ADJUSTING FOR UNOBSERVED DISEASE SEVERITY USING INDIVIDUALS AS THEIR OWN CONTROLS – AN EXAMPLE FROM A SCHIZOPHRENIA STUDY

Juha Mehtälä[1], Maila Majak[1], Heidi Taipale[2], Antti Tanskanen[2,3,4], Jari Tiihonen[2,4], Ellenor Mittendorfer-Rutz[2], Jan Sermon[5], Amy Leval[5], Fabian Hoti[1]

[1] StatFinn EPID Research, Espoo, Finland; [2] Karolinska Institutet, Stockholm, Sweden; [3] National Institute for Health and Welfare, Helsinki, Finland
[4] University of Eastern Finland, Kuopio, Finland; [5] Janssen Cilag, Solna, Sweden / Beerse, Belgium

RATIONALE

Schizophrenia is an example of a heterogeneous disease that can vary greatly across patients. When analyzing observational data on schizophrenia patients it is important to adjust for disease severity. However, markers of disease severity may be incompletely observed making adjustment difficult using traditional methods.

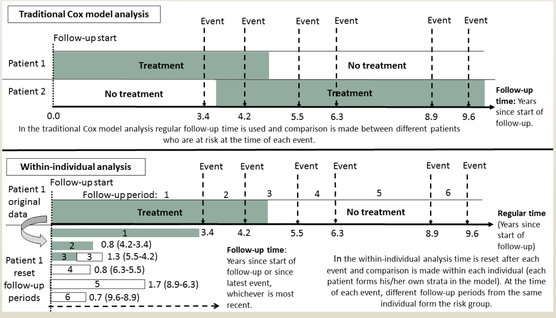
OBJECTIVES

To illustrate a within-individual approach to adjust for unobservable disease severity in comparison to a traditional multivariate Cox model.

METHODS

The within-individual approach[1] (Figure 1) is a stratified Cox model in which each individual forms his/her own stratum and time re-setting after each outcome event is used in order to allow comparison across treatment episodes from the same individual.

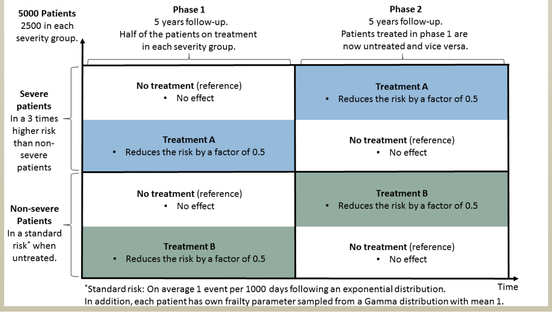
Figure 1. Illustration of follow-up time and subject comparison in the traditional Cox model and in the within-individual analyses.



A simulation study (Figure 2) was used to illustrate the performance of the traditional Cox model and the within-individual approach. In the simulation study, disease severity varied across patients and was left completely unobserved.

Observational data on 29,823 schizophrenia patients[2] in Sweden were analyzed as a real-world example when studying the comparative effectiveness of antipsychotic treatments against psychiatric rehospitalization outcome.

Figure 2. Illustration of the setting in the simulation study. Patients were followed in two phases in which they were either treated or untreated. When treated, severe and non-severe patients got either treatment A or B, respectively.



RESULTS

In the simulation experiments with unobservable disease severity across patients (Table 1), the traditional multivariate Cox models gave markedly biased results. In a similar setting, the within-individual approach was able to reduce the bias. Specifically, with the traditional Cox model, treatments given to non-severe patients were estimated to have too good treatment effects. Conversely, treatments given to severe patients were estimated to have too poor treatment effect.

In the real-world example (Table 2), the relative hazards of psychiatric rehospitalization during antipsychotic monotherapy with oral flupentixol, oral risperidone and long-acting olanzapine were estimated at 0.56 (0.47, 0.67), 0.56 (0.51, 0.61) and 0.84 (0.56, 1.26) using the traditional Cox model and at 0.92 (0.74, 1.14), 0.71 (0.64, 0.78) and 0.58 (0.44, 0.77) using the within-individual approach. A potential explanation for these discrepancies is that oral flupentixol and oral risperidone were given to less severe patients with a lower underlying risk of rehospitalization and long-acting olanzapine was given to more severe patients. For other antipsychotics, the estimated relative hazards of rehospitalization were less discrepant across the two methods.

The within-individual approach is applicable only if the outcome is recurrent.

Table 1. Simulation study results. Hazard ratios (HR) estimated using the within-individual approach and the traditional Cox model.

Treatment	True HR	Within HR	Traditional HR
Treatment A (Given to severe)	0.5	0.52 (0.50, 0.55)	0.77 (0.74, 0.79)
Treatment B (Given to non-severe)	0.5	0.50 (0.49, 0.52)	0.24 (0.23, 0.26)

Table 2. Real-world data results. Adjusted hazard ratios (HR) using the within-individual approach and the traditional Cox model. Traditional HRs were adjusted for several variables including potential markers of disease severity. Within HRs were adjusted for variables varying within each patient during the follow-up (order of treatments and time since cohort entry).

Treatment	Within HR	Traditional HR
LAI Paliperidone	0.51 (0.41, 0.64)	0.57 (0.47, 0.70)
LAI Zuclopenthixol	0.53 (0.48, 0.57)	0.57 (0.51, 0.63)
Oral Clozapine	0.53 (0.48, 0.58)	0.49 (0.44, 0.56)
LAI Perphenazine	0.58 (0.52, 0.65)	0.59 (0.52, 0.66)
LAI Olanzapine	0.58 (0.44, 0.77)	0.84 (0.56, 1.26)
LAI Risperidone	0.61 (0.55, 0.68)	0.53 (0.48, 0.59)
Oral Olanzapine	0.63 (0.59, 0.68)	0.56 (0.52, 0.61)
LAI Haloperidol	0.64 (0.56, 0.73)	0.59 (0.50, 0.68)
Oral Zuclophentixol	0.67 (0.59, 0.76)	0.64 (0.55, 0.75)
Oral Risperidone	0.71 (0.64, 0.78)	0.56 (0.51, 0.61)
Oral Aripiprazole	0.73 (0.66, 0.81)	0.62 (0.56, 0.69)
Oral Levomepromazine	0.76 (0.66, 0.89)	0.80 (0.69, 0.93)
LAI Flupentixol	0.78 (0.62, 0.98)	0.67 (0.54, 0.84)
Oral Haloperidol	0.81 (0.71, 0.93)	0.68 (0.61, 0.77)
LAI Fluphenazine	0.86 (0.35, 2.08)	0.67 (0.37, 1.23)
Oral Perphenazine	0.86 (0.77, 0.97)	0.91 (0.73, 1.12)
Oral Quetiapine	0.91 (0.83, 1.00)	0.88 (0.78, 0.99)
Oral Flupentixol	0.92 (0.73, 1.14)	0.56 (0.47, 0.67)

CONCLUSIONS

With unobservable disease severity across individuals, the traditional multivariate Cox model can lead to residual confounding. For recurrent outcomes, the within-individual approach can be a suitable method to adjust for unobservable heterogeneity across individuals, such as disease severity among schizophrenia patients.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

Jari Tiihonen has served as a consultant to the Finnish Medicines Agency Fimea, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon; he has received fees for giving expert testimonies to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka and Pfizer; lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, Pfizer; and grants from Stanley Foundation and Sigrid Jusélius Foundation. Tiihonen is a member of the advisory boards for AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka, and has participated in research projects funded by Janssen-Cilag and Eli Lilly with grants paid to Karolinska Institutet. Fabian Hoti, Maila Majak, and Juha Mehtälä are employed by EPID Research, which is a contract research organization that performs commissioned pharmacoepidemiological studies and thus its employees have been and currently are working in collaboration with several pharmaceutical companies. Antti Tanskanen and Heidi Taipale have participated in research projects funded by Janssen-Cilag and Eli Lilly with grants paid to the Karolinska Institutet, Tanskanen is a member of advisory board for Janssen-Cilag. Amy Leval, and Jan Sermon are employed by Janssen Cilag Pharmaceuticals. Ellenor Mittendorfer-Rutz reports no conflict of interest.

CONTACT: juha.mehtala@epidresearch.com