AS Project Analysis Notes

Friday, June 15, 2018

# AS case definition

* Denominator
  + At least 12 months of continuous enrollment
  + For annual prevalence (calendar year), continuous enrollment for at least 6 months of the calendar year
  + For overall, 12 months of continuous enrollment can span calendar years
  + Includes 65+ year-olds
* Numerator
  + At least 2 diagnosis codes of 720.0
  + Both must be from a rheumatologist ambulatory visit
  + Both must be between 7-365 days apart
  + AS date is set as the date of the 2nd diagnosis
  + AS date must be within enrollment window (i.e., patient must also be in the denominator)
* Protocol states the numerator should be single diagnosis of 720.0, but this was considered (a posteriori) to be not specific
* We also considered broadening the scope of ICD-9 diagnosis codes to 720.xx (at least two codes); but also considered this to be not specific

# Exposure ascertainment

* Follows protocol

# Prevalent condition ascertainment

* 12-month period prevalence (±6 months from exposure date)
  + Other time windows were calculated but only 12-month is reported

# Propensity score model

* Model was a multinomial logistic regression model
  + The link function used was a generalized logit
* TNF exposure was used as the reference exposure
* Model output is probability of exposure to TNF, DMARD, and NSAID or no exposure
* Model estimation performed separately for the 3 data sources: MPCD, Marketscan, and Medicare
* Inverse probability treatment weight (IPTW) for TNF exposure
* The common support region lower bound is the maximum of the lowest TNF propensity score among the 3 exposure groups. The common support region upper bound is the minimum of the greatest TNF propensity score among the 3 exposure groups

# Incident outcome modeling

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer
* Models are weighted using IPTW
* Subjects with propensity scores outside of common support region are excluded
* Additional covariates include
  + 6-month mean daily corticosteroid dose (5 level ordinal)
* Comparisons are between
  + TNF vs DMARD
  + TNF vs NSAID or no exposure

# Tables

Data in tables below do not reflect pending changes described in comment margins above.

## Prevalence of AS

Denominator:

* At least 12 months of continuous enrollment
* For annual prevalence, continuous enrollment for at least 6 months of the year
* For overall, 12 months of continuous enrollment can span calendar year
* Includes 65+ year-olds

Numerator:

* At least 2 diagnosis codes of 720.0
* Both must be from a rheumatologist ambulatory visit
* Both must be between 7-365 days apart
* AS date is set as the date of the 2nd diagnosis
* AS date must be within enrollment window (i.e., patient must also be in the denominator)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **year** | **numer5pct** | **denom5pct** | **numerEstimated** | **denomEstimated** | **prev** |
| 2006 | 37 | 637,960 | 740 | 12,759,200 | 0.006% |
| 2007 | 67 | 687,896 | 1,340 | 13,757,920 | 0.010% |
| 2008 | 90 | 687,227 | 1,800 | 13,744,540 | 0.013% |
| 2009 | 117 | 687,127 | 2,340 | 13,742,540 | 0.017% |
| 2010 | 143 | 695,742 | 2,860 | 13,914,840 | 0.021% |
| 2011 | 178 | 719,161 | 3,560 | 14,383,220 | 0.025% |
| 2012 | 214 | 756,610 | 4,280 | 15,132,200 | 0.028% |
| 2013 | 281 | 871,076 | 5,620 | 17,421,520 | 0.032% |
| 2014 | 328 | 873,627 | 6,560 | 17,472,540 | 0.038% |
| OVERALL 2006-2014 | 218 | 1,212,058 | 4,360 | 24,241,160 | 0.018% |

Differences from earlier estimates

* Numerator used single diagnosis code of 720.0 (determined to have low specificity)
* Numerator used 2 diagnosis codes of 720.xx (determined to have low specificity)

## Demographic characteristics

AS and non-AS cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **cohort** | **database** | **denom** | **age** | **female** |
| AS | MPCD | 2,855 | 43.3 (13.5) | 35.5% (n = 1,013) |
| AS | Marketscan | 12,566 | 45.7 (13.4) | 41.0% (n = 5,155) |
| AS | Medicare | 4,637 | 71.9 (5.8) | 38.8% (n = 1,801) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposed among AS cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **cohort** | **database** | **denom** | **age** | **female** |
| Exposed | MPCD | 1,223 | 45.1 (14.2) | 38.0% (n = 465) |
| Exposed | Marketscan | 5,205 | 45.4 (13.7) | 45.1% (n = 2,350) |
| Exposed | Medicare | 2,666 | 72.3 (5.8) | 40.8% (n = 1,087) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposure cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **database** | **exposure** | **denom** | **age** | **female** |
| MPCD | DMARD | 145 | 43.7 (15.0) | 42.1% (n = 61) |
| MPCD | NSAID | 265 | 43.6 (12.7) | 46.8% (n = 124) |
| MPCD | No exposure | 512 | 50.9 (13.9) | 34.6% (n = 177) |
| MPCD | TNF | 575 | 40.8 (12.7) | 37.4% (n = 215) |
| Marketscan | DMARD | 710 | 46.2 (13.2) | 54.9% (n = 390) |
| Marketscan | NSAID | 1,293 | 45.8 (14.0) | 47.8% (n = 618) |
| Marketscan | No exposure | 1,699 | 47.3 (14.6) | 40.5% (n = 688) |
| Marketscan | TNF | 2,864 | 43.8 (13.1) | 45.0% (n = 1,290) |
| Medicare | DMARD | 550 | 71.8 (5.3) | 50.2% (n = 276) |
| Medicare | NSAID | 1,108 | 72.1 (5.7) | 41.5% (n = 460) |
| Medicare | No exposure | 1,244 | 73.1 (6.3) | 36.0% (n = 448) |
| Medicare | TNF | 702 | 70.9 (4.9) | 42.5% (n = 298) |

## Prevalence of comorbidities

12-month prevalence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **outcomeCategory** | **disease** | **MPCD AS cohort**  **N = 2,855** | **Marketscan AS cohort**  **N = 12,566** | **Medicare AS cohort**  **N = 11,699** |
| Cancer | Hematologic Cancer | 0.2 (0.1-0.7) | 0.3 (0.2-0.5) | 1.4 (1.0-1.8) |
| Cancer | Non Melanoma Skin Cancer | 0 | 0.6 (0.4-0.8) | 1.8 (1.4-2.4) |
| Cancer | Solid Cancer | 3.0 (2.2-4.1) | 2.6 (2.2-3.1) | 13.5 (12.2-14.8) |
| Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 1.8 (1.2-2.7) | 1.1 (0.8-1.4) | 6.0 (5.1-7.0) |
| Cardiac disease | Conduction Block | 0.4 (0.2-0.9) | 0.8 (0.6-1.1) | 4.2 (3.5-5.0) |
| Cardiac disease | Myocardial infarction | 0.1 (0.0-0.4) | 0.2 (0.1-0.3) | 1.1 (0.7-1.5) |
| Infection | Hospitalized infection | 0.7 (0.3-1.2) | 2.6 (2.2-3.1) | 7.9 (6.9-9.0) |
| Infection | Opportunistic infection | 0.9 (0.5-1.6) | 1.0 (0.7-1.3) | 2.1 (1.6-2.7) |
| Inflammatory bowel disease | Crohn’s Disease | 3.2 (2.3-4.3) | 3.5 (3.0-4.0) | 3.3 (2.6-4.0) |
| Inflammatory bowel disease | Ulcerative Colitis | 2.6 (1.8-3.6) | 2.3 (1.9-2.7) | 2.2 (1.7-2.8) |
| Kidney disease | Amyloidosis | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.1 (0.0-0.2) |
| Kidney disease | IgA nephropathy | 0.3 (0.1-0.8) | 0.2 (0.1-0.3) | 0.0 (0.0-0.1) |
| Kidney disease | Nephrotic syndrome | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.3 (0.1-0.5) |
| Lung disease | Apical Pulmonary fibrosis | 0.0 (0.0-0.2) | 0 | 0 |
| Lung disease | Interstitial lung disease | 0 | 0.1 (0.0-0.2) | 0.3 (0.2-0.6) |
| Lung disease | Restrictive lung disease | 0.8 (0.4-1.4) | 0.8 (0.6-1.1) | 3.5 (2.8-4.2) |
| Neurological Disease | Cauda Equina syndrome | 0.1 (0.0-0.4) | 0.0 (0.0-0.1) | 0.2 (0.1-0.5) |
| Neurological Disease | Spinal Cord compression | 0.1 (0.0-0.4) | 0.1 (0.0-0.2) | 0.2 (0.1-0.4) |
| Osteoporotic fracture | Clinical vertebral fracture | 1.2 (0.7-2.0) | 0.7 (0.5-0.9) | 2.6 (2.0-3.2) |
| Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.8 (1.2-2.7) | 0.9 (0.6-1.1) | 3.5 (2.8-4.2) |
| PsO/PsA | Psoriasis | 2.0 (1.3-2.9) | 3.1 (2.6-3.5) | 2.8 (2.2-3.5) |
| PsO/PsA | Psoriatic arthritis | 3.3 (2.4-4.4) | 3.9 (3.4-4.5) | 4.7 (3.9-5.5) |
| Uveitis | Uveitis | 8.1 (6.7-9.7) | 8.2 (7.5-9.0) | 5.3 (4.5-6.2) |

## Crude incidence

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| type | outcomeCategory | disease | MPCD TNF | MPCD DMARD | MPCD NSAID or no exposure | Marketscan TNF | Marketscan DMARD | Marketscan NSAID or no exposure | Medicare TNF | Medicare DMARD | Medicare NSAID or no exposure |
| Comorbidity | Cancer | Hematologic Cancer | 0.14 (0.00-0.79) | 0.00 (0.00-2.44) | 0.47 (0.13-1.19) | 0.12 (0.04-0.29) | 0.70 (0.23-1.63) | 0.41 (0.22-0.70) | 0.79 (0.49-1.20) | 0.52 (0.24-0.99) | 0.47 (0.32-0.65) |
| Comorbidity | Cancer | Non Melanoma Skin Cancer | 1.43 (0.69-2.64) | 1.33 (0.16-4.82) | 1.17 (0.56-2.16) | 0.93 (0.65-1.28) | 1.54 (0.77-2.76) | 0.75 (0.48-1.12) | 3.27 (2.60-4.06) | 2.79 (2.04-3.72) | 3.22 (2.81-3.69) |
| Comorbidity | Cancer | Solid Cancer | 1.46 (0.70-2.68) | 2.05 (0.42-5.98) | 3.78 (2.57-5.36) | 1.35 (1.01-1.77) | 2.22 (1.24-3.67) | 2.41 (1.90-3.03) | 3.34 (2.63-4.18) | 4.37 (3.34-5.61) | 5.44 (4.86-6.08) |
| Comorbidity | Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 0.71 (0.23-1.66) | 0.66 (0.02-3.70) | 1.31 (0.65-2.35) | 0.48 (0.29-0.74) | 0.84 (0.31-1.84) | 0.63 (0.38-0.97) | 2.35 (1.78-3.04) | 1.94 (1.32-2.76) | 2.93 (2.52-3.38) |
| Comorbidity | Cardiac disease | Conduction Block | 0.28 (0.03-1.02) | 0.00 (0.00-2.44) | 1.06 (0.48-2.01) | 0.55 (0.35-0.83) | 0.56 (0.15-1.43) | 1.07 (0.74-1.50) | 2.08 (1.55-2.73) | 2.26 (1.59-3.12) | 2.73 (2.34-3.16) |
| Comorbidity | Cardiac disease | Myocardial infarction | 0.43 (0.09-1.24) | 0.00 (0.00-2.44) | 0.00 (0.00-0.43) | 0.20 (0.09-0.39) | 0.14 (0.00-0.77) | 0.22 (0.09-0.45) | 0.79 (0.49-1.21) | 0.87 (0.48-1.43) | 0.96 (0.75-1.22) |
| Comorbidity | Infection | Hospitalized infection | 3.05 (1.89-4.66) | 0.67 (0.02-3.71) | 2.01 (1.17-3.21) | 5.36 (4.65-6.14) | 6.14 (4.43-8.30) | 4.75 (4.01-5.59) | 8.43 (7.26-9.73) | 9.85 (8.33-11.58) | 9.18 (8.43-9.97) |
| Comorbidity | Infection | Opportunistic infection | 0.85 (0.31-1.85) | 2.05 (0.42-5.99) | 0.47 (0.13-1.20) | 1.54 (1.18-1.97) | 2.26 (1.29-3.67) | 1.01 (0.69-1.43) | 1.67 (1.21-2.25) | 1.74 (1.16-2.50) | 1.98 (1.66-2.35) |
| Comorbidity | Kidney disease | Amyloidosis | 0.00 (0.00-0.52) | 0.00 (0.00-2.44) | 0.35 (0.07-1.02) | 0.02 (0.00-0.14) | 0.00 (0.00-0.51) | 0.00 (0.00-0.11) | 0.04 (0.00-0.20) | 0.00 (0.00-0.21) | 0.06 (0.02-0.14) |
| Comorbidity | Kidney disease | IgA nephropathy | 0.14 (0.00-0.79) | 0.00 (0.00-2.45) | 0.12 (0.00-0.65) | 0.07 (0.02-0.22) | 0.00 (0.00-0.51) | 0.09 (0.02-0.27) | 0.11 (0.02-0.32) | 0.11 (0.01-0.41) | 0.04 (0.01-0.12) |
| Comorbidity | Kidney disease | Nephrotic syndrome | 0.28 (0.03-1.02) | 0.00 (0.00-2.44) | 0.00 (0.00-0.43) | 0.05 (0.01-0.18) | 0.14 (0.00-0.77) | 0.03 (0.00-0.17) | 0.07 (0.01-0.27) | 0.06 (0.00-0.32) | 0.04 (0.01-0.12) |
| Comorbidity | Lung disease | Apical Pulmonary fibrosis | 0.00 (0.00-0.52) | 0.00 (0.00-2.44) | 0.12 (0.00-0.65) | 0.00 (0.00-0.09) | 0.00 (0.00-0.51) | 0.00 (0.00-0.11) | 0.00 (0.00-0.14) | 0.00 (0.00-0.21) | 0.00 (0.00-0.05) |
| Comorbidity | Lung disease | Interstitial lung disease | 0.00 (0.00-0.52) | 0.00 (0.00-2.44) | 0.00 (0.00-0.43) | 0.07 (0.02-0.22) | 0.14 (0.00-0.77) | 0.00 (0.00-0.12) | 0.45 (0.23-0.78) | 0.52 (0.24-0.98) | 0.18 (0.10-0.31) |
| Comorbidity | Lung disease | Restrictive lung disease | 0.57 (0.16-1.46) | 0.00 (0.00-2.44) | 1.17 (0.56-2.15) | 0.60 (0.39-0.89) | 0.57 (0.15-1.45) | 0.66 (0.41-1.01) | 1.73 (1.26-2.33) | 1.33 (0.83-2.02) | 1.80 (1.49-2.15) |
| Comorbidity | Neurological Disease | Cauda Equina syndrome | 0.00 (0.00-0.52) | 0.00 (0.00-2.44) | 0.12 (0.00-0.65) | 0.02 (0.00-0.14) | 0.00 (0.00-0.51) | 0.00 (0.00-0.12) | 0.04 (0.00-0.20) | 0.06 (0.00-0.32) | 0.06 (0.02-0.14) |
| Comorbidity | Neurological Disease | Spinal Cord compression | 0.00 (0.00-0.52) | 0.00 (0.00-2.44) | 0.12 (0.00-0.65) | 0.25 (0.12-0.46) | 0.14 (0.00-0.77) | 0.28 (0.13-0.53) | 0.07 (0.01-0.27) | 0.11 (0.01-0.41) | 0.18 (0.10-0.31) |
| Comorbidity | Osteoporotic fracture | Clinical vertebral fracture | 0.57 (0.15-1.45) | 0.00 (0.00-2.47) | 0.70 (0.26-1.53) | 0.37 (0.21-0.62) | 0.14 (0.00-0.78) | 0.72 (0.46-1.09) | 1.63 (1.18-2.21) | 1.95 (1.33-2.75) | 1.70 (1.41-2.04) |
| Comorbidity | Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.43 (0.69-2.63) | 1.34 (0.16-4.82) | 2.14 (1.27-3.38) | 1.16 (0.85-1.55) | 0.99 (0.40-2.03) | 1.01 (0.69-1.43) | 1.99 (1.48-2.62) | 2.46 (1.75-3.36) | 2.20 (1.86-2.59) |
| Disease manifestation | Inflammatory bowel disease | Crohn’s Disease | 1.95 (1.04-3.33) | 0.70 (0.02-3.88) | 1.55 (0.82-2.65) | 1.69 (1.31-2.16) | 1.46 (0.70-2.69) | 1.41 (1.02-1.89) | 0.83 (0.52-1.27) | 0.41 (0.17-0.85) | 0.59 (0.42-0.80) |
| Disease manifestation | Inflammatory bowel disease | Ulcerative Colitis | 0.73 (0.24-1.70) | 0.00 (0.00-2.44) | 0.94 (0.41-1.86) | 1.35 (1.01-1.77) | 1.27 (0.58-2.41) | 1.08 (0.75-1.51) | 1.03 (0.67-1.51) | 0.71 (0.37-1.24) | 0.57 (0.41-0.77) |
| Disease manifestation | PsO/PsA | Psoriasis | 1.89 (1.00-3.23) | 0.67 (0.02-3.74) | 0.94 (0.41-1.86) | 2.04 (1.61-2.54) | 1.72 (0.89-3.01) | 1.34 (0.97-1.81) | 1.26 (0.86-1.78) | 0.80 (0.42-1.36) | 0.81 (0.61-1.05) |
| Disease manifestation | PsO/PsA | Psoriatic arthritis | 2.37 (1.36-3.86) | 1.36 (0.16-4.91) | 1.06 (0.49-2.02) | 2.16 (1.72-2.69) | 2.62 (1.55-4.13) | 1.09 (0.75-1.52) | 1.33 (0.91-1.86) | 0.49 (0.21-0.97) | 0.59 (0.42-0.80) |
| Disease manifestation | Uveitis | Uveitis | 2.61 (1.52-4.18) | 3.71 (1.20-8.65) | 4.27 (2.95-5.96) | 3.55 (2.96-4.21) | 2.67 (1.58-4.22) | 4.04 (3.35-4.83) | 1.61 (1.14-2.20) | 0.92 (0.52-1.52) | 1.17 (0.92-1.45) |

## Hazard ratios

* Weighted using stabilized IPTW and adjusted for 6-month prednisone equivalent daily dose
* Comparisons are between
  + TNF vs DMARD
  + TNF vs NSAID or no exposure
* Only HRs significantly different from 1.0 are shown

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **disease** | **comparison** | **database** | **nTNF** | **nComparator** | **HazardRatio** | **RobustWaldLower** | **RobustWaldUpper** |
| Hospitalized infection | TNF vs DMARD | MPCD | 537 | 139 | 13.80 | 1.76 | 108.13 |
| Hospitalized infection | TNF vs NSAID or no exposure | MPCD | 537 | 663 | 3.66 | 1.61 | 8.36 |
| Psoriatic arthritis | TNF vs NSAID or no exposure | MPCD | 519 | 656 | 3.24 | 1.07 | 9.80 |
| Psoriatic arthritis | TNF vs DMARD | Medicare | 669 | 503 | 2.70 | 1.19 | 6.12 |
| Uveitis | TNF vs DMARD | Medicare | 667 | 507 | 2.01 | 1.07 | 3.78 |
| Psoriatic arthritis | TNF vs NSAID or no exposure | Marketscan | 2,705 | 2,607 | 2.00 | 1.28 | 3.14 |
| Ulcerative Colitis | TNF vs NSAID or no exposure | Medicare | 680 | 1,900 | 1.86 | 1.05 | 3.31 |
| Psoriatic arthritis | TNF vs NSAID or no exposure | Medicare | 669 | 1,883 | 1.85 | 1.11 | 3.09 |
| Cauda Equina syndrome | TNF vs DMARD | MPCD | 537 | 139 | 0.84 | 0.84 | 0.84 |
| Solid Cancer | TNF vs NSAID or no exposure | Medicare | 647 | 1,814 | 0.75 | 0.56 | 1.00 |
| Solid Cancer | TNF vs NSAID or no exposure | MPCD | 530 | 658 | 0.38 | 0.17 | 0.84 |
| Hematologic Cancer | TNF vs NSAID or no exposure | Marketscan | 2,817 | 2,648 | 0.22 | 0.07 | 0.71 |
| Hematologic Cancer | TNF vs DMARD | Marketscan | 2,817 | 708 | 0.20 | 0.05 | 0.74 |
| Conduction Block | TNF vs NSAID or no exposure | MPCD | 537 | 663 | 0.18 | 0.04 | 0.86 |