Who's at risk?
Identifying risk groups for adverse drug reactions using VigiBase

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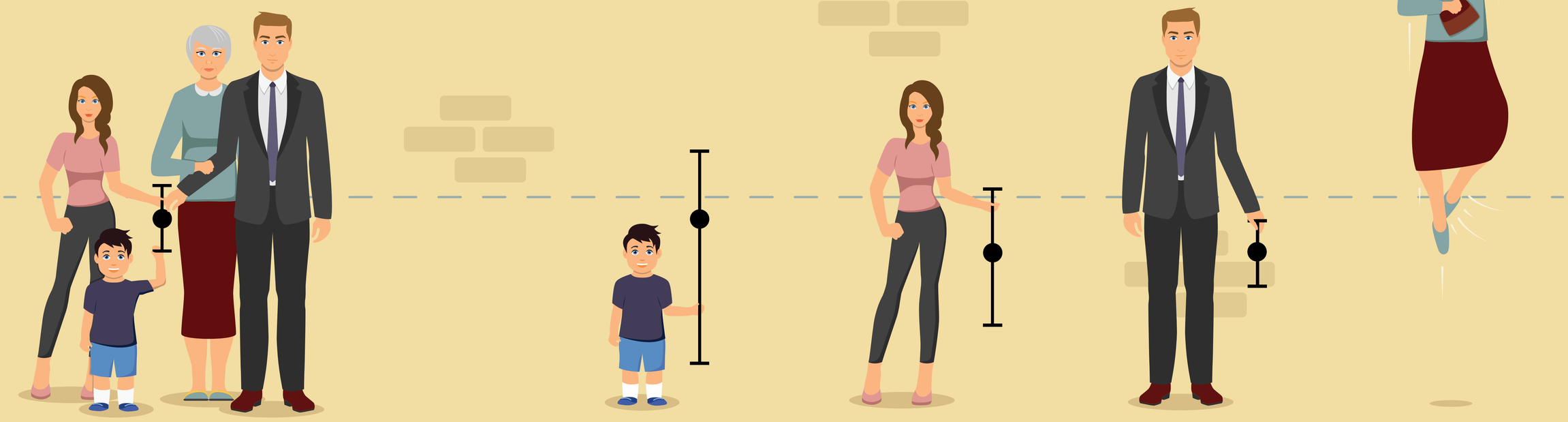
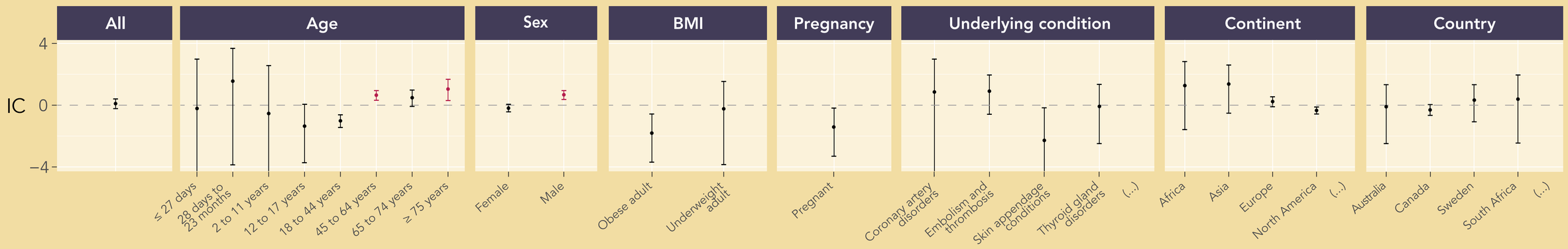


Example of a subset disproportionality analysis
Information Component (IC) measures of disproportionality for a specific drug and adverse event, across different data subsets, with 95% credibility intervals for the overall analysis and 99% credibility intervals for the subsets to avoid highlighting spurious associations.[1]



Background

In recent years, Uppsala Monitoring Centre has initiated a shift toward signal characterisation and risk group identification in support of our vision for wise therapeutic decisions. As a first attempt at broader open-ended risk group detection, we conducted a signal screening focused on identifying risk groups for adverse drug reactions (ADRs).

Objective

To explore the possibility of identifying signals of ADRs in risk groups using VigiBase, the WHO global database of individual case safety reports.

Methods

Dataset: 15.4 million reports retrieved on 28 August 2017 from VigiBase

Subset disproportionality analysis

Disproportionality analyses performed for drug-adverse event (AE) pairs (1) in the entire database and (2) across a range of data subsets. Drug-AE pairs disproportionally overreported in such subsets but not in the whole data were identified.

Prioritization

Identified drug-AE-subset associations ordered by (1) vigiRank [2] for strength of evidence, and (2) weighted random sampling for subset balancing.

Manual process

Initial review

Manual review of top-ordered drug-AE-subset associations including review of the reports and consultation of literature in search for support for possible risk group.

In-depth review

In-depth review of potential signals performed by clinical experts.

Signals of ADRs in risk groups

Results

Initial review

Out of 386 manually reviewed drug-AE-subset associations, **18** (4.6%) were classified as **potential signals**. The highest yield was identified in **females** (5), **underweight** adults (3), and the **elderly** (3).

Covariate	Potential signals	Assessed associations	Proportion
Sex	6	44	14%
BMI	4	39	10%
Continent	4	77	5%
Age	3	65	5%
Country	1	62	2%
Pregnancy	0	33	0%
Underlying condition	0	75	0%

In-depth review

As of August 2018, in-depth clinical reviews have been completed for 14 out of 18 potential signals, resulting in **seven signals** describing potential risk groups for ADRs.[3]

Signals of ADRs in risk groups
Aflibercept – Deep vein thrombosis and pulmonary embolism – **Males**
Esomeprazole – Gynaecomastia – **Obese**
Glibenclamide – Palpitations – **Asian population**
Levofloxacin – Myoclonus – **75 years and older**
Omalizumab – Anaphylactic shock – **Females**
Selegiline – Hypoglycaemia – **Underweight**
Ceftriaxone – Hepatitis – **75 years and older**

All ages
228 observed reports
267 expected reports

Elderly
67 observed reports
39 expected reports

The drug-AE pair was disproportionally overreported in the elderly subgroup and the case series (n=67) suggested causality through 1) plausible time to onset (n=52), 2) recovery upon withdrawal (n=47), and 3) ceftriaxone reported as the only suspected drug (n=27). Ceftriaxone is known to cause raised liver enzymes, and the elimination half-life of the drug in patients over 75 is increased.[4,5]

Conclusions

Signals of ADRs in risk groups can be identified from a global database using subset disproportionality analysis. Continued development of statistical screening methodologies to highlight potential signals within subgroups could usher in a new era of "precision pharmacovigilance".

References

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Disclosure

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