

# BMJ Open Inappropriate prescribing among older persons in primary care: protocol for systematic review and meta-analysis of observational studies

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## ABSTRACT

**Introduction:** Inappropriate prescribing has a significant impact on older persons in primary care. Previous reviews on inappropriate prescribing included a heterogeneous range of populations and may not be generalisable to primary care. In this study we aim to conduct a comprehensive systematic review and meta-analysis of the prevalence, risk factors and adverse outcome associated with inappropriate prescribing, specifically among older persons in primary care.

**Methods and analysis:** We will search PubMed, Embase, CINAHL, Web of Science, Scopus, PsycINFO and references of other review articles for observational studies related to the keywords ‘older persons’, ‘primary care’ and ‘inappropriate prescribing’. Two reviewers will independently select the eligible articles. For each included article, the two reviewers will independently extract the data and assess the risk of bias using the Newcastle–Ottawa Scale. If appropriate, meta-analyses will be performed to pool the data across all the studies. In the presence of heterogeneity, meta-regression and subgroup analyses will also be performed. The quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Ethics and dissemination:** The results will be disseminated through conference presentations and peer-reviewed publications. They will provide consolidated evidence to support informed actions by policymakers to address inappropriate prescribing in primary care, thus reducing preventable and iatrogenic risk to older persons in primary care.

**Trial registration number:** CRD42016048874.

## INTRODUCTION

### Rationale

Inappropriate prescribing refers to the practice of prescribing medications with potentially greater risk than benefit.<sup>1</sup> Holistic definitions of inappropriate prescribing have been suggested to encompass the assessment of prescriptions to older persons in the context of their multiple comorbidities,

## Strengths and limitations of this study

- This systematic review and meta-analysis will provide a comprehensive summary of the various aspects of inappropriate prescribing among older persons in primary care.
- The results will provide the highest level of evidence that can be generalised to primary care and will facilitate informed actions by policymakers.
- This protocol has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement and has been registered with the Prospective Register of Systematic Reviews (PROSPERO).
- The overall quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
- This systematic review will be limited to studies in English language.

complex medication regimes, functional and cognitive status, treatment goals and life expectancy.<sup>2</sup> However, such holistic definitions are generally more challenging to operationalise in routine practice. Simpler definitions of inappropriate prescribing have been used by studies in the literature, including explicit (criterion-based) tools such as the Beers and Screening Tool of Older Persons’ potentially inappropriate Prescriptions (STOPP) criteria and implicit (judgement-based) tools such as the Medication Appropriateness Index.<sup>3 4</sup>

Inappropriate prescribing is a form of medical error<sup>5</sup> which is common and preventable in primary care. Its prevalence among older persons in primary care ranges from 16% to 60%.<sup>6–13</sup> Due to the changing pharmacokinetics and pharmacodynamics in older persons, inappropriate prescribing increases the risk of adverse effects in this population and leads to adverse drug reactions, morbidity and mortality.<sup>14 15</sup> From the societal perspective, inappropriate prescribing

results in higher healthcare cost due to increased hospitalisations, outpatient visits, emergency department visits and nursing home placements.<sup>1</sup> With recent evidence in the *British Medical Journal* highlighting medical error as the third leading cause of death,<sup>16</sup> there is an urgent need for action to address common and preventable areas of medical error in primary care such as inappropriate prescribing.

To facilitate informed actions by policymakers, the extant literature on inappropriate prescribing in primary care needs to be consolidated to provide a clearer understanding of the problem. However, to date, no systematic review or meta-analysis has comprehensively studied the prevalence, risk factors and adverse outcomes of inappropriate prescribing specific to the primary care setting. Although some of the previous reviews have included primary care populations, their results may not be generalisable to primary care settings due to the heterogeneous range of included populations, such as those from tertiary healthcare settings or nursing homes.<sup>1 4 17 18</sup>

## Objectives

In this study we intend to focus exclusively on the population of older persons in primary care. We seek to conduct a comprehensive systematic review and meta-analysis to evaluate the prevalence, risk factors and adverse outcomes associated with inappropriate prescribing among older persons in primary care. Specifically, we aim to address the following research questions:

1. What is the pooled prevalence of inappropriate prescribing among older persons in primary care?
2. What is commonly used as the working definition of inappropriate prescribing among older persons in primary care, and how do the various working definitions affect the prevalence?
3. What is the pooled effect size of each risk factor associated with inappropriate prescribing among older persons in primary care?
4. What is the pooled effect size of each adverse outcome associated with inappropriate prescribing among older persons in primary care?

## METHODS AND ANALYSIS

This protocol is developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.<sup>19 20</sup> It has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42016048874).

## Eligibility criteria

### Participants and settings

We will include studies:

- ▶ which recruited participants from primary care settings;
- ▶ with  $\geq 90\%$  of the participants who are  $\geq 60$  years old;

- ▶ with  $< 90\%$  of the participants who are  $\geq 60$  years old, but reported subgroup analyses on participants who are  $\geq 60$  years old.

Studies will be excluded if the recruitment was not from primary care settings, such as those from tertiary hospitals or nursing homes.

## Exposure and outcome measures

We will include studies which report on the prevalence, risk factors or adverse outcomes related to inappropriate prescribing. We will include all types of adverse outcomes that have been reported in the literature, including but not limited to those related to adverse drug reactions, emergency department visits, hospitalisation and mortality. We will exclude studies that:

- ▶ are not related to inappropriate prescribing;
- ▶ do not have a working definition of inappropriate prescribing;
- ▶ only focus on inappropriate prescribing related to specific groups of medications.

## Study designs

We will only include observational studies such as cross-sectional, case-control and cohort studies. We will exclude the following study designs: qualitative studies, intervention studies, reviews, meta-analyses, case reports, case series, ecological studies, conference proceedings, letters, comments and policy papers.

## Language and time frame

We will only include studies which are reported in the English language. We do not impose any time restriction to the publication year of the studies.

## Information sources and search strategy

We will search PubMed, Embase, CINAHL, Web of Science, Scopus and PsycINFO for original articles related to the keywords of 'older persons', 'primary care' and 'inappropriate prescribing'. Our search strategy for PubMed is shown in [box 1](#). Similar search strategies will be used for the other databases. Additionally, we will also hand search the references of review articles related to the topic to retrieve relevant articles which are not captured through our search of the electronic databases.

## Study selection

All potential articles will be retrieved and organised in a data management software (Endnote software, Thomson Reuters). After removing duplicate records, two reviewers will independently screen through the titles and abstracts to retain eligible articles. The first 100 titles and abstracts will be subjected to a calibration exercise between the two reviewers to ensure mutual agreement.

After completing the screening phase, articles that are deemed as relevant by at least one of the reviewers will be subjected to full text review. The two reviewers will

**Box 1** Search strategy for PubMed (MeSH, Medical Subject Headings)

1. "Primary Health Care"[MeSH]
2. "general practice"[MeSH]
3. "general practitioners"[MeSH]
4. "Family Practice"[MeSH]
5. "Physicians, Family"[MeSH]
6. primary[title/abstract] AND care[title/abstract]
7. general[title/abstract] AND practice\*[title/abstract]
8. general[title/abstract] AND practitioner\*[title/abstract]
9. family[title/abstract] AND practice\*[title/abstract]
10. family[title/abstract] AND physician\*[title/abstract]
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. "Aged"[MeSH]
13. elder\*[title/abstract]
14. older[title/abstract]
15. 12 or 13 or 14
16. inappropriate\*[title]
17. prescri\*[title/abstract] OR medication\*[title/abstract] OR drug\*[title/abstract] OR medicine\*[title/abstract]
18. 16 and 17
19. "Inappropriate Prescribing"[MeSH]
20. 18 or 19
21. 11 and 15 and 20

independently confirm the eligibility of these articles based on the full texts. The first 10% of these full texts will again undergo a calibration exercise by the two reviewers. After the full text review, the included articles will be used for qualitative synthesis. The chance-corrected agreement between the two reviewers will be assessed using Cohen's  $\kappa$ .

At any point during study selection the reasons for excluding specific articles will be recorded. Moreover, any disagreements between the two reviewers will be resolved by discussion with a third reviewer. If more than one article reported results from the same study, then only the most recent and complete article will be included in the systematic review.

**Data extraction**

Data from the selected studies will be extracted by two reviewers independently, and disagreements between the reviewers will be resolved by discussion with a third reviewer. The extracted data will include the following information:

1. Study identification (first author, year of publication, geographical location).
2. Study characteristics (study setting, study design, inclusion criteria, sampling method, sample size, data source of medication prescriptions, study duration, non-response or drop-out rate).
3. Participant characteristics (age, gender, ethnicity, number of comorbidities, number of prescribed medications).
4. Characteristics of inappropriate prescribing (prevalence, working definition, risk factors and adverse outcomes).

**Assessment of risk of bias**

The risk of bias for each study will be assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS).<sup>21</sup> For case–control and cohort studies, the original 8-item NOS will be used to assess the three key areas of potential bias—selection of participants, comparability of groups and measurement of information. The exact items in the NOS are shown in online supplementary appendices 1 and 2. For cross-sectional studies, only the relevant items in the NOS will be used (see online supplementary appendices 3 and 4). Any disagreements between the two reviewers will be resolved by discussion with a third reviewer.

**Statistical analysis**

When two or more studies are included, we will conduct meta-analyses to quantitatively synthesise the results. If there are at least five included studies, we will use the random effects model (DerSimonian and Laird method)<sup>22</sup> to pool the results because this model does not assume homogeneity among the pooled studies. If there are fewer than five included studies, the random effects model is imprecise in its estimations<sup>23 24</sup> and we will choose the fixed effect model (Mantel–Haenszel method)<sup>25</sup> instead. When studies report more than one model of statistical adjustment, we will only include the result with the largest number of confounders adjusted for in the statistical model. For each risk factor or adverse outcome of inappropriate prescribing, we will pool the effect size in the form of OR.

We will use the  $I^2$  statistic and the  $Q$  test to assess heterogeneity in the pooled studies. In the presence of substantial heterogeneity ( $I^2 > 50\%$ ),<sup>26</sup> we will further evaluate the source of heterogeneity using meta-regression analysis and subgroup analyses provided there are at least 10 included studies. The meta-regression and subgroup analyses will be based on the following covariates: year of publication, geographical location, study setting, study design, inclusion criteria, sampling method, sample size, data source of medication prescriptions, study duration, non-response or drop-out rate, age, gender, ethnicity, number of comorbidities, number of prescribed medications, working definition of inappropriate prescribing and study quality.

Separately, we will also evaluate for possible publication bias using funnel plots and Harbord's test<sup>27 28</sup> if there are at least 10 included studies. In the presence of possible publication bias, we will conduct a sensitivity analysis using the trim and fill method.

All analyses will be done in STATA statistical software package V.13 (Statacorp, 2013) using the commands *metaprop* (to pool results related to prevalence), *metan* (to pool results related to risk factors or adverse outcomes), *metareg* (to conduct meta-regression), *metafunnel* (to produce funnel plot), *metabias* (for Harbord's test) and *metatrim* (for the trim and fill method).

**Assessment of quality of evidence**

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to

report the quality of evidence on the risk factors and adverse outcomes of inappropriate prescribing. Based on five key domains (methodology quality, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias), we will classify the quality of evidence into one of four levels—high, moderate, low and very low.<sup>29</sup>

## ETHICS AND DISSEMINATION

This systematic review will provide the consolidated evidence to support policymakers to redesign the processes in primary care and enhance medication safety for older persons, thus reducing the preventable and iatrogenic risk to older persons in primary care.

The review will be reported in accordance with the recommendations of the PRISMA statement.<sup>19 20</sup> The results will be disseminated through conference presentations and publications in peer-reviewed journals.

**Contributors** TML and CSL conceived the idea for this systematic review. TML developed the methodology and search strategy. TML and CSL wrote the manuscript and approved the final version of the manuscript.

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