Author's response to reviews

Title: Data-driven identification of co-morbidities associated with rheumatoid arthritis in a large US health plan claims database

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Author's response to reviews: see over

Response to comments of reviewers manuscript 'Data-driven identification of co-morbidities associated with rheumatoid arthritis..' Hans Petri 15-4-2010
(also on behalf of co-authors)

Reviewer GJT:

1) Four references have been added in the first paragraph of the Background to support the statement in the introductory sentence and the one about reporting of adverse events.

2) Existing studies on co-morbitities in RA (infectious conditions and cardiovascular disease) are covered in six references (last paragraph Background)

3) The section on confidentiality of patient data in the Methods section has been expanded, this includes explanation that use of these de-identified data do not require patient consent according US law.

4) The section on the limitations of the observational data not collected for research purposes in the last part of the Discussion has been expanded; absence of relevant data such as smoking status and ethnicity is acknowledged.

5) Boot-strapping: our statistical consultant informed us this could be an alternative approach , however would not affect relative risk and only marginally confidence intervals as events analyzed are not rare (occurring in at least 20 persons in control group). Hence we have not re-analyzed.

6) A sentence has been added to the last part of the Discussion [next to addition covering issue raised in point 4 above] explaining that clinical knowledge about co-morbidities of RA or eczema is likely to drive testing/recording behaviour.

7) Though we have not directly compared prevalence data with literature, Table 1 shows the most prevalent co-morbidities. Prevalence is highly dependent on method of assessment and on the age of the population and hence hard to compare with external sources. Relative Risk was calculated with age/sex matched cases and controls from same database. We believe RR should be more reliable for external comparisons. As mentioned in Discussion, a number of associations reported in the literature could be confirmed.

8) Sentence in Background section of Abstract has been changed, to make it more clear.

9) We have expanded the phrase 'Adverse effect to medicine/biological' in the Results section of the Abstract, showing it is a category to catch adverse drug reactions not elsewhere classified in the International Classification of Diseases.

10) Meaning abbreviation FDA now provided on page 4.

11) 'Capitated' 'Medicare' and 'Medicaid' now explained in text as requested.

Reviewer SV:

1) We agree with the reviewer there are considerable limitations to the use of these observational data. We have expanded on these in the Discussion (please see points 4 and 6 regarding remarks of the other reviewer). Main goal was to provide descriptive data on a large number of co-morbidities in rheumatoid arthritis to profile the RA patient population and to provide some context for drug safety issues.

We have added a cautionary remark at the end of the Introduction that associations found should not be assumed to be causal, with the addition that the results can be a base for further analyses and for hypothesis testing in different data sets. Indeed we believe the data in Additional file 1 on more than 2,000 co-morbitities may be useful for this purpose.

2) We have no explanation for the relationship found between psoriatic arthropathy and RA, apart from assumptions we presented. Indeed there are limitations to the interpretation of these observational data (please see point 1)

3) Eczema/dermatitis population was chosen as control group, as a non-systemic chronic condition with no direct relation to RA. We cannot exclude this could include some misdiagnosed patients with psoriasis, as the reviewer remarks. We could indeed have chosen other control groups however we believe these would have posed other challenges, e.g. an age distribution skewed to the elderly or an association with hypertension or diabetes as in some eye diseases.

4) Sicca syndrome appears in Additional 1 file with an RR of 4.5 but not in Table 2 as it has an Arthritis/RA-related ICD codes excluded from Table 2 (codes listed below the table).

Response to minor/discretionary points raised:

1) We chose RR as it is a well-established measure. The use of one-year period prevalence is explained in Methods section.

2) We have added an explanation of ‘level 5’ ICD-9 code in the Methods section as requested.

3) To clarify ‘Tuberculin test reaction’ we have added ‘abnormal or positive’, it is indeed a test result according to the ICD-9 manual.