# Risk of serious infections with biologics

## Methodological choices

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# No conflict of interest and/or other significant information to declare

# Study population - BADBIR

## Data sources : Register (BADBIR)

**British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)** - prospective safety registry established in 2007 in the UK and Republic of Ireland


**162 centres have recruited to BADBIR**

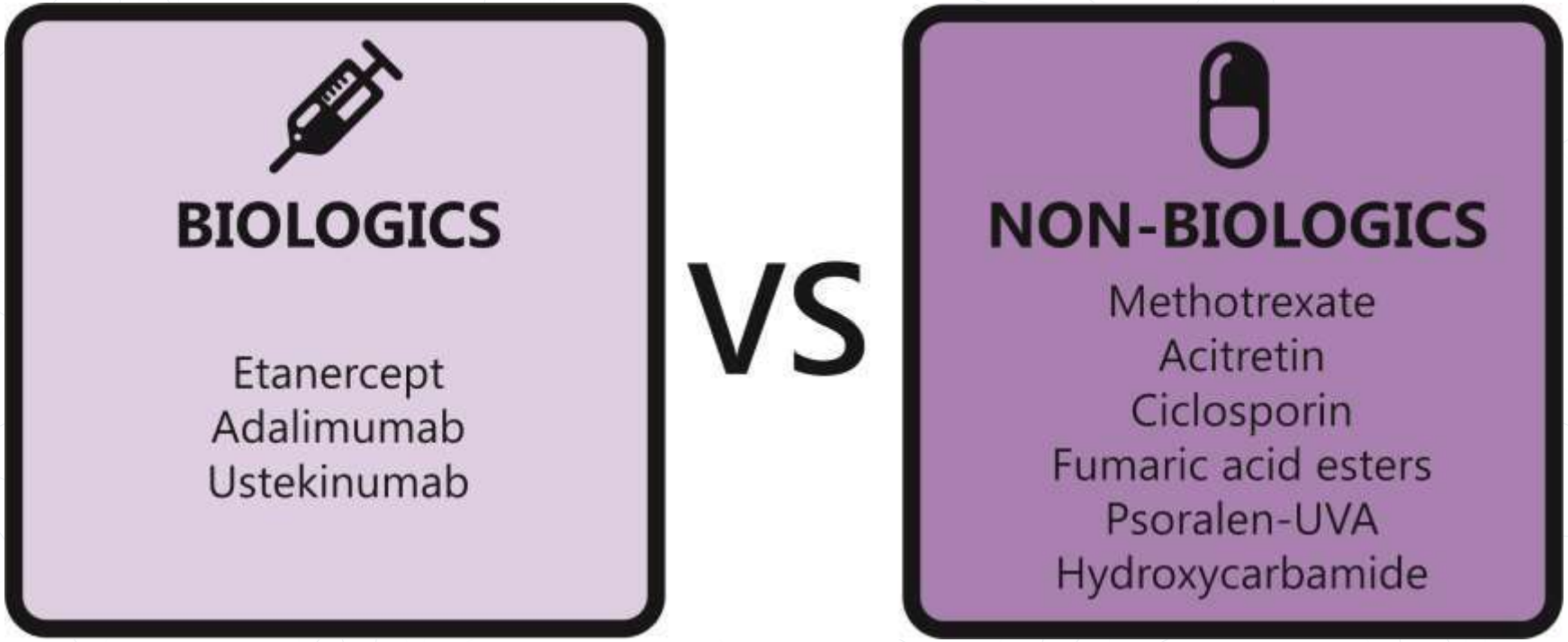
- 126 England
- 4 Northern Ireland
- 10 Republic of Ireland
- 13 Scotland
- 9 Wales

**17,755**
**Total Registrations**

*Yiu ZZ et al. (2018) J Invest Dermatol 138:534-541*

# Study population - BADBIR

## Data sources : Register (BADBIR)




**Psoriasis Area and Severity Index (PASI) ≥ 10**
**Dermatology Life Quality Index (DLQI) > 10**

*Yiu ZZ et al. (2018) J Invest Dermatol 138:534-541*

# Study population - BADBIR

Data sources : Register (BADBIR)

The research question to be answered:

Are etanercept, adalimumab and ustekinumab associated with a higher risk of serious infection as compared with non-biologic systemic therapies and each other in patients with psoriasis outside of the trial setting?

# Study population - BIOBADADERM

## Data sources : Register (BIOBADADERM)

**Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology (BIOBADADERM)** - prospective safety registry established in 2008 in the Spain (part of PSONET)

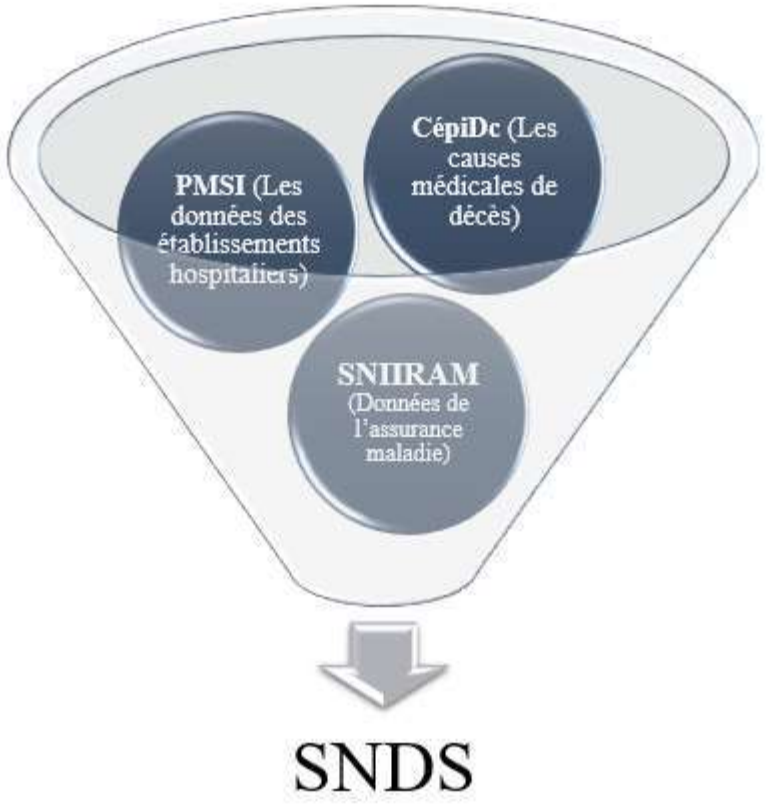
Prospective cohort

At that time: 2153 patients, 7867py

On-line and on-site monitoring

# Study population – French medico-administrative data

Data sources : SNDS, Medico-administrative data



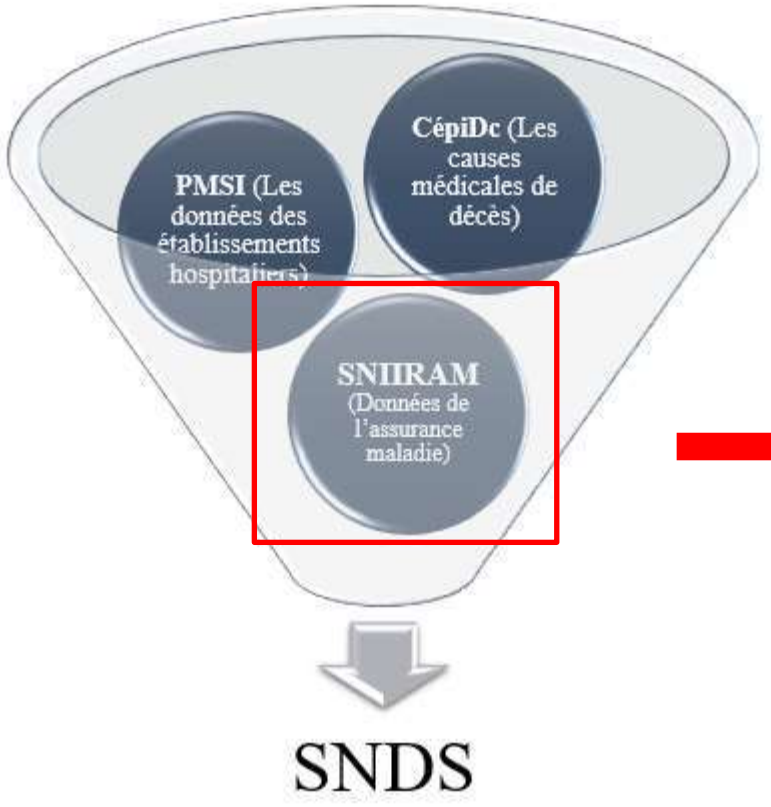

French National Health Data System Definition of the population (SNDS)

- 65 million individuals (98.8% of the French population)
  - Socio-demographic characteristics
  - Vital status
  - Drug dispensation (number of units; date; date and nature of medical and paramedical interventions; etc.)
  - LTD
  - Hospitalization data (admission date; discharge diagnoses)

Tuppin, P. et al, 2017. *Rev. DÉpidémiologie Santé Publique*

# Study population – French medico-administrative data

## Data sources : Medico-administrative data




Population and exposure based on healthcare fulfilment of prescription data

- Psoriasis population : At least 2 vitamin D derivatives within a 2-year period (Se. 85%)
  - January 1, 2008, to May 31, 2019 [Regularly updated]

Aleshaki et al, 2018. *Expert Rev Pharmacoecon*.
Egeberg et al, 2016. *J. Invest. Dermatol*.
Sbidian et al, 2019. *Br. J. Dermatol*.

# Study population – French medico-administrative data

Data sources : Medico-administrative data

The research question to be answered:

Is the risk of serious infections differential between biologic or targeted exposures in patients with psoriasis?

# Methodology

## Data sources

+ Real-world setting
+ Minimal disease/exposure misclassification
+ Minimized selection bias

- ≠ days of use

### Register

+ Account for potential intra-class variations by handling each biologic separately

- Not a full population set of data with potential for selection bias

### Medico-administrative data

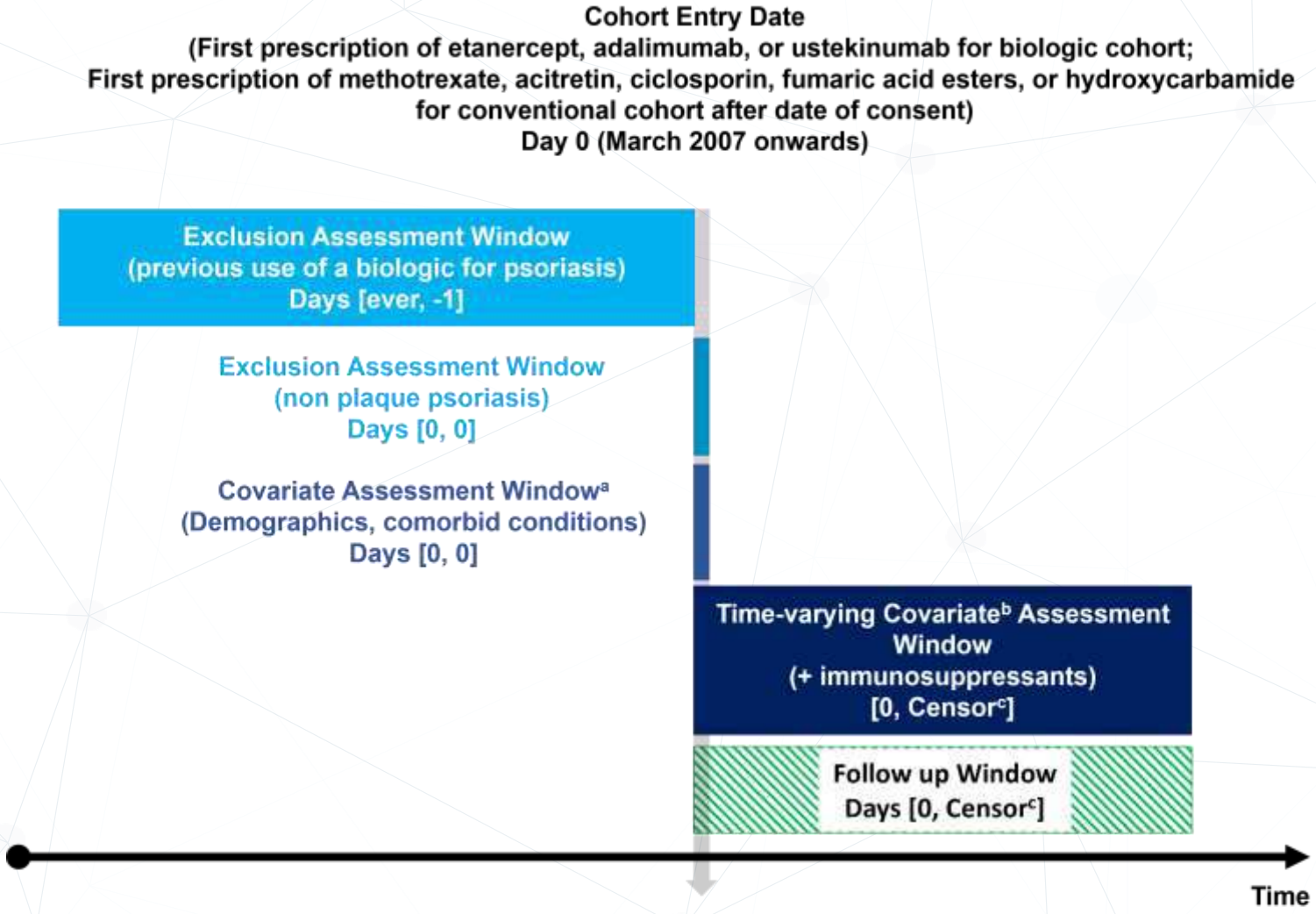
+ 98% French population

- Phenotype and severity assessment missing as well as other clinical variables (BMI, tobacco)

# Methodology

## Study population

BADBIR




a. Covariates included age, sex, body mass index, waist circumference, alcohol intake, disease severity (Psoriasis Area and Severity Index), psoriatic arthritis, smoking, diabetes, chronic obstructive pulmonary disease, asthma, immunodeficiency syndromes
b. Concomitant immunosuppressants included methotrexate, ciclosporin, fumaric acid esters, hydroxycarbamide.
c. Earliest of: outcome of interest (serious infection), switching or discontinuation of biologic (biologic cohort), death, last registered follow-up, end of the study period (October 2016)

# Methodology

## Study population

BIOBADADERM

Psoriasis patients attending hospital dermatological consultations

Patients enter the cohort when they receive for the first time in their live some systemic drug ( they could have received others before)

Followed at least once a year, but usually much more commonly ,as part of their usual care.

No limits for follow-up

# Methodology

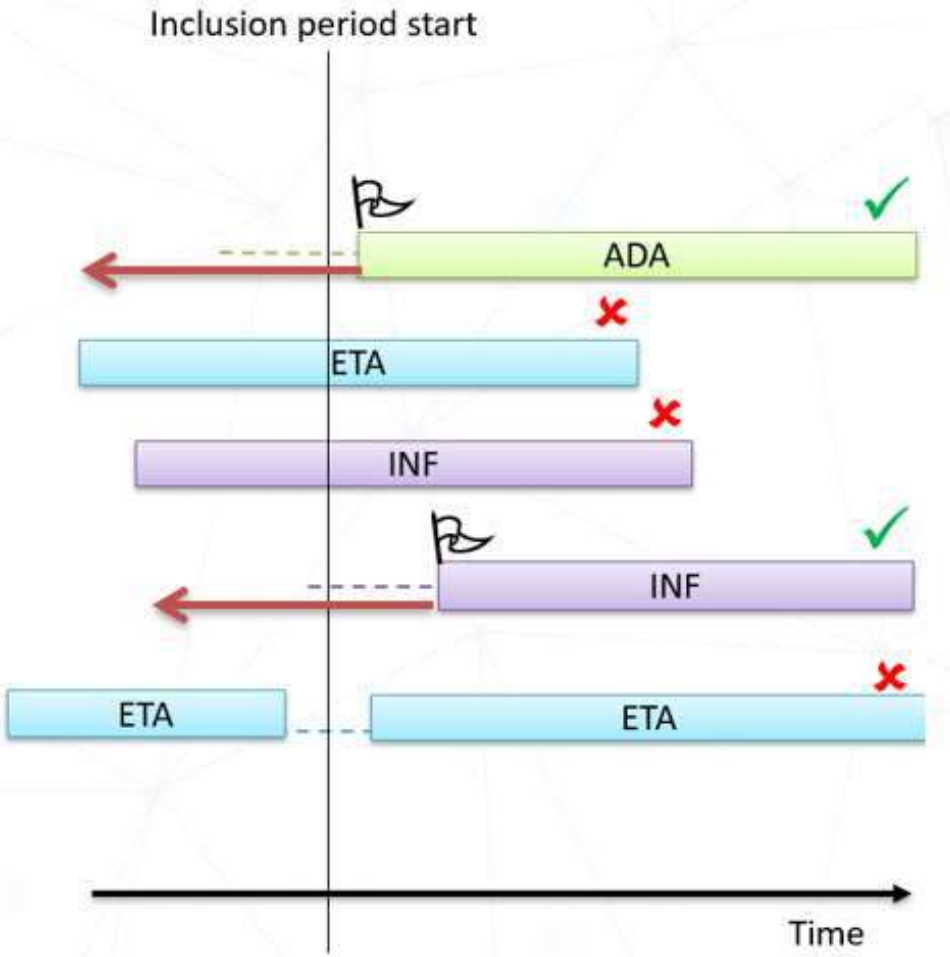
## Study population

SNDS

New user : Ø BsDMARDs the year before (----)

- Follow up starts at the biologic initiation (⚑)
  - Until the occurrence serious infections or the censorship dates: death, switch, end of exposure, lost to follow-up or the study point date (January 31, 2020),
- Baseline covariate assessment window (2years; ←)

New user → Etanercept



# Methodology

## Study population

| | New-user design | Active comparator |
|---|---|---|
| Yiu ZZ et al | ✓ | Non-biologics |
| García-Doval I et al | ✓ | Methotrexate |
| Penso L et al | ✓ | Etanercept |

Yoshida et al, 2015. *Nat Rev Rheumatol*.

+ New user : incident exposure easier to handle with less confounding

+ Active comparator : another active drug used in clinical practice to treat the same disease at the ~ same severity

+ Active comparator + New user: reducing potential for immortal time bias / measured and unmeasured confounding

+ Closest counterfactual to “no biologics” outside of trial setting

- Conventional cohort still unsatisfactory as they are at different stage in their treatment/disease trajectory

- ≠ days of use

# Methodology

## Outcome: serious infection

| | Serious infection definition | Definition validated | Separated by subtypes of LRTI, SSTI |
|---|---|---|---|
| Yiu ZZ et al | Any infection that was associated with or prolonged hospitalisation, required the use of intravenous antimicrobial therapy, or led to death | ✓ | ✓ |
| García-Doval I et al | Any infection that was associated with or prolonged hospitalization, or led to death | ✓ | |
| Penso L et al | Hospital discharge diagnosis for an infection | ✓ | |

# Methodology

## Outcome: serious infection

+ Linkage with hospitalisation data minimises outcome misclassification
+ Serious infection much less likely to have differential outcome misclassification and reporting bias than all infections
- outcome is rare and therefore there is imprecision and uncertainty in estimates

### Register

+ Based on the International Conference on Harmonisation definition of serious adverse event specific to infections validated by separate review
+ Separated by subtypes of LRTI, SSTI

### Medico-administrative data

+ Positive predictive values of recorded cases and type of infections were 97%

- Based on discharge only
- Subtypes poorly informed
- Severity of the hospitalisation for infection not taken into account

Sahli et al, 2016. *Pharmacoepidemiol. Drug Saf*.

# Methodology

## The covariates

| | Time dependent covariables | IPTW | Missing handled |
|---|---|---|---|
| Yiu ZZ et al | ✓ | ✓ | Imputation |
| García-Doval I et al | * | ✓ | Total cases |
| Penso L et al | ✓ | ✓ | No missing data |

* combinations excluded

BADBIR : takes into account uncertainty of missing data with MI

BIOBADADERM / SNDS : Total cases ( few missing data + probability of missing data assumed at random)

# Methodology

## The covariates : Time dependent covariables

| Patient X | Biologic initiated | age | … | NSAIDs | MTX | Systemic Corticosteroids | START | STOP | SI |
|---|---|---|---|---|---|---|---|---|---|
| A | ADA | 56 | … | 0 | 1 | 0 | 0 | 64 | 0 |
| A | ADA | 56 | … | 0 | 1 | 1 | 64 | 90 | 0 |
| A | ADA | 56 | … | 1 | 1 | 1 | 90 | 220 | 0 |
| . . . | ADA | 56 | . . . | 0 | 1 | 1 | 220 | 577 | 0 |
| A | ADA | 56 | … | 0 | 0 | 1 | 577 | 630 | 0 |
| B | USK | 33 | … | 0 | 1 | 1 | 0 | 160 | 0 |
| B | USK | 33 | … | 0 | 1 | 0 | 160 | 210 | 1 |

+ Reduce confounding bias
- ≠ disease severity
- Complicated to interpretate

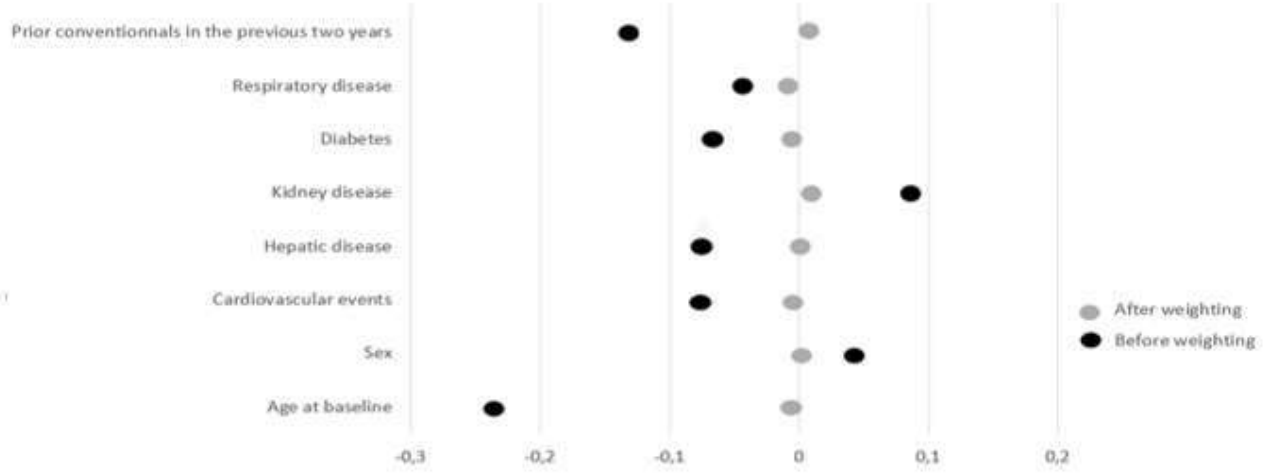
Concomitant methotrexate, NSAIDs and systemic corticosteroids exposure changed over time: Used as time dependent covariables using a Start and stop design the Cox regression model

Brassard et al, 2014. *American Journal of Gastroenterology.*

# Methodology

## The covariates : Inverse Probability of Treatment Weighting (IPTW)

*a.* Standardized differences before and after IPTW weighting comparing covariate values for patients with adalimumab or with etanercept




| | AGE AT BASELINE | SEX | CARDIOVASCULAR EVENTS | HEPATIC DISEASE | KIDNEY DISEASE | DIABETES | RESPIRATORY DISEASE | PRIOR CONVENTIONNALS IN THE PREVIOUS TWO YEARS |
|---|---|---|---|---|---|---|---|---|
| BEFORE WEIGHTING | -0.24 | 0.04 | -0.08 | -0.08 | 0.09 | -0.07 | -0.04 | -0.13 |
| AFTER WEIGHTING | -0.01 | 0.001 | -0.004 | 0.001 | 0.01 | -0.002 | -0.01 | 0.004 |

+ Propensity score = all patient characteristics at baseline in 1 variable
+ Weighting = treatment assignment independent of baseline covariates (Patient characteristics balanced)
+ Reduce potential bias due to treatment allocation
+ Reduce confounding bias

- Unmeasured covariables
- No formal causal diagram drawn

Austin et al, 2015. *Stat Med.*

# Methodology

## Statistical model

| | Statistical model |
|---|---|
| Yiu ZZ et al | Cox |
| García-Doval I et al | Poisson |
| Penso L et al | Cox |

Cox regression

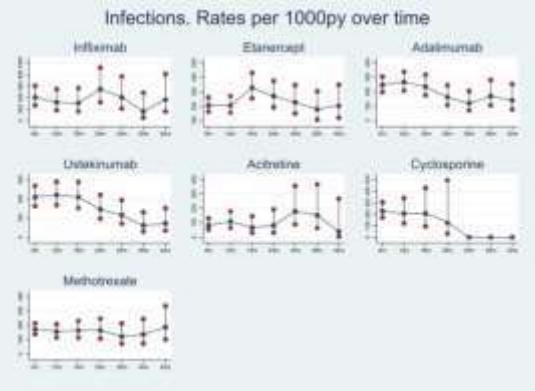
+ Little assumptions needed for shape of baseline hazard or constant rate, good for relative risks

- Only deals with first event, harder to look at absolute risks

Poisson regression:

+ Outcome is incidence rate ratio (easier to understand), easier to develop multilevel models ( hospital, patient grouping of events)

- Requires constant baseline rate (checked).



# Methodological choices to answer the research question

| | Data Sources | New-user design | Active comparator | Time dependent covariables | IPTW | Missing handled | Statistical model |
|---|---|---|---|---|---|---|---|
| Yiu ZZ et al | REGISTER | ✓ | Non-biologics | ✓ | ✓ | Imputation | Cox |
| García-Doval I et al | REGISTER | ✓ | Methotrexate | | ✓ | Total cases | Poisson |
| Penso L et al | Medico-administrative data | ✓ | Etanercept | ✓ | ✓ | No missing data | Cox |

# Discussion

## Final words

| | | | | |
|---|---|---|---|---|
| Ideas for limitations | Different populations | Low power (need to update for Biobadaderm) | Immortal time bias ( MTX use limited over time)<br><br>Non-biologics can have different risks ( cyclosporin higher in Biobadaderm)<br><br>Which is the best comparator ( Adalimumab more realistic?, acitretine  less favourable ???) | Baseline risks are very coherent (differences can be explained by different drugs).<br><br>FRANCE study less standard error (but maybe more measurement error/bias) |