Armitage Workshop 2009

Modelling Issues in the Clinical Epidemiology of Psoriatic Arthritis
- Be Alert to Bias!

Brian Tom
MRC Biostatistics Unit
At the Onset…

• This talk is about bias*… but not due to
  - Selection (e.g. outcome dependent sampling)
  - Information (e.g. misclassification, measurement error, categorisation)
  - Confounding
• But resulting from seemingly innocuous simplifying modelling assumptions for quite complex statistical models

* Any deviation of results or inferences from the truth, or processes leading to such deviations - Last, JM (1988) A Dictionary of Epidemiology
Outline

• The Disease - Psoriatic Arthritis (PsA)

• Epidemiological Research and Clinic

• Longitudinal Work on Patient-Centred Outcomes
  - Functional disability (Two-Part Models)
  - Fatigue (Multi-state Models)
The Disease
Psoriatic Arthritis

Definition

• An inflammatory arthritis
• Associated with the skin disease psoriasis

• Majority seronegative for rheumatoid factor (> 85%)

It is a distinct entity!
Epidemiological “Facts”

• Prevalence of psoriasis in UK: 2%
• Prevalence of PsA in those with psoriasis: > 14%
• Equates to a UK prevalence: ~ 0.3%
• For RA, UK prevalence: > 0.7%
Epidemiological “Facts”

- It can occur at any time
- Skin involvement precedes joint disease: 70-80% of pts. (~ 10 yrs after skin lesions first appear)
- 10-15% joint disease before psoriasis
- 10-15% more or less simultaneously
- Cause of disease and reason for its persistence not well understood
Clinical Characteristics

• Unique clinical characteristics (cf RA)
  - Equal gender frequency
  - Asymmetric presentation involving large joints and DIPs
  - 50% have spinal involvement (neck and back)

• Clinical features:
  - Disease activity (joint pain and swelling)
  - Erythema, stiffness (ankylosis), nail changes
  - Enthesitis, iritis, dactylitis (sausage digit)
  - Damage - lytic and periarticular new bone formation x-ray features
Epidemiological Research and Toronto PsA Clinic
Where are we at?

- Although originally thought a mild disease
- Over last two decades found to be much more aggressive
- ~20% develop clinical deformities and damage resulting in functional disability
- Some achieve complete remission
- Disease activity is shown repeatedly to be associated with progression to damage
Where are we at?

- Increased risk of cardiovascular morbidities, but not malignancies
- Increased mortality risk (1978-2004)
  - 36% (95% CI: 12% - 64%) more deaths occurred than expected
  - ~3 (95% CI: 1.1 - 4.8) life years lost
- Leads to reduced quality of life
- Both activity and damage implicated in rate of physical functioning decline
- Fatigue is an extremely common symptom
- A number of genetic variants and markers (e.g. HLA) found to be associated with PsA and disease severity
- New Biologic Therapies available
Where are we at?

- Increased risk of cardiovascular morbidities, but not malignancies
- Increased mortality risk (1978-2004)
  - 36% (95% CI: 12% - 64%) more deaths occurred than expected
  - ~3 (95% CI: 1.1 - 4.8) life years lost
- Leads to reduced quality of life
- Both activity and damage implicated in rate of physical functioning decline
- Fatigue is an extremely common symptom
- A number of genetic variants and markers (e.g. HLA) found to be associated with PsA and disease severity
- New Biologic Therapies available
Data come from?

- Toronto PsA Clinic
- Established in 1978 by Dafna Gladman
- Pts have been prospectively followed up since then
- Reviewed at regular intervals
- Largest PsA cohort data-base in the world
- Over 1000 patients at present

Valuable resource for research!
Longitudinal Work on Patient-Centred Outcomes

![Graph showing data with categories such as "> 5 active joints", "0 deformed joints", "1-5 deformed joints", and "6-20 deformed joints" over time. The x-axis represents arthritis duration, and the y-axis represents mean HAQ score.]
Patient-centred Outcomes

- Current Area of Research Interest
- What matters more to the patients
- Quality of life (QoL)
- Profound impact on QoL from both skin and joint aspects of disease
  - Social, Professional, Physical, Emotional
- Functional Disability and Fatigue Outcomes
Functional Disability

- Ability to do basic activities (dressing, grooming, eating, walking, gripping, simple errands and chores) can be impaired
- Important to know whether proper treatment and management of the disease can help improve the QoL of patients
Aims

• Better understanding of the pattern of physical disability over time
• To determine factors associated with functional disability
• To investigate changing (over disease duration) effects of disease activity and damage on physical functioning
Outcome

• Health Assessment Questionnaire (HAQ)
• Measure of choice in Cost-Effectiveness
• Assesses physical functional status over the past week
• Includes questions related to
  - fine movements of upper extremity
  - locomotor activities of lower extremity
  - activities that include both upper and lower extremities
• 20 questions covering eight categories of daily living
• Overall HAQ score range between 0 and 3 (3 worst)
• Data collected over time
Modelling Issues

- How should we treat HAQ?
- In light of the preponderance of HAQ scores equal to zero
  - 35% of patient visits had HAQ=0
  - 15% of patients had HAQ=0 at all visits
- Concerns about floor effects when studying relationship between HAQ, activity and damage
Possibilities

• Dichotomize or Categorize Outcome
• Transformation of Closed Interval Data to Whole Real Line or (0,1)
• Beta Regression Model for bounded outcomes
• Truncated Model
• Two-part Model
  - Part I models probability of a binary response
  - Part II models the level of a non-zero response
• All these models must take account of the repeated nature of the data
Longitudinal Two-Part Model

\[
\log\left( \frac{\Pr(HAQ_{ij} > 0)}{1 - \Pr(HAQ_{ij} > 0)} \right) = \theta^T X_{ij} + U_i
\]

\[
g(HAQ_{ij}) \mid HAQ_{ij} > 0 = \beta^T X_{ij}^* + V_i + \epsilon_{ij}
\]

\[
\begin{pmatrix} U_i \\ V_i \end{pmatrix} \sim BVN\left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_u^2 & \rho \sigma_u \sigma_v \\ \rho \sigma_u \sigma_v & \sigma_v^2 \end{pmatrix} \right)
\]

\[
\epsilon_{ij} \sim N(0, \sigma_e^2) \quad i = \text{patient}; \ j = \text{clinic visit}
\]
Longitudinal Two-Part Model

• Model corresponds to two processes
  - one allowing us, at any time, to distinguish between functionally able and functionally disabled patients
  - the other allowing us to investigate what characteristics influence the level of disability for the functionally disabled

• Note probabilistically the two-parts are explicitly linked!

• Explanatory variables influence 2 processes differently
Simplifying Assumption

• For practical reasons
  - Computational feasibility
  - Model assessment and selection
• Assumed that the random effects were independent (i.e. $\rho = 0$)
• Allows the likelihood components for the two parts to become separable
  - Maximization of likelihood is computationally simpler and faster
• Our intuition was that if untrue, should only affect standard errors (making them larger)
• But the parameter estimates would be unbiased

This is not the case!
Why?

- Our argument - if we specify the mean structure correctly then consistent estimation would result whether or not random effects were dependent
- Why is this not the case?
- When random effects are correlated - informative cluster size aspect to data structure
Why?

• Consider the case when random effects from two-parts are positive correlated
• Subjects with larger random effects, V, will contribute more obs’ns to the estimation in the continuous part (Part II)
• Further these contributed obs’ns will over-represent larger values of HAQ in this continuous part
• Under misspecification of the correlation, \( \rho \), this will produce a clear positive bias in the intercept parameter of Part II
• Impact on estimation of other elements in \( \beta \) will depend on the other parameters in the model (Part I parameters and variance components) and true value for \( \beta \)
Table 2: Parameter estimates in the continuous part of the model for the HAQ data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Misspecified model</th>
<th>Full model</th>
<th>Latent process model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (SE)</td>
<td>$p$</td>
<td>Estimate (SE)</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.3176(0.0567)</td>
<td>&lt; .0001</td>
<td>0.2149(0.0556)</td>
</tr>
<tr>
<td>Age at onset of PsA</td>
<td>0.1011(0.0242)</td>
<td>&lt; .0001</td>
<td>0.1009(0.0245)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.1811(0.0506)</td>
<td>0.0004</td>
<td>0.2225(0.0512)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PsA disease duration</td>
<td>0.0039(0.0033)</td>
<td>0.2272</td>
<td>0.0036(0.0032)</td>
</tr>
<tr>
<td>Actively inflamed joints</td>
<td>0.0219(0.0028)</td>
<td>&lt; .0001</td>
<td>0.0239(0.0027)</td>
</tr>
<tr>
<td>Clinically deformed joints</td>
<td>0.0058(0.0031)</td>
<td>0.0627</td>
<td>0.0052(0.0031)</td>
</tr>
<tr>
<td>PASI score</td>
<td>0.0128(0.0140)</td>
<td>0.3636</td>
<td>0.0247(0.0134)</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.1502(0.0274)</td>
<td>&lt; .0001</td>
<td>0.1573(0.0263)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.0395(0.0132)</td>
<td>0.0028</td>
<td>0.0388(0.0127)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>−0.0240(0.0289)</td>
<td>0.4065</td>
<td>−0.1770(0.0281)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>0.0224(0.0280)</td>
<td>0.4252</td>
<td>0.0235(0.0272)</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.0457(0.0453)</td>
<td>0.3135</td>
<td>0.0453(0.0441)</td>
</tr>
<tr>
<td>Interaction of actively inflamed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>joints with arthritis duration</td>
<td>−0.0004(0.0002)</td>
<td>0.0290</td>
<td>−0.0004(0.0002)</td>
</tr>
<tr>
<td>Interaction of clinical deformed</td>
<td>0.0002(0.0001)</td>
<td>0.1122</td>
<td>0.0003(0.0001)</td>
</tr>
<tr>
<td>joints with arthritis duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2_v$</td>
<td>0.1587(0.0154)</td>
<td>&lt; .0001</td>
<td>0.1732(0.0166)</td>
</tr>
<tr>
<td>$\sigma^2_u$</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\sigma^2_e$</td>
<td>0.0755(0.0040)</td>
<td>&lt; .0001</td>
<td>0.0774(0.0039)</td>
</tr>
<tr>
<td>$\rho$</td>
<td>(p = 0)</td>
<td>0.9423(0.0373)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>$-2 \log$ likelihood (both parts)</td>
<td>2116.0</td>
<td>2018.1</td>
<td>2022.2</td>
</tr>
<tr>
<td>AIC</td>
<td>2175.0</td>
<td>2082.1</td>
<td>2084.2</td>
</tr>
</tbody>
</table>
Therefore...

- In the HAQ analysis, the simplifying assumption was inappropriate ($\rho = 0.94 >> 0$)
- Clear impact on parameter estimates, with positive bias observed for the intercept in continuous part of the two-part Model
- This, in general, will have ramifications for inference
- In our published paper, we concluded that
  - The influence of disease activity on HAQ scores declines with increased disease duration
  - Could not demonstrate strong evidence that the effect of clinical damage increases over time
Fatigue

• Defined as an overwhelming, sustained sense of exhaustion and decreased capacity for physical and mental work
• Common symptom reported in many rheumatic disorders (e.g. RA and SLE)
• May interfere with all aspects of a person’s life
• Its causes are poorly understood and most likely multi-factorial
What is known

• In PsA, data on fatigue are sparse
• However recently recognized as a potential core domain in clinical trials in PsA (OMERACT8)
• General impression (perception) is that it is somehow tied up with disease activity
• Also there is some evidence to suggest associations with pain, psychological distress or depression, sleep quality, co-morbidities, disability, medication and socio-demographic characteristics
Objective

• To investigate in PsA patients the factors associated with transitions between fatigue states over follow-up
Objective

• To investigate in PsA patients the factors associated with transitions between fatigue states over follow-up, after controlling for the complex relationship between fatigue and disease activity
Preliminaries

• Data used are that obtained at mFSS clinic visits
  - mFSS visits were scheduled to be approximately 1 year apart

• 390 patients with 2 or more mFSS visits (total of 1628 records ~ 4 records per patient)

• Fatigue states:
  - F=1; Mild (mFSS < 5)
  - F=2; Moderate (5 ≤ mFSS < 7)
  - F=3; Severe (mFSS ≥ 7)
Initial Stab at Analysis

- Fit a 3-state Multi-state model for panel data
- Allow 4 different transitions
  - Mild to Moderate
  - Moderate to Mild
  - Moderate to Severe
  - Severe to Moderate
- No direct transitions from Mild to Severe and vice versa (restriction in continuous time)
- Model the effects of covariates through the transition intensities

\[
\lambda_{ij}(t; \mathbf{z}(t)) = \lambda_{ij}^0(t) \exp(\psi_{ij}^T \mathbf{z}(t)),
\]

where \( \mathbf{z}(t)^T = (x(t)^T, a_2(t), a_3(t)) \) and \( \psi_{ij}^T = (\phi_{ij}, \alpha_{ij}, \beta_{ij}) \)
Simplifying Assumption

• Most of the variables are time-dependent
• So we focus on the relationship between observed transitions in fatigue level and the value of these time-dependent variables at the last mFSS clinic visit
• That is, $z(t)$ is a vector of piecewise constant variables changing only at mFSS visits - thus well defined for all $t$!
However...

- Is this a reasonable assumption?
- Maybe for variables, $x(t)$, that are not the main drivers of patient management in the PsA clinic
- But probably not for disease activity ($a_2(t)$ and $a_3(t)$)
- The relationship between fatigue and disease activity is expected to be complex
- Activity will be the primary trigger for treatment
- Therefore activity and treatment will be highly time-dependent
- But does this matter, in respect to estimation of the parameters associated with the other variables?
Learning my lesson

• Set up a simulation to investigate
• Ingredients
  - Fatigue process (3 states)
  - Activity process (3 states, with similar transitions to Fatigue process)
  - Fatigue (locally) dependent on Activity
  - Time-dependent confounding variable, say arthritis duration (rounded down to the year)
  - Time-independent binary variable (say, gender) associated with Fatigue but not Activity
  - Treatment variable which is associated with Activity
  - Processes only observed at yearly visits over a six-year period
Activity Process Model:
\[
\mu_{kl}(t) = \mu_{kl}^0 \exp(\theta_{kl} \text{trt}([t - 1]) + \phi_{kl} z([t - 1])), \quad \text{if } |k - l| = 1
\]

True Fatigue Process Model:
\[
\lambda_{ij}(t) = \lambda_{ij}^0 \exp(\alpha_{ij} a_2(t) + \beta_{ij} a_3(t) + \delta_{ij} z([t - 1]) + \varepsilon_{ij} \cdot \text{sex}), \quad \text{if } |i - j| = 1
\]

Misspecified Fatigue Process Model:
\[
\lambda_{ij}(t) = \lambda_{ij}^0 \exp(\alpha_{ij} a_2([t - 1]) + \beta_{ij} a_3([t - 1]) + \delta_{ij} z([t - 1]) + \varepsilon_{ij} \cdot \text{sex}), \quad \text{if } |i - j| = 1
\]
## Simulation Results

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>BIAS</th>
<th>MONTE CARLO SE</th>
<th>ASYMPTOTIC SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRUE MODEL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta_{12}$</td>
<td>-0.0044</td>
<td>0.0680</td>
<td>0.0698</td>
</tr>
<tr>
<td>$\delta_{21}$</td>
<td>-0.0052</td>
<td>0.1269</td>
<td>0.1183</td>
</tr>
<tr>
<td>$\delta_{23}$</td>
<td>0.0053</td>
<td>0.0595</td>
<td>0.0586</td>
</tr>
<tr>
<td>$\delta_{32}$</td>
<td>0.0022</td>
<td>0.0743</td>
<td>0.0728</td>
</tr>
<tr>
<td>$\epsilon_{12}$</td>
<td>0.0008</td>
<td>0.0677</td>
<td>0.0684</td>
</tr>
<tr>
<td>$\epsilon_{21}$</td>
<td>-0.0054</td>
<td>0.0976</td>
<td>0.1001</td>
</tr>
<tr>
<td>$\epsilon_{23}$</td>
<td>-0.0039</td>
<td>0.0540</td>
<td>0.0552</td>
</tr>
<tr>
<td>$\epsilon_{32}$</td>
<td>-0.0015</td>
<td>0.0857</td>
<td>0.0786</td>
</tr>
<tr>
<td><strong>MISSPECIFIED MODEL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta_{12}$</td>
<td>0.3064</td>
<td>0.0813</td>
<td>0.0809</td>
</tr>
<tr>
<td>$\delta_{21}$</td>
<td>-0.3443</td>
<td>0.1339</td>
<td>0.1315</td>
</tr>
<tr>
<td>$\delta_{23}$</td>
<td>0.3136</td>
<td>0.0642</td>
<td>0.0608</td>
</tr>
<tr>
<td>$\delta_{32}$</td>
<td>-0.1399</td>
<td>0.0684</td>
<td>0.0700</td>
</tr>
<tr>
<td>$\epsilon_{12}$</td>
<td>0.0010</td>
<td>0.0769</td>
<td>0.0763</td>
</tr>
<tr>
<td>$\epsilon_{21}$</td>
<td>0.0041</td>
<td>0.1071</td>
<td>0.1109</td>
</tr>
<tr>
<td>$\epsilon_{23}$</td>
<td>-0.0108</td>
<td>0.0606</td>
<td>0.0611</td>
</tr>
<tr>
<td>$\epsilon_{32}$</td>
<td>-0.0067</td>
<td>0.0942</td>
<td>0.0873</td>
</tr>
</tbody>
</table>
So...

• Simulation results provide evidence of bias estimation of confounder, \( z(t) \), when functional form of activity misspecified

• Time-independent variable, sex, which is not associated with activity, is found to be unbiased under this misspecification

• How do we then proceed, knowing that
  - activity is highly time-dependent; and
  - we have intermittently observed Fatigue and Activity (i.e. panel data)?

• Proposal is to jointly model activity and fatigue processes – but still under investigation
New Multi-state Model Diagram

- F=3, A=1 (3)
- F=2, A=2 (6)
- F=1, A=3 (9)
- F=2, A=1 (2)
- F=2, A=2 (5)
- F=2, A=3 (8)
- F=1, A=1 (1)
- F=1, A=2 (4)
- F=1, A=3 (7)
In Conclusion...

• A lot of consideration should be given when contemplating simplifying assumptions for complex statistical models
• Knowing what impact these assumptions can have in terms of bias estimation is important
• Consequences can be substantial in terms of conclusions drawn
• Clinically important epidemiological questions in PsA has motivated a lot of my statistical methodology research
Thank you for your attention!