Reviewer's report

Title: Drug-related admissions and hospital-acquired adverse drug events in Germany: a longitudinal analysis from 2003 to 2007 of ICD-10-coded routine data

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Reviewer: Zachary Marcum

Reviewer's report:

Overall comment to authors: The proposed manuscript addresses an important topic of drug-related hospitalizations and hospital-acquired adverse drug events (ADEs). The authors propose to use ICD-10-coded routine data to determine the frequency and type of drug-related admissions and hospital acquired-ADEs.

Internal validity:

Major Compulsory Revision:

1) The main concern is potential misclassification of ADEs due to the detection method of only using ICD-10-coded routine data to classify ADE events. Medical record review or ADE evaluation using standardized algorithms were never used. Ideally, such an evaluation should be done and then compared to ICD-10 codes in order to determine a positive predictive value (PPV). Previous research has shown that even for narrow therapeutic index drugs, the PPV is poor using similar methods (Leonard et al, 2008). The authors do state in the manuscript that they “recently proved that routinely collected hospital reimbursement data from 2006 can be used to identify frequency and type of ADE” but it is not clear how this was proven upon reading the referenced paper (Stausberg, 2010).

Minor Essential Revisions:

2) There are no data presented on medications implicated in these events. In their previous publication, the authors were able to report on the most commonly associated drugs with admissions (Stausberg, 2010). However, this issue is not listed as a limitation in the current proposed manuscript. Without this information, the reader is left with several questions regarding how to interpret the findings.

3) The authors state in their previously referenced publication that “The incidence of ADE in hospitals cannot be estimated on the basis of the data used because for secondary diagnoses, no distinction is possible for “present at time of admission” and “acquired during hospital inpatient stay.” However, in the current proposed manuscript the authors state the following rationale in their methods section (hospital-acquired ADE header): “Secondary diagnoses display both comorbidities and complications. A definite distinction between prior to admission and acquired during hospitalization is not possible because a “present on admission” indicator is not available. Nevertheless, the results related to the secondary diagnoses are used as a proxy for hospital-acquired adverse drug
events.” This reviewer agrees with the idea that using the data presented does not allow for a valid method to report on “hospital-acquired ADEs” as the authors had initially stated in their prior publication. Thus, the validity of hospital-acquired ADEs as reported in this manuscript is questionable.

Furthermore, the authors overstate the level of certainty that these secondary diagnoses are in fact hospital-acquired ADEs in the results section (hospital-acquired ADE header, 2nd sentence) when they state: “For these, one can very likely assume a drug-induced disease and an acquisition during hospitalization. The results represent an upper estimate because pre-admission diseases are recorded as well.” This reviewer finds such language to be overstated and in contrast to another of the author’s prior statements in the referenced prior publication in which they state: “If complete and correct coding is assumed, the data about overall frequency thus constitute an overestimate.”

4) Finally, the statistical analysis section has limitations. It is unclear why ¾ of the data were used and what happened to the other ¼ of the target population. Also, the authors state that a linear regression was performed, but there is no mention of controlling for any covariates which may (and likely do) influence the outcome of drug-related admissions and ADEs (e.g., age, co-morbidity). One of the main concerns is that the reader is unable to determine if the increasing trend in hospital-acquired ADEs is simply due to increasing co-morbidity in the target population since secondary diagnoses were used to measure this outcome. In addition, there was no mention of controlling for clustering or site of the hospital where the patient was admitted.

External validity:
Minor Essential Revision:

5) There are no demographic data reported on the population studied, leading to a limitation in the study’s generalizability. The study assessed all “hospital episodes” in Germany from 2003-2007; however, it is not possible from the data presented to determine if these were elective vs. unplanned admissions, pediatric vs. geriatric populations, surgical vs. medical admissions, etc.

References:


Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Needs some language corrections before being published
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.