Multi population analysis of electronic health records reveal biases in the administration of known drug-drug interactions

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The co-administration of drugs known to interact has a high impact on morbidity, mortality, and health economics, previously highlighted by our own work [1]. We present a large-scale longitudinal study of the drug-drug interaction (DDI) phenomenon, focusing on age and gender biases found in drug dispensation data from three distinct health care systems. We analyze drug dispensations from population-wide electronic health records (EHR) in Blumenau (Brazil; pop. 330K), Catalonia (Spain; pop. 7.5M), and Indianapolis (USA; pop. 864K) with an observation window ranging from 1.5 to 10 years. We compute a stratified risk of DDI for several severity levels per patients' gender and age at time of dispensation. We investigate the role of polypharmacy in the observed DDI rates by building a statistical null model that shuffles drug labels while accounting for cohort specific drug availability. In addition, we build DDI networks to help explore and identify drugs involved in the DDI phenomena as well as interactions with increased gender and age risk[†].

Our results show that in total, 149 shared DDI were found in the three populations. The risk of such DDI as patient age is also characteristically similar in all three populations. We confirm that in general women are at an increased risk of DDI—with the exception of males over 50 years-old in Indianapolis. Importantly, we find that the increased risk of DDI cannot be solely explained by polypharmacy or increased co-administration rates in the elderly. Finally, we show that proton pump inhibitor alternatives to Omeprazole can reduce the number of patients affected by known DDIs by up to 21% in Blumenau and Catalonia, exemplifying how analysis of EHR data can lead to significant reduction of DDI dispensation and its associated human and economic costs.

Our work characterizes the heavy burden of DDI for health systems that are very distinct in geography, population, and policy. Although the risk of DDI increases with age, especially for patients with comorbidities, dispensation patterns point to a complex DDI phenomenon driven by culture and economics, in addition to biological factors. The lack of safer drug alternatives, particularly for chronic conditions, further overbur-

[†]An interactive version of these networks is available at http://disease-perception.bsc.es/ddinteract/

dens health systems with patients taking a multitude of DDIs, highlighting the need for disruptive drug research.

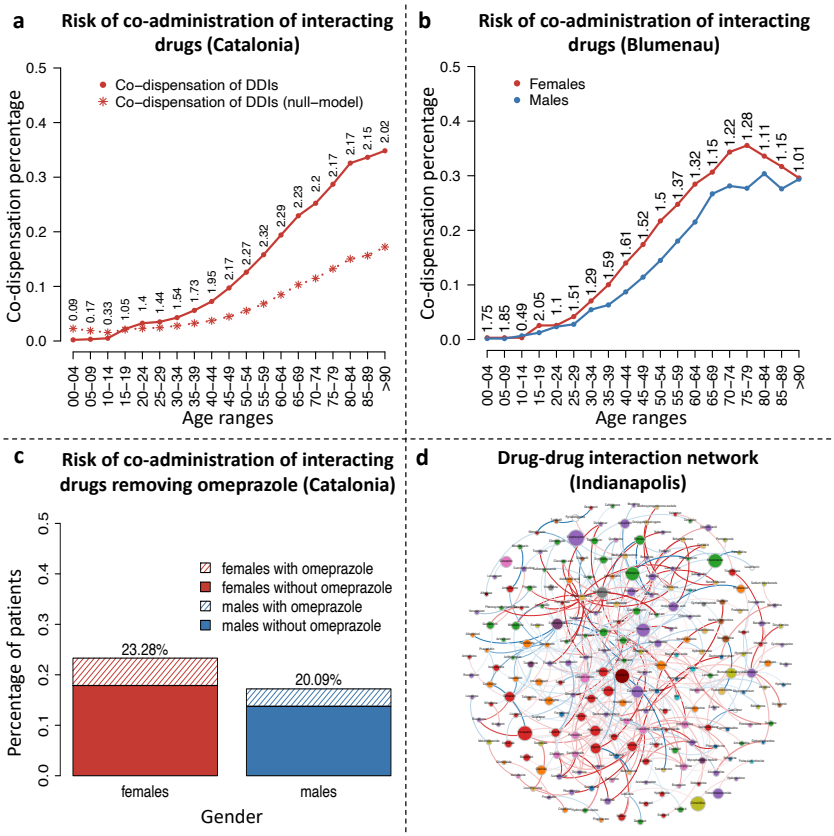

Fig. 1. (A) Risk of DDI dispensation (circles) and the associated null model (stars) stratified by age in Catalonia. (B) Risk of DDI dispensation stratified by age and gender in Blumenau, where women (men) are shown in red (blue). (C) Percentage of Catalonian patients affected by DDI before and after the simulated exchange of Omeprazole for alternative proton pump inbihitors. (D). A network visualization of the DDI found in Indianapolis; nodes are drugs (size denote the probability of interaction; color their class); edges weights represent the DDI association strength; edge color the gender associated risk.

References

1. Brattig Correia, R., de Araújo Kohler, L., Mattos, M.M. et al. City-wide electronic health records reveal gender and age biases in administration of known drug–drug interactions. npj Digit. Med. **2**, 74 (2019). https://doi.org/10.1038/s41746-019-0141-x