < 0.001) in favor of the NB over the Poisson. As we can see from Table 5, all the parameter estimates for Poisson model are significantly associated with the sick leave days, while in NB model only presenteeism-lag1 is significant. The parameter estimate for dispersion in NB model was significantly larger than 0.

However, in case overdispersion is due to excess of zero, the NB regression model is not a proper choice. In our case, the data were better fitted using the ZIP and ZINB models than the NB model based on a comparison in the corresponding AIC (Table 5). The Vuong's test (Vuong 1989) for zero inflation was significant (test statistic: -4.02; p-value < 0.001), which indicated that a classical Poisson model was not appropriate for these data. Vuong's test for the comparison between the NB and ZINB models was also significant (test statistic: -5.15; p-value < 0.001).

The AIC's indicated a preference of the ZINB model to ZIP model. The likelihood ratio test for comparing these two models was significant (test statistic: 27.69; p-value < 0.001). Coefficients for gender and BASFI.lag1 were significant in the ZIP model, but not significant in the ZINB model, which indicated that the overdispersion was not handled in the ZIP model, but was in ZINB model.

The probability of having zero day of sick leave depends only on presenteeism-lag1. The odds of having zero day of sick leave decreased by 25% with an increase of one unit in presenteeism. For the count part, the number of sick leave days was related to time and presenteeism-lag1 where an increase of one unit in presenteeism yielded an increase by 29% (exp(0.255057) = 1.29) in the expected sick leave days.

3.2.2.2. Zero-inflated mixed models for sick leave

To take into account the repeated measures from the same patient, random effects were introduced in the ZIP and ZINB models in section 3.2.2.1. Based on the variance structure plots for data sets with and without the outliers (Figure 10), we proposed to use two different variance structures in the models for these data sets: the unstructured variance function with different variances at different time points for data set 1 (with outliers) and the curvature variance function (time and time^2 random effects in log component) for data set 2 (without outliers). Unfortunately, Proc NLMIXED in SAS for fitting ZIP and ZINB models does not allow customizing values of variance at different time points. Therefore, we used only the data set 2 with the curvature variance function for the model fitting.

The ZIP (ZINB) mixed models for data set 2 have two components as following:

(1) the probability of getting 0 days of sick leave is modeled by

$logit(p_i) = (beta + b_i) + Presenteeism$, where $b_i \sim N(0, \sigma^2)$ represents the random intercept effect for patients

(2) the number of sick leave days for patients who have less likely to get 0 sick leave day has Poisson (Negative Binomial) distribution with mean λ_{ij} and

$$\log(\lambda_{ij}) = (\mu + b_{1i}) + (time + b_{2ij}) + (time^2 + b_{3ij}) + gender + BASDAI.lag1 + BASFAI.lag1 + presenteeism.lag1$$

where b_{1i}, b_{2ij}, b_{3ij} are unobservable random effects for subject and time, time^2 effects, and we assumed those random effects normal distributed with mean 0 and variance ${\sigma^2}_{1i}, {\sigma^2}_{2ij}, {\sigma^2}_{3ij}$ respectively.

We further assumed that all the random effects were mutually independent. Proc NLMIXED was also used to fit the models with a number of quadrature points of 20. Unfortunately, we could not get the parameter estimates for the ZIP and ZINB mixed models because the convergence criteria were not met.

3.2.3. Model diagnostic for ZINB model

According to Aldo (2011), there are few studies on diagnostics and influence analysis for zero inflated models. To explore the goodness of fit of ZINB model, the observed proportions as well as the average predicted count proportions for sick leave from the Poisson, NB, ZIP and ZINB models were plotted in Figure 11. Values of the observed and predicted probabilities under these models were provided in Table S2 in Appendix 2. The Poisson model clearly underestimated the proportion of zero sick leave days, while the other models (ZIP and ZINB) were more accurate. The ZINB model was preferred to ZIP model based on the AIC values and likelihood ratio test.

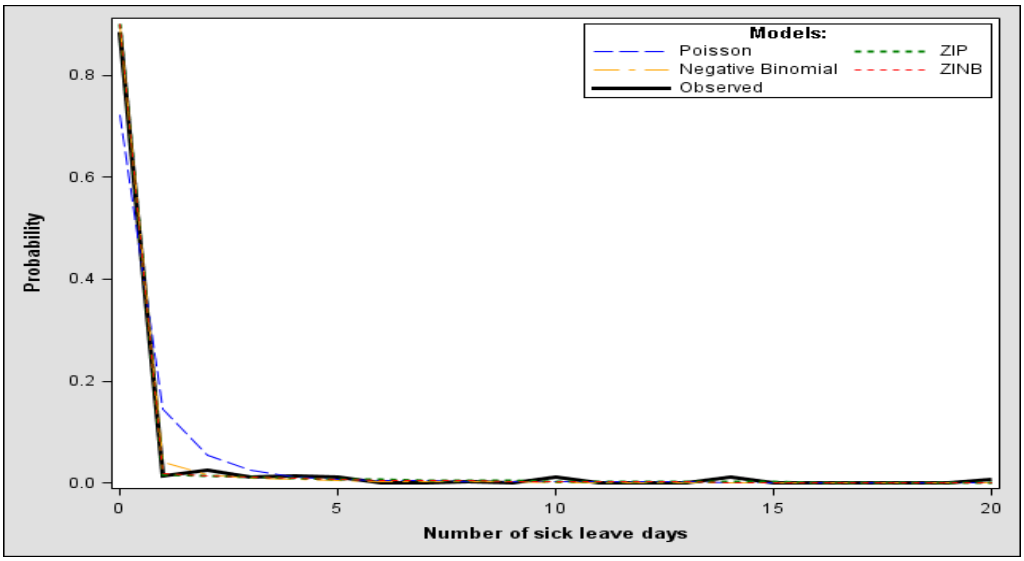


Figure 11: Plot for observed and predicted probabilities of sick leave

The plot of standardized Pearson residuals against the fitted values of sick leave showed non-random pattern of residuals (Figure S5 in Appendix 2).

4. Discussion and conclusion

4.1. Longitudinal study on presenteeism

4.1.1. Linear mixed model for presenteeism

In this study, the trend of change in presenteeism of 71 patients with AS that are optimally treated with TNF-α inhibitors has been investigated. Measurements were taken on individuals every six months in two years. As this was a longitudinal data, appropriate modeling techniques were applied since the classic approaches were not appropriate. Mixed-effects models provide a very flexible approach for analyzing longitudinal data. The linear mixed model (LMM) is often used to analyze continuous data and the generalized linear mixed model (GLMM) is used for discrete repeated measurements. In our case, presenteeism was a continuous variable with a range from 0 to 10. The observations from different patients were assumed to be independent and observations from the same patient were expected to be correlated. The random effects were introduced into the LMM to take into account this correlation. Although these random effects are not of interest in marginal evolution (fixed effects) of presenteeism for the whole AS population, they lead to more efficient inferences for the fixed effects (Verbeke and Molenberghs 2009).

From the results of LMM, presenteeism of AS patients was found independent of time, but dependent on BASDAI and BASFI. Another important finding in this study was that presenteeism was significantly influenced by the interaction effect between BASDAI and BASFI. The inter-variability between the patients was found significant larger than the intra-variability within a patient.

4.1.2. The appropriateness of the LMM for presenteeism under the condition of missing data

In the present study, the properties of missing observations were not examined because of time constraint. The LMM is valid under the assumption that data are (1) missing *completely* at random (MCAR), i.e. the missing is independent of observed data as well as unobserved data) and (2) missing at random (MAR), i.e. the missing is dependent only on observed data. The validity of using LMM rests on the use of maximum likelihood, under which the missing data mechanism is ignorable. (Verbeke and Molenberghs 2009).

When the missing data cannot be ignored, i.e. the missing depends not only on observed data but also on unobserved data (referred to as “missing not at random”, MNAR), selection models (Little and Rubin 1987) and pattern mixture models (Little 1993) are good candidates to analyze the data.

4.1.3. Model extensions for presenteeism

An extension of LMM for presenteeism can be done by considering the countries as an additional level, yield to multi-levels hierarchical model for presenteeism.

Apart from LMM approach, Bayesian model can be also considered for presenteeism. The main ideas in Bayesian model are the contribution of prior distributions for the coefficients of the covariates. A prior is often the purely subjective assessment of an experienced expert or can be the results from similar experiments. The use of Bayesian methods can provide a valuable approach in study of presenteeism, especially when the sample size is often small.

4.2. Predictors of sick leave

4.2.1. Zero-inflated negative binomial model for sick leave

The second objective of this study was to (1) investigate the trend of sick leave over two years of study in AS patients and (2) examine if presenteeism can be used to predict sick leave better than clinical measurements: BASDAI and BASFI.

Count data for sick leave contained more than 88% of zero count, thus Poison regression model failed to predict the numbers of sick leave days for AS patients. Zero inflated Poison (ZIP) model was an alternative to analyze data with excess zeros. However, in practice, count data are often over-dispersed so that zero inflated Negative Binomial (ZINB) model was found more appropriate than ZIP model to fit the data.

The inter-patient variations were adjusted by included random effects in ZINB model which was referred as the ZINB *mixed* model. However, the inclusion of both fixed and random effects may complicate the likelihood equations, leading to the possibility of non-convergence (Atkins and Gallop 2007). In our case, SAS failed to obtain the estimates for the ZINB mixed model due to non-convergence problem. As a consequence, the ZINB model was considered as the best model for sick leave among the models of which their parameters could be estimated. The ZINB model fitted by Proc NLMIXED is also valid under MAR mechanism. The number of sick leave days depended on time with quadratic function. Presenteeism was better than BASDAI and BASFI in prediction of the probability of getting sick leave and number of sick leave days.

4.2.2. Model extension for sick leave

A finite mixture model can be an alternative model for sick leave days because it can handle the absence of some possible important covariates in the data set, such as disease duration and properties of work (manual or unmanual). An important assumption of this model is that the outcome has a mixture distribution. The number of support points in a mixture as well as the probability of belonging to such subpopulation (mixing probability) can be estimated using Non parametric maximum likelihood estimation (NPMLE) method.

Let Y_i $(\mathrm{i} = 1,2,..\mathrm{n})$ represent the sick leave days of the patient i when n is the total number of patients. Suppose Y_i comes from a mixture of g^{th} component Poisson distribution, f_k with mean $\mu_{k,i}$, where k indicates the k^{th} subgroup . Then, the Poisson finite mixture model is

$$P(Y_i = y_i) = \sum_{k=1}^{g} p_k f_k(y_i) = \sum_{k=1}^{g} p_k \frac{\mu_{k,i}}{y_i} \exp(-\mu_{k,i})$$

where $\mathrm{p_k}$ indicates the mixing probability.

Using logit and log-linear links to model $\mathrm{p_k}$ and $\mu_{\mathrm{k,i}}$ respectively:

$$logit(\mathrm{p_k}) = \omega_{\mathrm{k,i}}^{\mathrm{T}}\alpha_{\mathrm{k}} \text{ and } \log(\mu_{k,i}) = \mathrm{u_{k,i}^T}\beta_{\mathrm{k}}$$

where $\omega_{\mathrm{k,i}}^{\mathrm{T}}$ and $\mathrm{u_{k,i}^T}$ indicate transpose vectors of covariates for i^{th} patient corresponding to regression coefficients α_{k} and β_{k} in $\mathrm{k^{th}}$subgroup (Verbeke and Lesaffre 1996).

The ZIP and ZINB models that we have applied in this study are special cases of mixture distributions model.

4.3. Study limitations

In this study we used the data sets with a small sample size. Because of this, parameter estimates of the candidate models and model selection might be biased. In addition, not all explanatory variables of interest were available in the data set and the total follow-up time of two years is a short period in the life time for patients with a life long illness. As a consequence, the fitted models in this study might not truly reflect the relationships among the variables in reality, especially during the course of disease over a long period.

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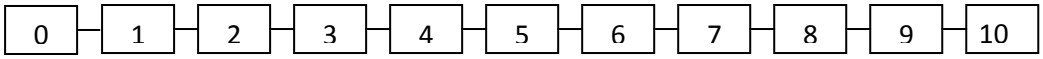
6. Appendices

Appendix 1

NRS BASDAI

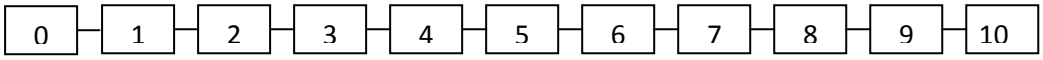
Please tick the box which represents your answer.
All questions refer to **last week**. (i.e. ~~10~~)

41. How would you describe the overall level of fatigue/tiredness you have experienced?



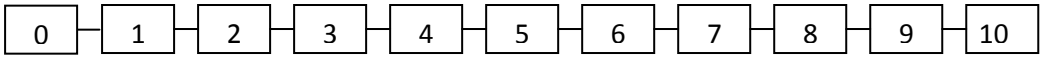
none very severe

42. How would you describe the overall level of AS **neck, back or hip** pain you have had?



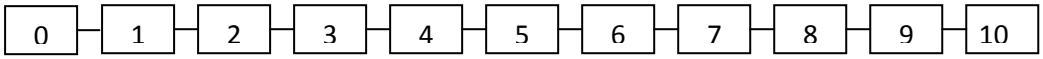
none very severe

43. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?



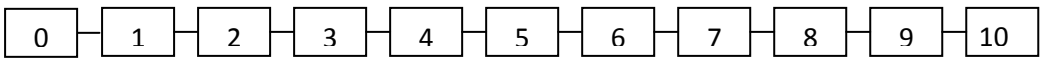
none very severe

44. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?



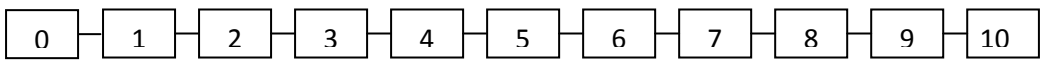
none very severe

45. How would you describe the overall level of morning stiffness you have had from the time you wake up?



none very severe

46. How long does your morning stiffness last from the time you wake up?



NRS BASFI

Please indicate your level of ability with each of the following activities during **the last week**.
(i.e. ~~10~~)

(An aid is a piece of equipment which helps you to perform an action or movement)

47. Putting on your socks or tights without help or aids (e.g. sock aid).

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

easy impossible

48. Bending forward from the waist to pick up a pen from the floor without an aid.

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

easy impossible

49. Reaching up to a high shelf without help or aids (e.g. helping hand).

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

easy impossible

50. Getting up out of an armless dining room chair without using your hands or any other help.

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

easy impossible

51. Getting up off the floor without help from lying on your back.

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

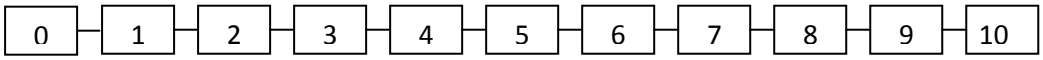
easy impossible

52. Standing unsupported for 10 minutes without discomfort.

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

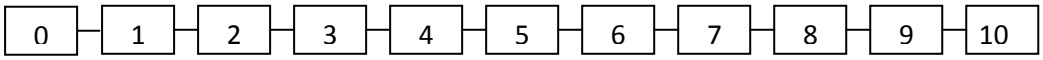
easy impossible

53. Climbing 12-15 steps without using a handrail or walking aid. **One foot at each step**.



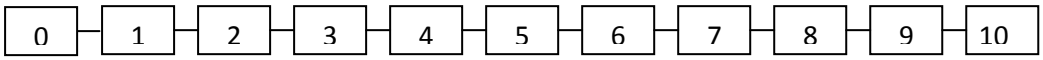
easy impossible

54. Looking over your shoulder without turning your body.



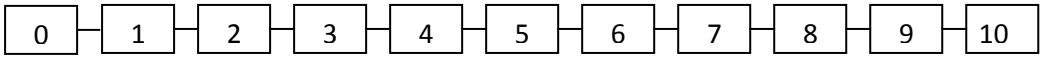
easy impossible

55. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).



easy impossible

56. Doing a full days activities, whether it be at home or at work.



easy impossible

Appendix 2

Figure S1: Scatter plot and Q-Q plot for studentized residuals in model for presenteeism

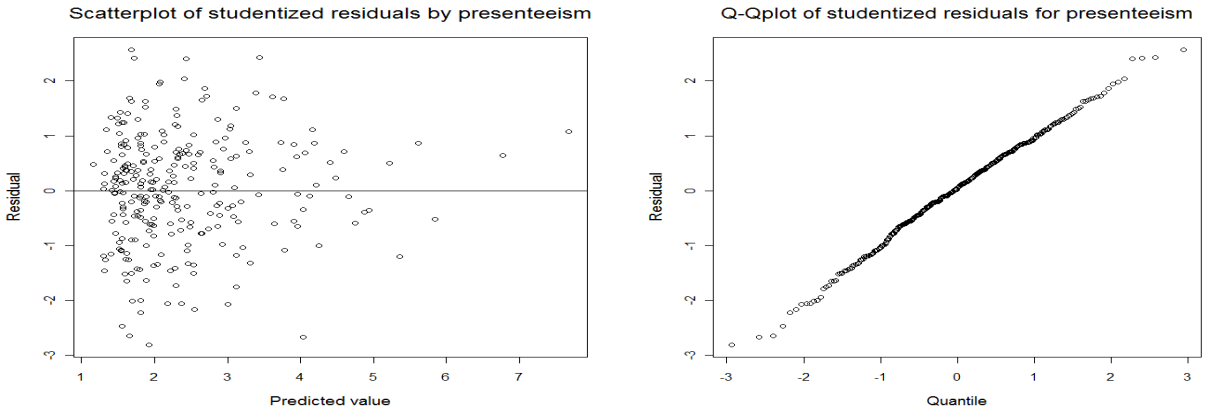


Table S1: Parameter estimates for LMM of presenteeism before and after excluding outliers

	With outliers		Without outliers	
Effects	**Estimate**	**SD**	**Estimate**	**SD**
Intercept	1.6248	0.4566	1.5891	0.5062
BASDAI	-0.0355	0.1433	-0.0295	0.1129
BASFI	-0.1532	0.1344	-0.1809	0.1554
BASDAI* BASFI	0.1451	0.0355	0.1480	0.0407

Figure S2: Covariance parameters influence plots

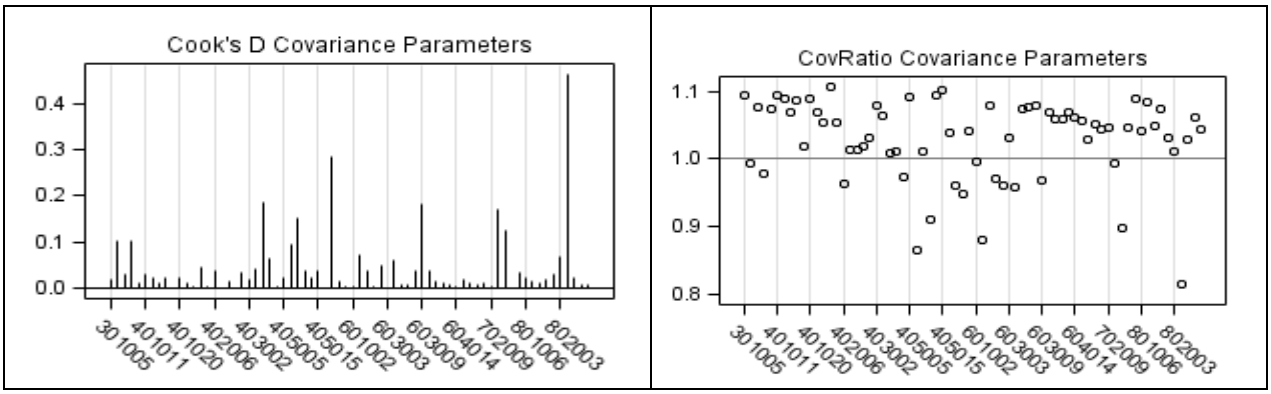


Figure S3: Profile plot for non-zero values of sick leave

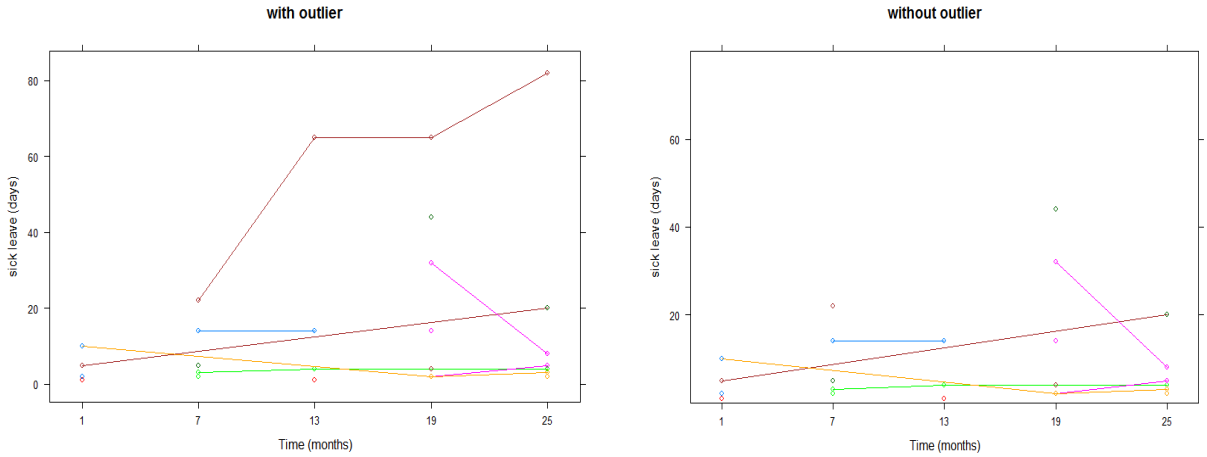


Figure S4: Mean and variance structures for non-zero count

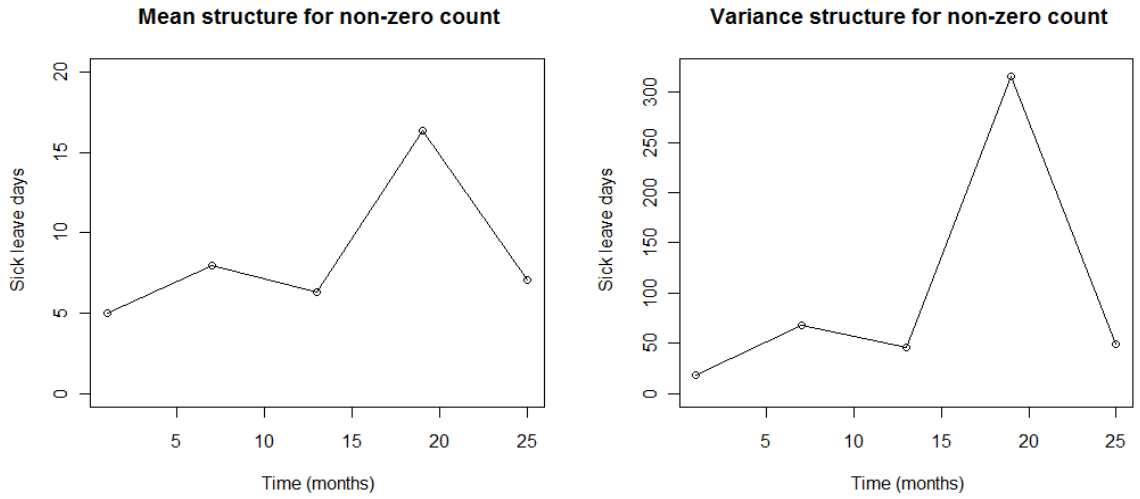
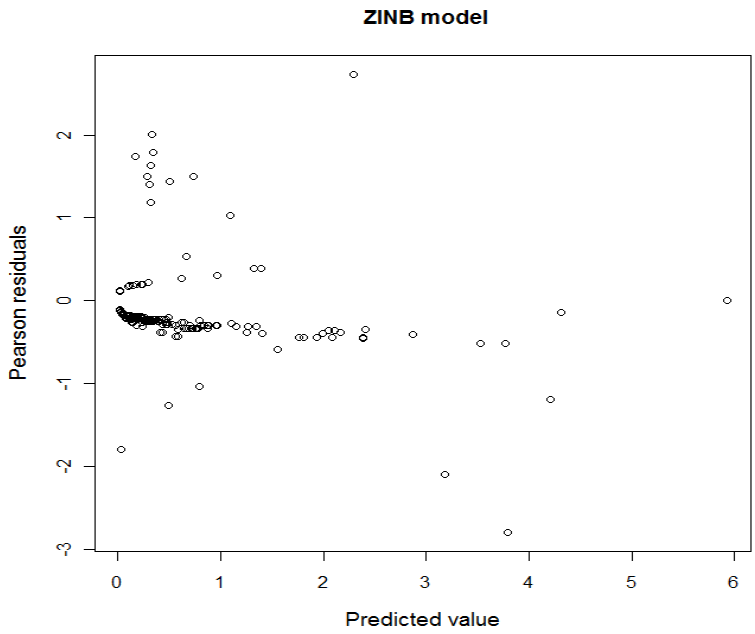


Table S2: Observed and predicted probabilities of sick leave under Poisson, NB, ZIP and ZINB models

Number of sick leave	COUNT	Observed value	Poisson	NB	ZIP	ZINB
0	245	0.884477	0.721489	0.898028	0.900866	0.900696
1	4	0.01444	0.145464	0.040639	0.015495	0.019269
2	7	0.025271	0.054997	0.016829	0.013274	0.014919
3	3	0.01083	0.024969	0.009519	0.011282	0.011618
4	4	0.01444	0.0125	0.00619	0.009569	0.009143
5	3	0.01083	0.007216	0.004365	0.008042	0.007272
6	0	0	0.005026	0.003246	0.006661	0.005845
7	0	0	0.004042	0.002509	0.005453	0.004747
8	1	0.00361	0.003462	0.001996	0.004454	0.00389
9	0	0	0.002992	0.001624	0.003669	0.003215
10	3	0.01083	0.002558	0.001347	0.003073	0.002677
11	0	0	0.002164	0.001134	0.002626	0.002244
12	0	0	0.001831	0.000967	0.002283	0.001893
13	0	0	0.001575	0.000834	0.002008	0.001606
14	3	0.01083	0.001392	0.000727	0.001771	0.00137
15	0	0	0.001266	0.000638	0.001554	0.001174
16	0	0	0.001169	0.000565	0.001346	0.00101
17	0	0	0.001079	0.000503	0.001147	0.000873
18	0	0	0.00098	0.000451	0.000958	0.000758
19	0	0	0.000865	0.000407	0.000786	0.000659
20	2	0.00722	0.000738	0.000368	0.000636	0.000576
21	0	0	0.000605	0.000335	0.000509	0.000504
22	0	0	0.000477	0.000306	0.000407	0.000443
23	0	0	0.000362	0.000281	0.000327	0.00039
24	0	0	0.000264	0.000259	0.000267	0.000344
25	0	0	0.000185	0.000239	0.000223	0.000304
26	0	0	0.000125	0.000221	0.00019	0.000269
27	0	0	8.19E-05	0.000206	0.000165	0.000239
28	0	0	5.17E-05	0.000192	0.000145	0.000212
29	0	0	3.16E-05	0.000179	0.000128	0.000189
30	0	0	1.87E-05	0.000167	0.000113	0.000168

Figure S5: Plot of Pearson residuals against fitted values of ZINB for sick leave



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Richting: **Master of Statistics-Biostatistics**
Jaar: **2013**

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Nguyen, Thien Thi Vinh

Datum: **4/02/2013**