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# Adverse drug reaction risks obtained from meta-analyses and pharmacovigilance disproportionality analyses are correlated in most cases

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## Declaration of interest

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## **Abstract**

### Objective

We aimed at testing if a correlation between adverse drug reactions relative risks estimated from meta-analyses and disproportionality analyses calculated from pharmacovigilance spontaneous reporting systems databases exist, and if methodological choices modify this correlation.

### Study Design

We extracted adverse drug reactions (ADR) odds ratios (ORs) from meta-analyses used as reference and calculated corresponding Reporting Odds Ratios (RORs) from the WHO pharmacovigilance database according to 5 different designs. We also calculated the relative bias and agreement of ROR compared to ORs.

### Results

We selected 5 meta-analyses which displayed a panel of 13 ADRs. A significant correlation for 7 out of the 13 ADRs studied in the primary analysis was found. The methods for ROR calculation impacted the results but none systematically improved the correlations. Whereas correlation was found between OR and ROR, agreement was poor and relative bias was important.

### Conclusion

Despite the large variation in disproportionality analyses results due to design specification, this study provides further evidence that relative risks obtained from meta-analyses and from disproportionality analyses correlate in most cases, in particular for objective ADR not associated with the underlying pathology.

**Key words:** Disproportionality analysis, meta-analysis, adverse drug reaction, pharmacovigilance, drug safety

**Running title:** correlation between meta-analyses and disproportionality analyses.

**Word count:** 2637

## **What is new?**

- key findings
  - Results of disproportionality analyses are highly variable according to design specifications
  - Despite this variability relative risks obtained from meta-analyses and from disproportionality analyses correlate in most cases, in particular for objective adverse drug reactions (ADR) not associated with the underlying pathology
  - Agreement between methods is poor and relative bias extremely important
  
- what this adds to what is known
  - The correlation between relative risks obtained from meta-analyses and from disproportionality analyses is mainly dependent of the type of ADR.
  
- what is the implication/what should change now
  - In the case of no data from epidemiological studies or clinical trials exist, using pharmacovigilance database to hierarchize a risk among a drug class could be of interest to design pharmacoepidemiological studies or to explore adverse drug reaction mechanisms.

## 1. Introduction

Disproportionality analyses are statistical methods widely used by national drug agencies, industries and researchers for safety signal detection in pharmacovigilance spontaneous reporting systems databases. They aim at quantifying the extent to which a drug-event pair is reported more often than it would be at random. A signal of disproportionate reporting (SDR) is a statistical association that does not imply a causal relationship between the administration of the drug and the occurrence of the adverse event [1,2]. Generally, disproportionality analyses cannot be used to assess a drug-relative risk because they don't provide risk quantification [3]. Nevertheless, Maciá-Martinez and colleagues found a significant correlation between disproportionality analyses and relative risks estimated in epidemiological studies and meta-analyses [4]. Moreover, several studies have recently used a mixed pharmacoepidemiological-pharmacodynamic design to explore the pathophysiology of some adverse drug reactions (ADR), hypothesizing a correlation between the measures of disproportionality and drug-related risks of ADR<sup>5-8</sup>. However, disproportionality analyses are affected by several bias, which may modify disproportionality effect sizes, performances for SDR detection and eventually the correlation with drug-related risks, if not properly controlled [3]. Among them, the time after drug approval (Weber effect), the reporting region (induced by heterogeneity in pharmacovigilance national systems), media attention (notoriety bias) affect drug reporting [9,10]. A competition between the studied drug or event with other drugs or events widely reported can also affect disproportionality effect sizes (competition bias or masking effect) [11,12]. Lastly, the choice of the control group does affect disproportionality and is an important concern in every epidemiological study. Several strategies to minimize the above-mentioned bias have been developed (e.g. time trend analysis, exclusion of competitors, subgroup analysis) but their impact on the relationship between disproportionality effect sizes and drug-related risks has never been studied [13].

In this context, several questions remain (1) Does the correlation between disproportionality analyses and relative risks exists for a variety of ADR? (2) Could the ADR characteristics or the disproportionality analyses methodological choices modify this correlation?

To further address these questions, we compared and correlated ADR relative risks obtained from meta-analyses of clinical trials to disproportionality analyses and assessed the impact of study design and bias minimization methods on the results.

## **2. Methods**

### **2.1. Data sources**

#### ***2.1.1. Selection of meta-analyses***

We extracted all meta-analyses published over five years (August 2013-August 2018) in seven high impact journals: NEJM, JAMA, Plos Medicine, BMJ, JAMA Internal Medicine, Lancet and Annals of Internal Medicine. We considered that these journals guaranteed a good methodological quality of meta-analyses.[14] Then, we selected all meta-analyses evaluating the safety of a pharmacological drug class containing at least 5 different drugs.

#### ***2.1.2. Pharmacovigilance database***

VigiBase<sup>®</sup> is the World Health organization's (WHO) global safety database of individual case safety reports (ICSRs). The database contained over 20 million ICSR from 131 member countries and 29 associated members of the WHO Programme for International Drug Monitoring. VigiBase<sup>®</sup> provides ICSR with patient information such as gender, age, medical history, country, drug and concomitant drug taken with chronological information, indication of the drug, adverse effects and their severity and outcome [15].

#### ***2.1.3. Adverse drug reactions***

In VigiBase<sup>®</sup>, all ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [16]. In the present study, we identified Standardized Medical Queries and MedDRA terms corresponding as accurately as possible to ADRs extracted from meta-analyses. We characterized each ADR by its frequency, severity, objective or subjective (i.e. patient reported) nature and time to onset (Appendix A). Furthermore, for each ADR, a potential protopathic bias was searched. A protopathic bias occurs when a drug is initiated in response to the first symptoms of an undiagnosed disease that will cause the studied ADR [17].

### **2.2. Statistical analysis**

#### ***2.2.1. Meta-analysis***

All risk estimates from the selected meta-analysis were extracted. When several drug dosages were available for a given drug, they were meta-analyzed to obtain a summary measure. Moreover, continuous outcomes were back transformed into odds ratio (OR) through standardized mean differences [18].

### ***2.2.2. Disproportionality analyses***

Several disproportionality methods have been developed and are currently applied in pharmacovigilance databases, but no gold standard in terms of performance, accuracy and reliability has been established [19,20]. In the present study, disproportionality analyses were performed using the Reporting Odds Ratio (ROR) method, with 95% confidence intervals (CI) [21]. Given the poor accuracy of the ROR calculated with less than three individual cases, drug-adverse effect pairs for which the number of cases was lower than 3 were excluded from analysis [13,20,22].

To explore factors that may influence the correlation between RORs and ORs, several disproportionality analyses were performed in Vigibase<sup>®</sup>. A primary disproportionality analysis was performed for each drug or drug class considered as suspect at the publication date of the corresponding meta-analysis, to minimize the notoriety bias and the modification of reporting rates over time. Then, the following secondary analyses were performed: (1) adding the concomitant reports to the studied drug; (2) standardizing the time on the market of different drugs five years after approval date, to assess the influence of time on the market on the reporting rate [9,23]; (3) adjusting on the reporting continent (North America: Canada and USA) [24]; (4) restricting SDR detection within a therapeutic area to limit indication and confusion bias [25,3,26]; (5) excluding competitors to take into account potential drug-event competition bias. Competitors were identified using the competition index at the PT level with a cut off at 5% [11,27,28].

### ***2.2.3. Correlation, relative bias and agreement between disproportionality analyses and risk estimates***

To estimate the variation in disproportionality analyses results we calculated the “relative ROR” which is the ratio between the higher and the smaller ROR estimated according to the primary or secondary analyses. [29]

To take into account the variability of OR and ROR estimates we performed an orthogonal regression analysis with the assumption of equal variance. We used natural logarithms of both values to reduce heteroscedasticity as previously used by Maciá-Martinez et al. [4,30]. Moreover, we calculated goodness of the fit (Pearson production moment correlation coefficients) and performed t-tests of the regression slopes. Strong correlations were defined by a Pearson’s r coefficient >0.6 and a significant t-test of slope (p<0.05).[31]

As suggested by a reviewer, we explored the association between ADR characteristics and correlation coefficients through non-parametric Kruskal Wallis tests. Median and

standard errors are presented, a p-value <0.05 was considered significant given the exploratory nature of these analyses.

We also assessed the relative bias of ROR compared to OR. We thus calculated the prediction errors between the two estimates divided by the ROR value; using this formulae  $RB = (|pred - obs|) / pred$ ; pred=predicted value (ROR); obs=observed values (OR) [32]. Lastly, we calculated the agreement between OR and ROR through Bland-Altman method [33].

All analyses were performed using R statistical software (Version 3.3.0)

### **3. Results**

#### **3.1. Meta-analyses selection**

Among the 425 meta-analyses published between 2013 and 2018 in the 7 selected high impact journals, 43 assessed the safety of several pharmacological interventions. However, only five meta-analyses assessed the risk of specific ADRs and were selected [34–38]. The reasons for exclusion were the presence of only pooled results (n=8), no safety analysis or no specific ADR (e.g. proportion of severe ADR or drop out for ADR) (n=21), not enough drug groups (n=8) and only combined treatment results (n=1) (Table S1). Five drug classes were involved in the selected meta-analyses: anti-psychotics, anti-depressants, blood pressure-lowering agents, oral anticoagulants and anti-diabetics.

#### **3.2. Description of adverse drug reactions**

These 5 meta-analyses evaluated 13 ADRs: extrapyramidal syndrome, prolactin increase, QTc prolongation, sedation, weight gain with antipsychotics; cough hyperkalemia, oedema, presyncope with blood pressure-lowering agents; suicide with antidepressant; gastrointestinal and intracranial bleeding with oral anticoagulants and hypoglycemia with anti-diabetics. The ADRs are described in Table 1.

#### **3.3. Disproportionality analyses**

The criteria (MedDRA terms, cases selection, drug class, drug competitors) used for ROR calculations in Vigibase® are described in Table S2. The variation of disproportionality analyses results ranged from a relative ROR of 2.7 (risperidone and prolactin increase) to 710.8 (quetiapine and QTc prolongation) (Figure 1). In the later, the ROR for QTc prolongation with quetiapine was of 1.2 (1.1, 1.4, n=267) when restricting the analysis by



therapeutic area and was of 854.8 (450.5, 1622.2, n=14) when conducting the analysis 5 years after FDA labelling.

### **3.4. Relationship between disproportionality analysis and relative risks**

In the primary analysis, we found a significant correlation between ORs from meta-analyses and the corresponding RORs for 7 of the 13 ADRs studied: extrapyramidal syndrome ( $r=0.75$  (0.38, 0.91),  $n=15$ ) and prolactin increase ( $r=0.77$  (0.35, 0.93),  $n=15$ ) with antipsychotics, hyperkalemia ( $r=0.90$  (0.53, 0.98),  $n=8$ ) and cough ( $r=0.65$  (0.09, 0.9),  $n=11$ ) with blood pressure-lowering agents, gastrointestinal bleeding ( $r=0.97$  (0.60, 1.00),  $n=5$ ) with oral anticoagulants and hypoglycemia ( $r=0.66$  (0.10, 0.90),  $n=11$ ) with anti-diabetics. The goodness of the fit and the results of the t-test of the slope are presented in Figure 2 and in Figure S1 and Table S3. Interestingly, some correlations remain significant in all secondary and sensitivity analyses despite the wide variation in results of disproportionality analyses. Examples of good and bad correlations are presented in Figure 3.

None of the methods for ROR calculation (time, region or population standardization, drug considered concomitant) systematically improved the correlation results. Excluding competitors slightly improved the correlation in 7 on the 8 affected ADRs. The wider variation in the correlations was induced by time and regional standardization.

The presence of protopathic bias was significantly associated with lower correlations (0.21 (0.09) vs 0.64 (0.12),  $p=0.045$ ) and objective ADR with higher correlations versus subjective (patient reported) ADR (0.66 (0.08) vs 0.15 (0.18),  $p=0.02$ ).

Whereas correlation was found between OR and ROR agreement was poor and prediction error extremely important. The prediction error of ROR ranged from 0.1% to 2742%. Only 8.3% of the ROR displayed a prediction error inferior to 50% of the OR value. According to Bland and Altman method, mean differences between OR and ROR ranged from 37.6 (-122.7, 197.8) for time standardization to -0.1 (-7.7, 7.6) in restricting the analysis to a therapeutic area (Table S4)

## **4. Discussion**

To our knowledge, this is the first study exploring the impact of disproportionality analyses study design for ROR calculation on the correlation with ADR relative risks

estimated from clinical trials. We found a significant correlation for 7 out of the 13 ADRs studied in the primary analysis. In the case of no data from epidemiological studies or clinical trials exist, because the ADR is a new signal or is difficult to assess by these methods (e.g. extremely rare or very long time to onset), using pharmacovigilance database to hierarchize a risk among a drug class could be of interest. Those disproportionality results could subsequently be used in routine pharmacovigilance activities, to design pharmacoepidemiological studies or to explore ADR mechanisms by correlating the results with drug-receptor affinity, physico-chemical or pharmacokinetic properties.

The ADR frequency, seriousness or time to onset do not appear to influence the correlations among risk estimates, whereas subjective ADR and the presence of protopathic or indication bias are associated with weaker correlations. This is striking in the first meta-analysis in which sedation and weight gain with antipsychotics are far less correlated than prolactin increase, extrapyramidal syndromes and QTc prolongation. Nevertheless, the discrepancy between intracranial and gastrointestinal bleeding with oral anticoagulants are surprising and these results are limited by the low number of studied correlations.

In the study conducted by Macià-Martinez and colleagues, which investigated the relationship between disproportionality results and relative risks estimated from epidemiological studies or meta-analyses for safety signals discussed at the European level, wide discrepancies were found for asthma/bronchospasm and salmeterol or suicide and antidepressant. [4] These results are in line with our concerns about the difficulty to approximate risk by disproportionality analyses for ADR linked to the underlying pathology.

In this study, despite significant correlation between ROR and OR, agreement was poor and in about half of cases the relative bias was extremely important. This finding is similar to the study conducted by Macià-Martinez and colleagues [4] and should be related to the heterogeneity of the control group or to the preferential reporting of already reported ADRs. Thus, a ROR value cannot be used as a surrogate for an OR. However, surprisingly, the agreement between OR and ROR calculated in restricting the background to a homogeneous therapeutic area was good, the robustness of this results remains to be further validated.

Importantly, this study highlighted the wide variation of disproportionality analyses results according to the methodological choices. Considering the growing use of disproportionality analyses and the lack of standardized methods, this could lead to a major distortion of pharmacovigilance SDR. The pattern of variations in disproportionality analyses

according to ADR characteristics and to disproportionality measures is unknown; the relationship between this variation and the performances of SDR should thus be further explored. Otherwise, while the 5 secondary analyses provided heterogeneous results correlation with ADR risks remained for the 7 ADR correlated in the primary analysis confirming the stability of these associations against the method used. However, none of the methods systematically improved the results.

This study suffers from several limitations. First, only one pharmacovigilance database was studied, we did not tested for other databases, such as national databases which may be more homogenous. On another hand, the WHO pharmacovigilance database has the advantage of being more representative and is larger. Furthermore, it should be interesting to compare these results with some Bayesian estimates of disproportionality such as the Multi-item Gamma Poisson Shrinker or the Bayesian Confidence Propagation Neural network which probably significantly differ from frequentist methods.

The choice of meta-analysis for estimation of relative risk could be criticized. Indeed, the lack of power, the exclusion of patients with multiple comorbidities or concomitant medications, intensive patient monitoring, short-term follow-up or selective reporting of harms in clinical trials could underestimate risks and do not allow accurate identification of rare adverse effects (type B) and/or adverse effects with a long latency (type C) [39–41]. Given that we were mainly interested in this study by comparing risks among a drug class meta-analyses of RCT seemed to us more accurate than pharmaco-epidemiological studies for which estimates may substantially vary between studies and drugs due choice of comparators, time-related bias or selective prescription of new drugs [42,43]. However, the impact of methodological choices for data synthesis, sensitivity analyses (e.g. excluding high risk of bias trials or non-serious ADRs) or adjustment on confounding factors through metaregressions on ADR relative risk estimation in meta-analysis and on the correlation with other source of data need further research.

Pharmacovigilance databases are known to be mainly helpful in detecting type B adverse effects (i.e. effects that are often allergic or idiosyncratic reactions, characteristically occurring in only a minority of patients and usually unrelated to dosage and that are serious, unexpected and unpredictable), as well as unusual type A ADRs [44]. All ADRs in this study were type A (i.e. pharmacologically-expected and dose-related adverse effects), except suicide with antidepressants, thus further research is needed to assess our findings in different types of ADR. Furthermore, drug dosage was not taken into account in ROR calculation.

Lastly, in this study we mixed individual and collection of PTs to reflect the data used in the meta-analyses. The impact of the PT selection at a medical concept level or at individual level on the results variation and on the disproportionality analyses performances remains to be further explored. It would be of interest to conduct this study with large epidemiological studies exploring other types and scarce ADRs which could be better correlated with pharmacovigilance data.

## 5. Conclusion

Despite the large variation in disproportionality analyses results due to design specification, this study provides further evidence that effect sizes obtained from meta-analyses and from disproportionality analyses correlate in most cases. However, agreement between methods was poor and relative bias extremely important. Further work is needed to understand the patterns of disproportionality analyses results variation and the ADR characteristics influencing the correlation with ADR risk.

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## CRedit author statement

**Charles Khouri:** Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing; **Camille Petit:** Investigation, Data Curation, Writing - Original Draft; **Michel Tod, Marion Lepelley, Bruno Revol, Matthieu Roustit, Jean-Luc Cracowski:** Writing - Review & Editing

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## Tables

Table 1. Description of 13 selected adverse drug reactions

| Drug class                     | Adverse drug reaction     | Frequency   | Seriousness | Time to onset | Type | Protopathic bias | Objective vs. subjective ADR |
|--------------------------------|---------------------------|-------------|-------------|---------------|------|------------------|------------------------------|
| Antipsychotics                 | Weight gain               | Very Common | NS          | D             | A    | Yes              | Subjective                   |
|                                | Extrapyramidal syndrome   | Very common | S           | D/I           | A    | No               | Objective                    |
|                                | Prolactin increase        | Common      | NS          | D             | A    | No               | Objective                    |
|                                | QTc prolongation          | Uncommon    | S           | I             | A    | No               | Objective                    |
|                                | Sedation                  | Very common | NS          | I             | A    | Yes              | Subjective                   |
| Blood pressure-lowering agents | Hyperkalemia              | Common      | S           | D/I           | A    | No               | Objective                    |
|                                | Presyncope                | Common      | S           | I             | A    | No               | Subjective                   |
|                                | Cough                     | Common      | NS          | D/I           | A    | No               | Subjective                   |
|                                | Oedema                    | Common      | NS          | I             | A    | Yes              | Objective                    |
| Antidepressant                 | Suicide                   | Uncommon    | S           | D             | B    | Yes              | Objective                    |
| Oral anticoagulants            | Intracranial bleeding     | Uncommon    | S           | I             | A    | No               | Objective                    |
|                                | Gastrointestinal bleeding | Common      | S           | I             | A    | No               | Objective                    |
| Anti-diabetics                 | Hypoglycemia              | Common      | NS          | I             | A    | No               | Objective                    |

D: Delayed; I: Immediate; NS: Non serious - S: Serious. A: type A adverse drug reactions (i.e. pharmacological and dose-related adverse effects); B: type B adverse drug reactions (idiosyncratic, bizarre or novel responses that cannot be predicted from the known pharmacology of a drug)



## Figure Legends

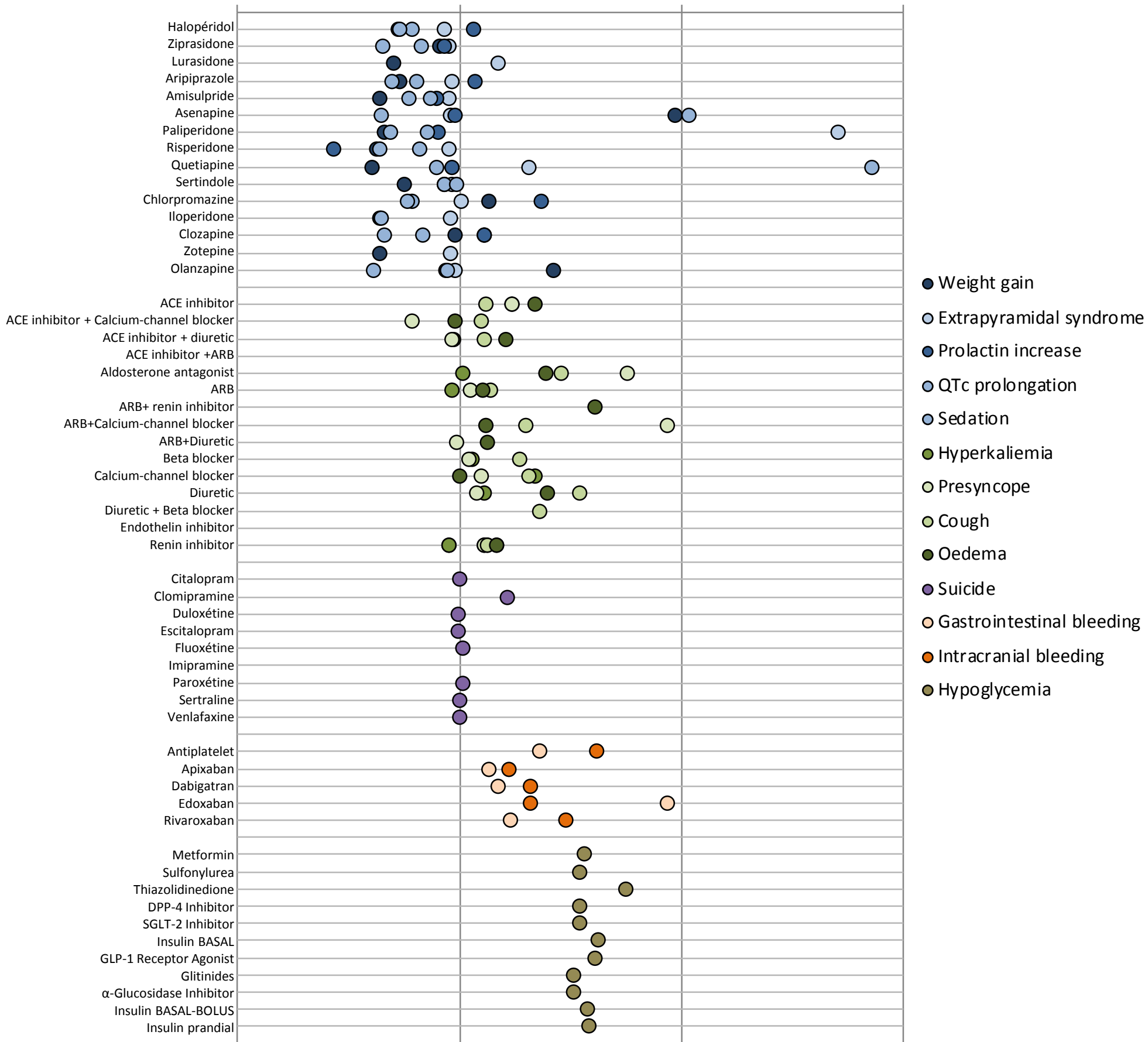
Figure 1. Relative Reporting Odds Ratio (ROR) calculated as a ratio between the higher and the smaller ROR estimated according to the primary and secondary disproportionality methods.

Figure 2. Heat map representing the goodness of the fit (Pearson product moment correlation coefficients) for each adverse drug reaction in primary, secondary and sensitivity analyses.

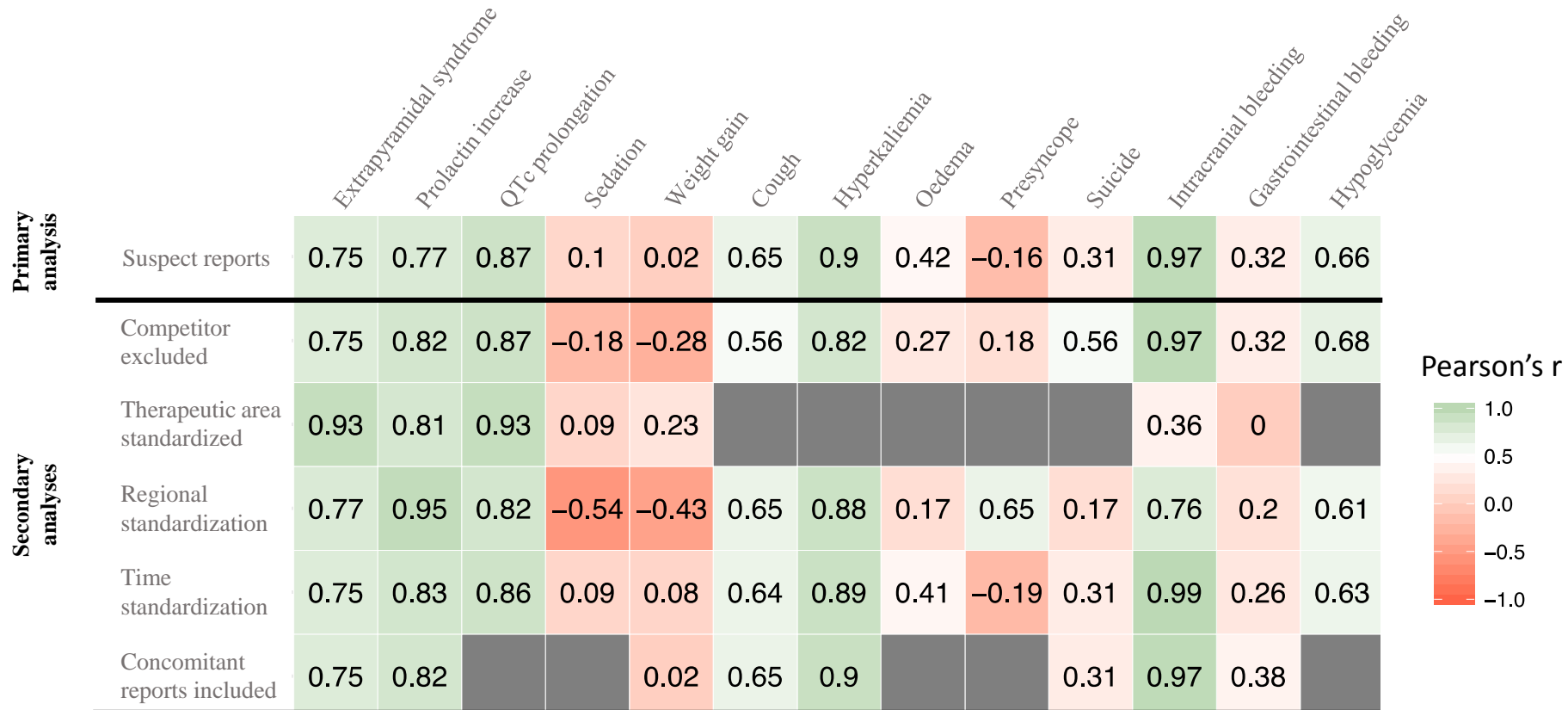
Figure 3. Examples of the best and the worst correlations between measures of association from meta-analyses (expressed as OR) and from Vigibase® (expressed as ROR) in the primary analysis. Each dot represents a drug.

# Relative ROR

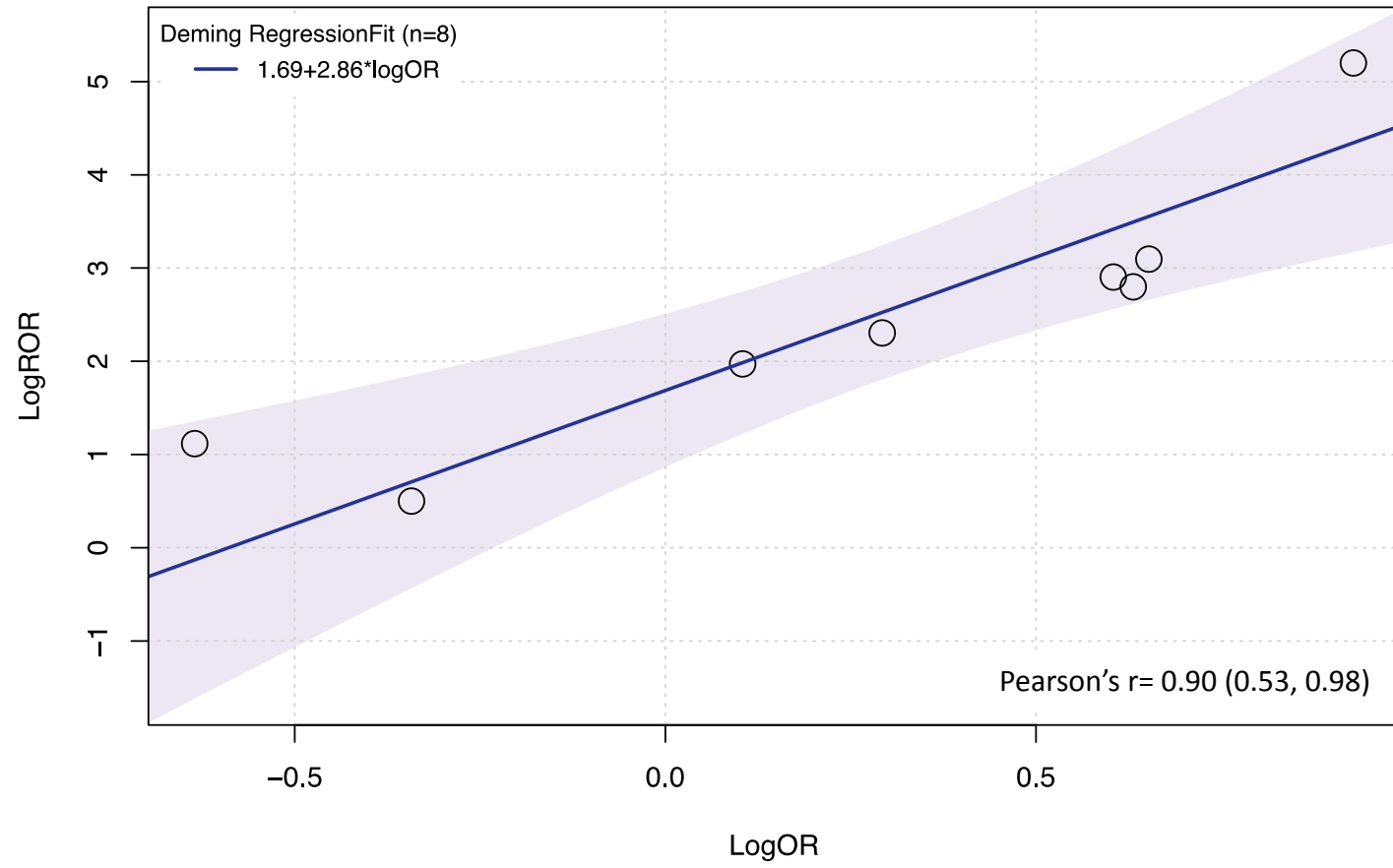
1 10 100 1000



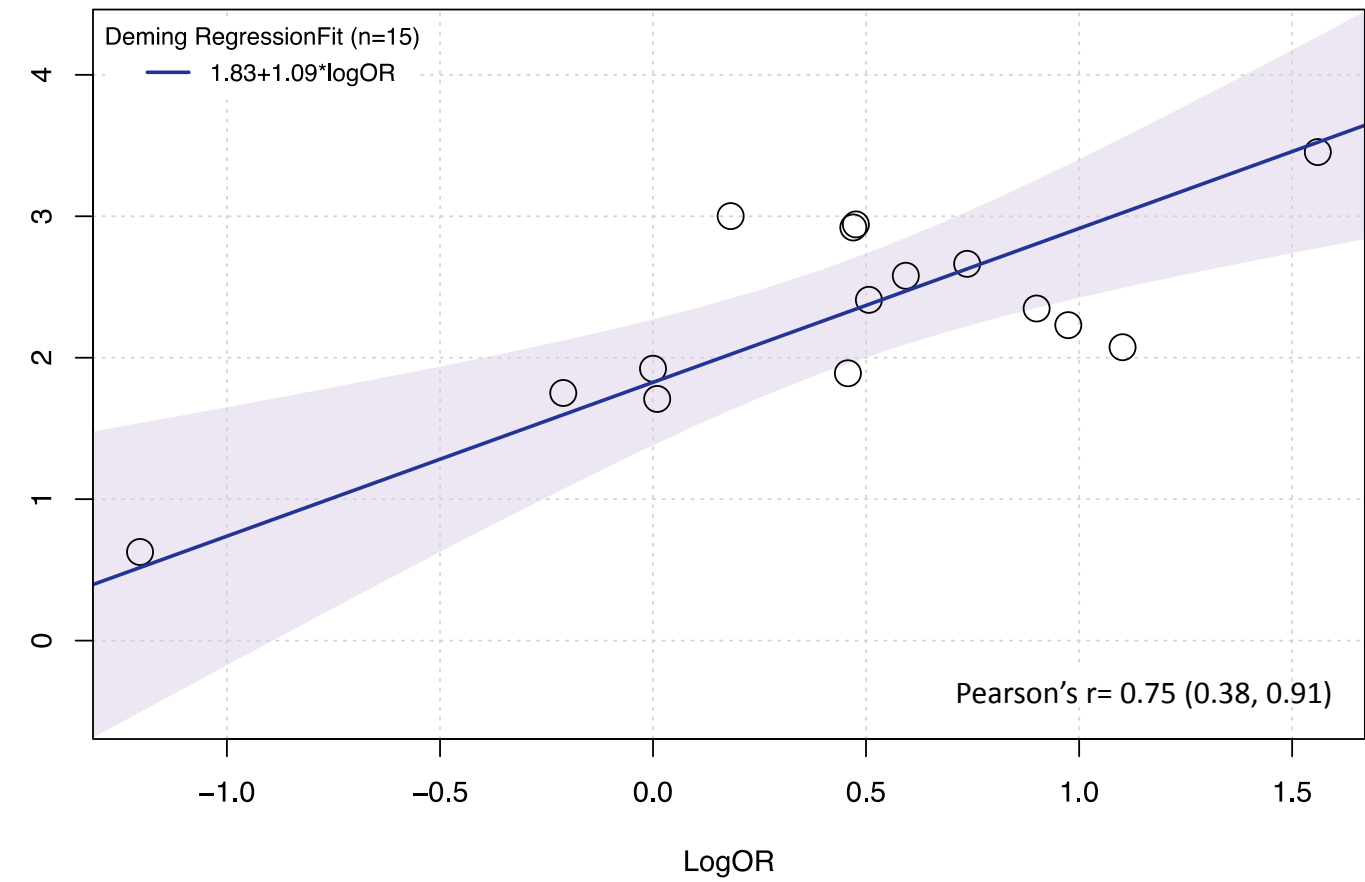
- Weight gain
- Extrapyramidal syndrome
- Prolactin increase
- QTc prolongation
- Sedation
- Hyperkalemia
- Presyncope
- Cough
- Oedema
- Suicide
- Gastrointestinal bleeding
- Intracranial bleeding
- Hypoglycemia



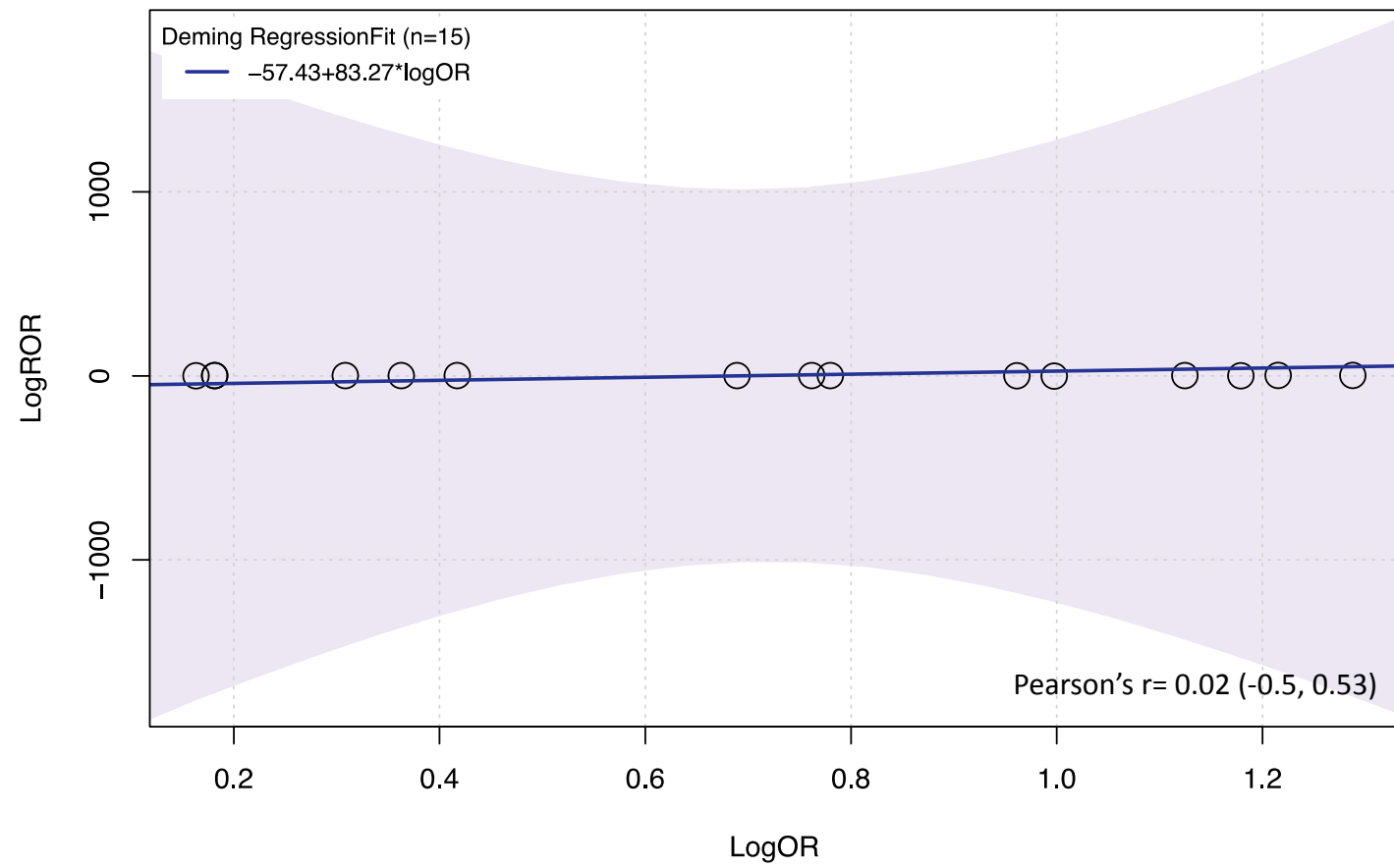
### Blood pressure-lowering agents and hyperkalemia



### Antipsychotics and extrapyramidal syndrome



### Antipsychotics and weight gain



### Blood pressure-lowering agents and presyncope

