PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	GLOBAL, REGIONAL, AND NATIONAL TRENDS IN STATIN UTILIZATION IN HIGH INCOME AND LOW- AND MIDDLE-INCOME COUNTRIES, 2015-2020
AUTHORS	Guadamuz, Jenny; Shooshtari, Andrew; Qato, Dima

VERSION 1 – REVIEW

REVIEWER	Zhou, Zhen University of Tasmania Menzies Institute for Medical Research
REVIEW RETURNED	25-Mar-2022

GENERAL COMMENTS	This paper is high-standard addressing an important clinical concern regarding the inequitable global access to statins at the income group, regional, and country levels.I only have few minor comments for the authors. Abstract. Page 3, Line 15- What does “TPD” stand for here? Results Page 7, Line 22, add ‘in 2020’ after ’68.3 DDD/TPD’ Page 7, Line 32. Replace ‘figure 2’ with ‘figure 2.a’ I understand that the figure 2.a presents the change in statin utilization by country from 2015 to 2020. However, it is not clear to me whether the using rates of statins in each country was increasing or decreasing. Is it possible for the authors to improve this figure by showing the both direction and the magnitude of changing rates?

REVIEWER	Amiri, Masoud Social Health Determinants Research Center, epidemiology
REVIEW RETURNED	03-May-2022

GENERAL COMMENTS	I would like to mention the following comments: 1- Abstract: TPD is not defined well. 2- It might be better to use "inequality" as well. 3- IQVIA is not the only pharmaceutical company that produce and distribute statin. 4- The reliability and quality of data in high-income compared to middle and low-income countries? 5- The data for CVD morbidity is missing. 6- The ICD Codes are missing. 7- The data for statin type (atorvastatin, simvastatin, ..) is missing. Good Luck

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Thank you for your thoughtful comments.

1. **This paper is high-standard addressing an important clinical concern regarding the inequitable global access to statins at the income group, regional, and country levels. I only have few minor comments for the authors.**

   Thank you for these encouraging words.

2. **Abstract. Page 3, Line 15- What does "TPD" stand for here?**

   TPD stands for "per 1000 population ≥40 years per day." We have included this definition in the abstract.

3. **Results. Page 7, Line 22, add 'in 2020' after '68.3 DDD/TPD'**

   We have added "in 2020" after 68.3 DDD/TPD'.

4. **Results. Page 7, Line 32. Replace 'figure 2' with 'figure 2.a'**

   We appreciate this comment. However, the findings from reported in this line are visually depicted in both Figure 2a and 2b. Therefore, referencing "Figure 2" is more appropriate.

5. **I understand that the figure 2.a presents the change in statin utilization by country from 2015 to 2020. However, it is not clear to me whether the using rates of statins in each country was increasing or decreasing. Is it possible for the authors to improve this figure by showing the both direction and the magnitude of changing rates?**

   Figure 2a represents the positive or negative changes in statin utilization (see legend "Decline < 0%). For example, Venezuela experience a substantial decline in statin utilization from 2015 to 2020 and it color-coded red.

Reviewer #2:

Thank you for your thoughtful comments.

1. **Abstract: TPD is not defined well.**

Thank you for this comment. DDD/TPD refers to defined daily doses per 1000 population per day (we include this information in the abstract). Considering word count constraints, we cannot further expand this definition; however, this term is commonly used in drug utilization research and further defined in the text.

2. **It might be better to use "inequality" as well.**

We are using the term “disparity” because this is a specific type of health inequality that denotes an unjust difference in health or health care access.[1]

3. **IQVIA is not the only pharmaceutical company that produce and distribute statin.**

IQVIA is a data aggregator. Specifically, IQVIA samples pharmaceutical sales from multiple distribution channels (*e.g.,* manufacturers, wholesalers, and medical facilities) to develop nationally representative estimates of retail and non-retail pharmaceutical sales in each country. If necessary, IQVIA projects its samples to represent 100% of the retail and non-retail sales in each country and reports >90% global precision in recent years. [2] However, IQVIA does not publicly disclose detailed information on data collection, projection, and validation. (See lines 140-143).

4. **The reliability and quality of data in high-income compared to middle and low-income countries?**

We appreciate this comment. While IQVIA reports a >90% global precision in recent years, it does not publicly disclose detailed information on data collection, projection, and validation.[2] (See lines 140-143). We are therefore unable to further comment on the quality of high-income versus low- and middle-income countries. We discuss these considerations in our limitations section. (See lines 324-332).

5. **The data for CVD morbidity is missing.**

We do not examine CVD morbidity. Instead, we report age-standardized IHD mortality rates which were obtained from the Global Burden of Disease (GBD) (2015-2019).[3] (See lines 146-149).

6. **The ICD Codes are missing.**

The GBD 2019 causes of death were mapped to International Classification of Diseases codes.[4] We have added an appropriate citation. (See lines 146-149).

7. The data for statin type (atorvastatin, simvastatin...) is missing.

We extracted country-level dispensing for WHO Anatomic Therapeutic Chemical codes relating to statins (C10AA).[5] We have added an appropriate citation. (See lines 156-157).

We do not report specific types of statins utilized, instead we report statins in aggregate. Of note, WHO ATC codes C10AA lists the following drugs: simvastatin, lovastatin, pravastatin, Fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin.

REFERENCES

1. Arcaya MC, Arcaya AL, Subramanian S V. Inequalities in health: definitions, concepts, and theories. *Glob Health Action*. 2015;8(1). doi:10.3402/GHA.V8.27106
2. IQVIA. Accuracy and Timeliness Statistics Annual Report, 2020. https://www.iqvia.com/library/publications/acts-2020. Published 2021. Accessed July 25, 2021.
3. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2019. http://www.healthdata.org/gbd. Published 2021. Accessed December 12, 2021.
4. Institute for Health Metrics and Evaluation. Global Burden of Disease Study 2019 (GBD 2019) Cause List Mapped to ICD Codes. https://ghdx.healthdata.org/record/ihme-data/gbd-2019-cause-icd-code-mappings. Published 2021. Accessed May 27, 2022.
5. WHO Collaborating Centre for Drug Statistics Methodology. Purpose of the ATC/DDD system. https://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/. Accessed April 6, 2020.