Statistical Methods in Psoriatic Arthritis

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Outline

• The Disease: Psoriatic Arthritis (PsA)

• Research Areas and Clinic

• Mortality

• Functional disability
THE DISEASE
Psoriatic Arthritis (PsA)

Definition
- An inflammatory arthritis
- Associated with psoriasis
- Seronegative for rheumatoid factor

It is a distinct entity!
Psoriatic Arthritis (PsA)

Epidemiological Evidence

• Prevalence of psoriasis in arthritis patients: 7%
• Prevalence of psoriasis in general population: 2-3%
• Prevalence of arthritis in psoriasis patients: 6-42%
• Prevalence of arthritis in general population: 2-3%
Psoriatic Arthritis (PsA)

Background

- Pre mid 1980’s, considered a benign disease (in comparison with RA)
- Since then PsA seen to be much more aggressive
- ~20% develop a destructive disabling form
- Some patients achieve remission
- PsA and RA patients similar - developing joint deformities and damage and in disease progression over time
Psoriatic Arthritis (PsA)

Pathogenesis
- Exact cause unknown
- Genetic, Environment and Immunologic Factors

Clinical Features
- Joint pain, swelling, erythema, stiffness
- DIP joint involvement, nail changes, asymmetry, dactylitis, enthesitis, spondylitis, iritis, lytic and periarticular new bone formation x-ray features
Psoriatic Arthritis (PsA)

Patterns or Subtypes

- Oligoarticular (< 5 joints), asymmetric
- Polyarticular (≥ 5 joints), often symmetric (RA-like)
- DIP joint (of fingers and toes) predominant
- Spinal Involvement
- Arthritis mutilans (highly destructive/lytic)
PsA Patterns

Oligoarthritis

Distal Arthritis
PsA Patterns

Polyarticular Pattern
PsA Patterns

Spondylitis
PsA Patterns

Arthritis Mutilans  Telescoping
Treatment

- NSAIDs (first line medications)
  Diclofenac, Cox-2 Inhibitors

- DMARDs (second line medications)
  Methotrexate

- Steroids (joint injections)

- Biologics (TNF-alpha inhibitors)
  Infliximab, Etanercept, Adalimumab)
Research Areas

Disease Progression and Course
• Damage Progression (Clinical & Radiological, Irreversible)
• Quality of Life and Physical Function (SF-36, HAQ)
• Disease Activity/Remission
• Fatigue

Disease-related Outcomes
• Cardiovascular disease
• Malignancies
• Mortality

Instruments
• Response Index for treatment (ACR-20, PsARC)
• Screening Index

Genetic Aspect
Clinic

- PsA Clinic at Toronto Western Hospital
- Established in 1978
- Patients have been followed prospectively since then
- Reviewed at “regular” intervals according to a standard protocol
- Toronto PsA Clinic is the holder of the largest PsA database in the world
- End 2006, 790 PsA patients
- Important resource!
MORTALITY
Background

• 1997 & 1998 Arthritis and Rheumatism papers
• Patients enrolled into the PsA Clinic between 1978 and 1993, and followed up to Sept 1994
• 428 patients, 53 deaths, leading causes - circulatory and respiratory
• SMR (standardized to Ontario) - Overall: 1.62 (95% CI: 1.21-2.12); Male: 1.65 (95% CI: 1.09-2.40); and Female: 1.59 (95% CI: 1.04-2.33)
• Prognostic indicators of death: ESR, Radiological damage, Prior medication use, Nail changes
Objectives

• Update mortality results of 1997 & 1998 Arthritis and Rheumatism papers

• To investigate whether mortality rates have changed over the last three decades
Mortality Update

- Update to include extra 10 years of follow-up (to end of 2004)
- 680 patients (385 males; 295 females)
- Death info: cancer registry, death notices, interviews & correspondence with relatives & physicians
- 106 deaths (51 males; 55 females)
- Reference Pop’n: Ontario mortality rates by 5-year age bands, sex and 1-year calendar periods from 1978-2004
Statistical Methods

• Standardized Mortality Ratios
  – Way of comparing our cohort’s death rates with those from the Ontario general pop’n
  – Indirect Standardization Method
  – Ratio of Observed no. of deaths in cohort to Expected no. of deaths
• Calculated using a Poisson regression model for the observed deaths, with log(Expected deaths) as an offset
• Assume patients lost to follow-up were still alive at end of 2004
SMR Results

SMR (1978-2004)
• Overall: 1.36 (95% CI: 1.12-1.64)
• Male: 1.25 (95% CI: 0.95-1.65)
• Female: 1.47 (95% CI: 1.13-1.91)

Recall, SMR (1978-Sept 1994)
• Overall: 1.62 (95% CI: 1.21-2.12)
• Male: 1.65 (95% CI: 1.09-2.40)
• Female: 1.59 (95% CI: 1.04-2.33)

Conclusion/Question:
• Apparent drop in SMR suggests mortality risk has improved over last decade (?)
Life Years Lost

- Relationship between SMR and expected years of life (Tsai et al. 1992, AJE)
- Assume that age-gender-period-specific mortality ratios is constant for all groups (overall)
- Calculate expected life year, $^{c}E_x$, for each subject in PsA Cohort at age of entry, $x$
- Calculate expected life year, $^{o}E_x$, for each subject in PsA cohort assuming the Ontario death rates applied

$$
E_x = E(T \mid T \geq x) = \int_x^{\infty} th(t) \left\{ \exp \left( - \int_x^t h(u) du \right) \right\} dt
$$

- Life years lost for a subject, entering at $x = ^{o}E_x - ^{c}E_x$
Life Years Lost

Assume

• The hazard, \( h(u) \), piecewise constant over agebands, \( A_t \), & calendar periods, \( P_k \)

• For calendar period, \( P_k \) & ageband, \( A_t \)
  i. \( h^o(t,k) = -\ln(1-\text{Ontario death rate}(A_t,P_k))/5 \)
  ii. \( h^c(t,k) = -\ln(1-\text{SMR} \times \text{Ontario death rate}(A_t,P_k))/5 \)

Life years lost for cohort = Average of subjects’ life years lost
Life Years Lost

Life years lost

• Overall: 2.99 yrs (95% CI: 1.14-4.77)
• Male: 2.30 yrs (95% CI: -0.51-4.96)
• Female: 3.60 yrs (95% CI: 1.15-5.96)
Time trend in Mortality

- Apparent drop in SMR suggests mortality risk has improved over last decade (?)
- How do we investigate this? If improvement, is it explainable?
- (1) Cox regression (Time from birth) with time-dependent calendar covariate
- (2) Time trend SMR analyses
  - Follow-up period specific SMRs stratified by entry cohort
  - Ten-year “Rolling Average” SMRs Unadjusted or (Baseline) Adjusted
- How to adjust?
## Time Trend Results (1)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1978-1986</td>
<td><strong>2.40 (1.45, 3.98)</strong></td>
<td><strong>1.45 (0.86, 2.44)</strong></td>
<td><strong>0.97 (0.58, 1.64)</strong></td>
</tr>
<tr>
<td>1987-1995</td>
<td>0.47 (0.07, 3.32)</td>
<td>0.85 (0.35, 2.04)</td>
<td>0.88 (0.22, 3.50)</td>
</tr>
<tr>
<td>1996-2004</td>
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</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
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</tr>
<tr>
<td>1978-1986</td>
<td><strong>1.30 (0.62, 2.73)</strong></td>
<td><strong>2.18 (1.45, 3.28)</strong></td>
<td><strong>1.45 (0.94, 2.25)</strong></td>
</tr>
<tr>
<td>1987-1995</td>
<td>0.67 (0.09, 4.76)</td>
<td>0.79 (0.30, 2.11)</td>
<td>----</td>
</tr>
<tr>
<td>1996-2004</td>
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</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1978-1986</td>
<td><strong>1.89 (1.25, 2.87)</strong></td>
<td><strong>1.63 (1.19, 2.24)</strong></td>
<td><strong>1.05 (0.79, 1.41)</strong></td>
</tr>
<tr>
<td>1987-1995</td>
<td>1.83 (1.33, 2.52)</td>
<td>1.21 (0.86, 1.69)</td>
<td>0.82 (0.43, 1.58)</td>
</tr>
<tr>
<td>1996-2004</td>
<td>0.55 (0.14, 2.20)</td>
<td>0.56 (0.14, 2.25)</td>
<td>---</td>
</tr>
</tbody>
</table>
Time Trend Results (2) – Unadjusted Rolling SMRs
Time Trend Results (2) – Adjusted Rolling SMRs
Summary

• Increased mortality risk in period 1978-2004
  – 36% more death occurred than expected
  – Approximately 3 years of life were lost
• SMR for extended cohort better than earlier cohort
• Indications of a trend downwards over time
  – SMRs for follow-up bands collapsed over entry periods
  – Unadjusted rolling average SMRs
• Downward trend particularly strong for men
• Remains for men, even after adjustment for baseline covariates to do with disease severity
Conclusions and Further Work

- Mortality risk has changed over last three decades
- Improved survival experience in last decade compared to earlier two decades
- May partly reflect disease severity at enrollment
- Additionally, better control of disease and co-morbidities in latter decade
- Investigate further using survival models with time-dependent covariates
FUNCTIONAL LIMITATION
Introduction

• Impact of PsA on daily living can be pronounce

• Ability to do basic activities (dressing, grooming, eating, walking, gripping, simple errands and chores) can be restricted

• How can proper treatment and management of the disease help (if at all) with improving the "quality of life" of patients
Clinical Perspective

Objectives

Initially,

• Better understanding of the pattern of physical disability over time
• To determine factors associated with progression and regression of disability

Later on,

• To investigate differential 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
- HAQ score derived between 0 and 3 (3 worst)
Data

• 341 & 382 patients who completed 2 or more HAQ assessments

• Covariate information
  – Demographic: sex, age (age at diagnosis)
  – Duration of PsA
  – Psoriasis severity (PASI)
  – Disease activity: active joints, ESR, Stiff AM
  – Clinical damage: damaged joints
  – Medication
Functional Limitation

Project 1

Address
• Better understanding of the pattern of physical disability over time
• To determine factors associated with progression and regression of disability

Multi-state Markov models
• HAQ disability states
  – State 1: 0 to 0.49 (No or mild disability)
  – State 2: 0.50 to 1.50 (Moderate disability)
  – State 3: 1.51 to 3 (Severe disability)
• Allow estimation of transition rates between the 3 functional disability states
• Easily incorporate the effects of covariates (time-indep or -dep) on transition rates
• Correlation modelled through Markov assumption
• No need to make any distributional assumptions about HAQ
• Assume – non-informative sampling scheme
Multi-state Model

- No direct transition from State 1 to State 3
- Observed transitions from State 1 to State 3 (or vice versa) implies passage through State 2
- Same covariate effect assumed for all forward transitions
- Same covariate effect assumed for all backward transitions
## Results

Table 2. Number and type of observed transitions between disability states for 341 PsA patients*

<table>
<thead>
<tr>
<th>Number and type</th>
<th>Disability state at time of first HAQ assessment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State 1 (n = 157)</td>
<td>State 2 (n = 134)</td>
<td>State 3 (n = 50)</td>
<td></td>
</tr>
<tr>
<td>No transitions (n = 157)</td>
<td>95</td>
<td>42</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>One transition (n = 91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deterioration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State 1 → 2</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>State 1 → 3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>State 2 → 3</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State 2 → 1</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>State 3 → 1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>State 3 → 2</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Two or more transitions (n = 93)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady observed deterioration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State 1 → 2 → 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Steady observed improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State 3 → 2 → 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fluctuating course, both deterioration and improvement</td>
<td>36</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>State 1 ↔ 2</td>
<td>0</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>State 1 ↔ 3</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td></td>
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</table>

* PsA = psoriatic arthritis; HAQ = Health Assessment Questionnaire.

Husted et al. (2005), Arthritis Care and Research
Table 3. Results from the multivariate analysis that identified predictors of transitions between disability states

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transitions</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 → 2</td>
<td>2 → 3</td>
<td>2 → 1</td>
<td>3 → 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk (95% CI)</td>
<td>Relative risk (95% CI)</td>
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</tr>
<tr>
<td>Sex</td>
<td>0.54 (0.38–0.76)</td>
<td>0.92 (0.66–1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.03)</td>
<td>0.99 (0.97–1.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of PsA, years</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>0.42 (0.16–1.00)</td>
<td>0.33 (0.14–0.77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5 years</td>
<td>0.33 (0.14–0.76)</td>
<td>0.44 (0.21–0.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>1.00 (0.99–1.01)</td>
<td>0.98 (0.97–0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of clinically deformed joints</td>
<td>1.03 (1.01–1.06)</td>
<td>0.99 (0.97–1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of actively inflamed joints</td>
<td>0.99 (0.97–1.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2 log-likelihood</td>
<td>1,716.885</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* 95% CI = 95% confidence interval; PsA = psoriatic arthritis.

Husted et al. (2005), Arthritis Care and Research
Summary

• Males showed a slower rate of decline in disability
• Increasing age decreased likelihood of improvement amongst patients with moderate or severe disability
• Older patients therefore more likely to experience persistent disability
• More variability in “levels” of disability during early course of disease
• Higher number of damaged joints, lower transition rate for improving
• Higher number of active joints quicker to show deterioration
Conclusions

• Variability in course of physical functional disability
  – Stable state of disability (46%)
  – Steady improvement or decline (~ 27%)
  – Fluctuating (~ 27%)
• Findings consistent with those found in RA
  – In particular wrt disease duration: more variability in “levels” of disability during early course
• Reasons (early disease)
  – Spontaneous changes in disease activity
  – Variability in timing and response to disease modifying drugs
  – Coping strategies
  – Adaptation to disease
• Reasons (later disease)
  – Joint damage accumulation (irreversible) leading to persistent disease
  – Efficacy of treatment reduces over time (or failure to respond) resulting in enduring disability
Functional Limitation
Project 2

To investigate further our findings
• We looked at the differential effects of disease activity and damage on physical functioning over PsA duration

In RA,
• inflammatory processes believed to be major determinant of physical disability early on
• joint damage considered major determinant in later disease
• less fluctuation in functional ability is expected over illness course

If true in PsA,
• Raise questions about utility of physical functioning (HAQ) as an outcome in clinical trial with patients in later stage of disease
Statistical Methods

Strategy

• Focus on the continuous HAQ score
• 645/2107 (35%) patient visits, HAQ=0
• 52/382 (14%) of patients had HAQ=0 for all visits
• Concern of floor effects when studying relationship between HAQ, activity and damage longitudinally
• Preponderance of zeroes impact on shape of distribution
• To overcome, we adopt a longitudinal two-part model
  – Part I models probability of a binary response
  – Part II models the level of a non-zero response
  – Both account for the repeated nature of the data
Longitudinal Two-Part Model

\[
\log \left( \frac{\Pr(HAQ_{ij} > 0)}{1 - \Pr(HAQ_{ij} > 0)} \right) = \alpha^T Z_{ij} + A_i
\]

\[
E(HAQ_{ij} \mid HAQ_{ij} > 0) = \beta^T Z_{ij} + B_i
\]

\[
\begin{pmatrix}
A_i \\
B_i
\end{pmatrix} \sim BVN \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_A^2 & 0 \\ 0 & \sigma_B^2 \end{pmatrix} \right)
\]
Longitudinal Two-Part Model

- Model corresponds to two processes
  - one allowing us 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
- Explanatory variables influence the processes differently
- Random effects in the two parts assumed independent
- If untrue, should only affect standard errors
- No bias
- Note probabilistically the two-parts are explicitly linked!
Cross-sectionally,

- Mean HAQ improving early on and then worsening
- Activity relatively stable over illness duration
- Increase in mean damage over illness duration
Part 1 Results

Table 3. Results of the random-effects logistic regressions in part 1 of the 2-part models*

<table>
<thead>
<tr>
<th>Fixed-effects variables</th>
<th>Part 1 (model a)†</th>
<th>Part 1 (model b)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.9597</td>
<td>-3.5878</td>
</tr>
<tr>
<td>Age at onset of PsA</td>
<td>0.0597</td>
<td>0.0562</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>2.1175</td>
<td>2.0064</td>
</tr>
<tr>
<td>Highest level of medication used prior to each HAQ assessment</td>
<td>0.0835 (overall)</td>
<td>0.1354 (overall)</td>
</tr>
<tr>
<td>None</td>
<td></td>
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<tr>
<td>NSAIDs</td>
<td>0.4004</td>
<td>0.3244</td>
</tr>
<tr>
<td>DMARDs</td>
<td>0.4658</td>
<td>0.3865</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.7973</td>
<td>0.8933</td>
</tr>
<tr>
<td>No. of actively inflamed joints</td>
<td>0.2510</td>
<td>0.1812</td>
</tr>
<tr>
<td>Arthritis duration‡</td>
<td>0.0222</td>
<td>0.0156</td>
</tr>
<tr>
<td>No. of clinically deformed joints</td>
<td>0.0258</td>
<td>0.0344</td>
</tr>
<tr>
<td>PASI score</td>
<td>0.0498</td>
<td>0.0242</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>-</td>
<td>1.6195</td>
</tr>
<tr>
<td>ESR</td>
<td>-</td>
<td>0.0163</td>
</tr>
<tr>
<td>Interaction of actively inflamed joints with arthritis duration‡</td>
<td>-0.0034</td>
<td>-0.0010</td>
</tr>
<tr>
<td>Interaction of clinical deformity with arthritis duration‡</td>
<td>0.0033</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

Husted et al. (2007), Arthritis and Rheumatism
Part 2 Results

Table 4. Results of the linear mixed-effects regressions in part 2 of the two-part models

<table>
<thead>
<tr>
<th>Fixed-effects variables</th>
<th>Part 2 (model a)†</th>
<th></th>
<th>Part 2 (model b)†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>P</td>
<td>Estimate</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.1111</td>
<td>0.0881</td>
<td>0.207</td>
<td>0.0105</td>
</tr>
<tr>
<td>Age at onset of PsA</td>
<td>0.0090</td>
<td>0.0022</td>
<td>&lt;0.001</td>
<td>0.0089</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>0.1992</td>
<td>0.0515</td>
<td>&lt;0.001</td>
<td>0.1812</td>
</tr>
<tr>
<td>Highest level of medication used prior to each HAQ assessment</td>
<td>0.2835 (overall)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>−0.0024</td>
<td>0.0280</td>
<td>0.931</td>
<td>−0.0240</td>
</tr>
<tr>
<td>DMARDs</td>
<td>0.0225</td>
<td>0.0267</td>
<td>0.400</td>
<td>0.0224</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.0751</td>
<td>0.0422</td>
<td>0.075</td>
<td>0.0457</td>
</tr>
<tr>
<td>No. of actively inflamed joints</td>
<td>0.0190</td>
<td>0.0015</td>
<td>&lt;0.001</td>
<td>0.0166</td>
</tr>
<tr>
<td>Arthritis duration‡</td>
<td>0.0039</td>
<td>0.0032</td>
<td>0.228</td>
<td>0.0039</td>
</tr>
<tr>
<td>No. of clinically deformed joints</td>
<td>0.0082</td>
<td>0.0019</td>
<td>&lt;0.001</td>
<td>0.0089</td>
</tr>
<tr>
<td>PASI score</td>
<td>0.0038</td>
<td>0.0017</td>
<td>0.032</td>
<td>0.0017</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.1502</td>
</tr>
<tr>
<td>ESR</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0022</td>
</tr>
<tr>
<td>Interaction of actively inflamed joints with arthritis duration‡</td>
<td>−0.0005</td>
<td>0.0001</td>
<td>&lt;0.001</td>
<td>−0.0004</td>
</tr>
<tr>
<td>Interaction of clinical deformity with arthritis duration‡</td>
<td>0.0003</td>
<td>0.0001</td>
<td>0.033</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Husted et al. (2007), Arthritis and Rheumatism
Conclusions

• Strong evidence of differential effect of disease activity over illness course on level of disability
• Possible explanation for reduced variability in physical functioning in later disease
• Less evidence of differential effect of damage over illness course, though a positive main effect remains
• Issues about what a HAQ score of zero indicates
Further Work

• Alternative models for fitting this type of data
  – Efficient methods for extending to non-independent random effects
  – Population-averaged approach
  – Models which explicitly account for ceiling and floor effects: e.g. Beta regression
  – A model which answers both sets of objectives (Project 1 and 2) simultaneously: Hidden Markov Models