Subset disproportionality analysis within a global database to uncover **adverse drug reactions in risk groups**

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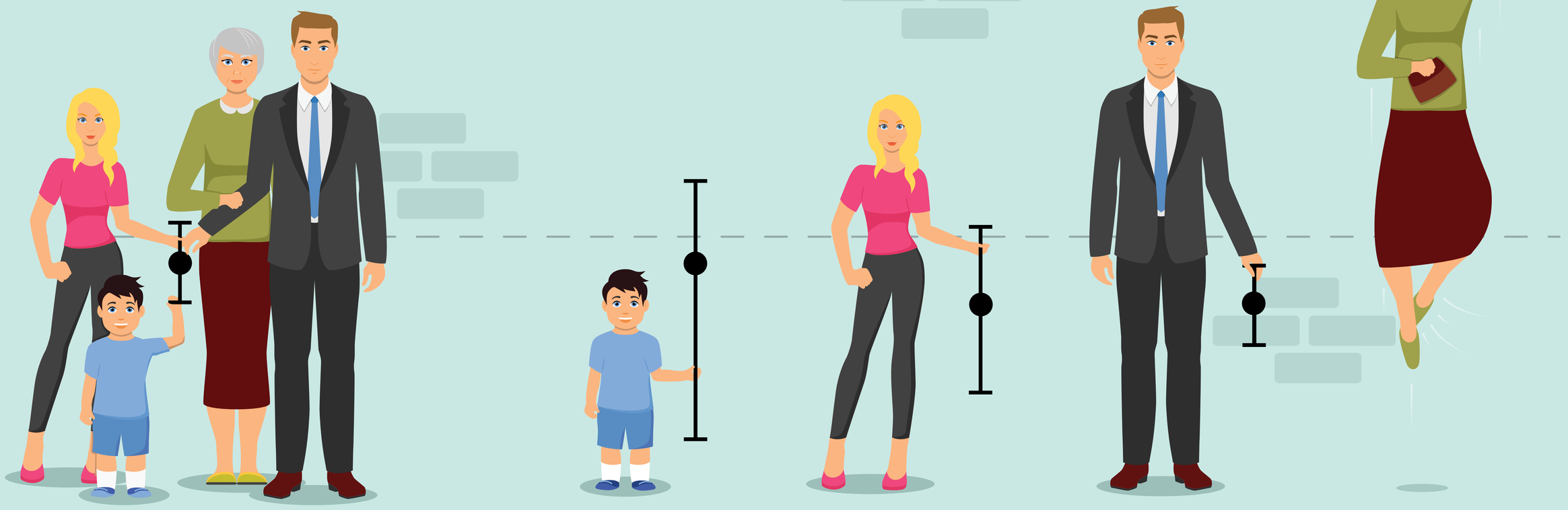
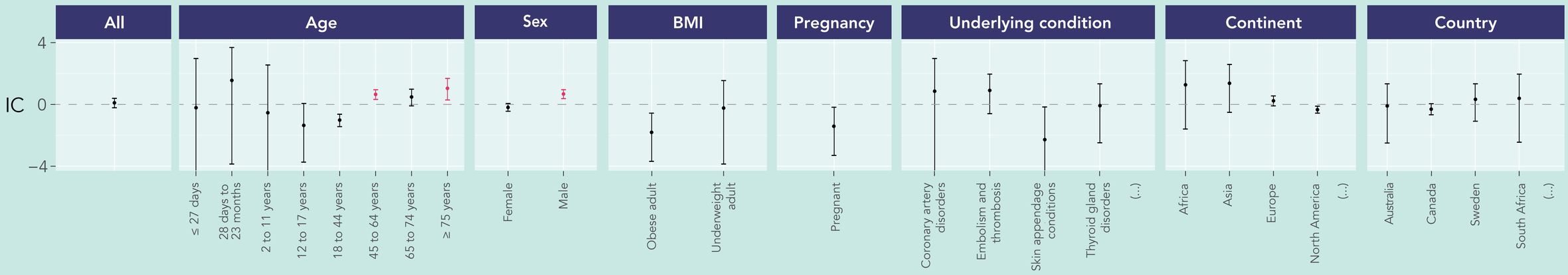


Example of a subset disproportionality analysis
Information Component (IC) measures of disproportionality for a specific drug and adverse event, across different data subsets, with 95% credibility intervals for the overall analysis and 99% credibility intervals for the subsets to avoid highlighting spurious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



Background

There is growing recognition of the variability between patients in both the benefits and harms from medicinal products. In pharmacovigilance, current statistical methods to screen large data sets are sensitive to associations at the population level but can fail to highlight suspected adverse drug reactions (ADRs) in sub-populations at risk.

Objective

To explore if disproportionality analysis across subsets of individual case reports within a global database can uncover signals of suspected adverse drug reactions in certain risk groups.

Methods

Dataset: 15.4 million reports retrieved on 28 August 2017 from VigiBase, the WHO global database of individual case safety reports

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, and with the observed-to-expected ratio in the subset at least twice that 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.

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

Conclusions

Signals of suspected adverse drug reactions in risk groups can be identified through subset disproportionality analysis within a global database. Further development of such methods could usher in a new era of "precision pharmacovigilance".

References

[1] Hopstadius J, Norén GN. Robust discovery of local patterns: Subsets and stratification in adverse drug reaction surveillance. Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium ACM: Miami, FL, 2012: 265–274.

[2] Caster O, Juhlin K, Watson S, Norén GN. Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank. Drug Saf. 2014;37(8):617-28.

Disclosure

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