Potentially Inappropriate Prescribing Among Older Persons: A Meta-Analysis of Observational Studies

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ABSTRACT

PURPOSE Potentially inappropriate prescribing (PIP) is a common yet preventable medical error among older persons in primary care. It is uncertain whether PIP produces adverse outcomes in this population, however. We conducted a systematic review with meta-analysis to pool the adverse outcomes of PIP specific to primary care.

METHOD We searched PubMed, Embase, CINAHL, Web of Science, Scopus, PsycINFO, and previous review articles for studies related to "older persons," "primary care," and "inappropriate prescribing." Two reviewers selected eligible articles, extracted data, and evaluated the risk of bias. Meta-analysis was conducted to pool studies with similar PIP criteria and outcome measures.

RESULTS Of the 2,804 articles identified, we included 8 articles with a total of 77,624 participants. All included studies had cohort design and low risk of bias. Although PIP did not affect mortality (risk ratio [RR] 0.98; 95% CI, 0.93-1.05), it was significantly associated with the other available outcomes, including emergency room visits (RR 1.63; 95% CI, 1.32-2.00), adverse drug events (RR 1.34; 95% CI, 1.09-1.66), functional decline (RR 1.53; 95% CI, 1.08-2.18), health-related quality of life (standardized mean difference −0.26; 95% CI, −0.36 to −0.16), and hospitalizations (RR 1.25; 95% CI, 1.09-1.44). A majority of the pooled estimates had negligible heterogeneity.

CONCLUSIONS This meta-analysis provides consolidated evidence on the wide-ranging impact of PIP among older persons in primary care. It highlights the need to identify PIP in primary care, calls for further research on PIP interventions in primary care, and points to the need to consider potential implications when deciding on the operational criteria of PIP.

Potentially inappropriate prescribing in older persons

- Potentially inappropriate prescribing (PIP) is defined as the prescribing, or underprescribing, of medications for older persons that may cause significant harm

- PIP can be screened with
  - Implicit tool (judgement based)
    - Medication Appropriateness Index (MAI)

  - Explicit tool (criterion based):
    - Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (Beers Criteria)
    - Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP)
    - Screening Tool to Alert Doctors to Right Treatment (START)

Known in the literature

- Pooled prevalence of PIP ranges from <u>22.6%</u> for community-dwelling older persons to <u>43.2%</u> for nursing home residents

- PIP associated with adverse drug events (ADEs), lower quality of life, hospitalizations, and higher health care costs, and mortality

Research Question

- Previous reviews evaluated PIP and its association to various outcomes included participants from heterogenous settings (such as tertiary healthcare settings, nursing homes and community dwelling).

- May not be applicable to primary care setting.

- We sought to conduct a <u>systematic review</u> with meta-analysis to pool the <u>adverse outcomes of PIP</u> reported in the literature, specifically focusing on older persons in <u>primary care</u>.

Search strategy

- We systematically searched PubMed, Embase, CINAHL, Web of Science, Scopus, and PsycINFO from inception to January 7, 2017, using keywords and controlled vocabulary related to "older persons," "primary care," and "inappropriate prescribing."

- Hand searched the references of review articles related to PIP

Selection criteria

- **Inclusion criteria:**
  - Studies recruited participants from **primary care settings**
  - ≥90% of the participants who were aged ≥65 years or reported subgroup analyses based on participants who were aged ≥65 years were
  - **Observational study designs**, such as cross-sectional, case-control, or cohort studies
  - reported the **adverse outcomes** related to PIP, such as accident and emergency department (A&E) visits, ADEs, functional decline, health-related quality of life (HRQoL), hospitalizations, and mortality

- **Exclusion criteria:**
  - Participants recruited from non–primary care settings, such as tertiary hospitals or nursing homes
  - Did not assess PIP based on published criteria
  - Focused only on PIP related to a single class of drug, such as analgesics or antibiotics.

Data extraction

- 2 **reviewers independently** selected eligible articles, extracted the relevant data, and assessed the risk of bias. Discordance resolved by discussion with a 3rd independent reviewer

- Extracted data included information on **participants, study characteristics, criteria of PIP, measurement of adverse outcomes, effect estimates, and their 95% CI**

- Risk of bias assessed with original **8-item Newcastle-Ottawa scale (NOS)** which focuses on 3 key areas of potential bias: selection of participants, comparability of groups, and measurement of outcome

Data analysis (Meta-analysis)

- Fixed-effect model (Mantel-Haenszel method)

- Continuous outcomes: Cohen's standardized mean difference (SMD)

- Binary outcomes: log-transformed the effect estimates

- Heterogeneity: Q test and the I^2 statistic

- Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to classify the overall certainty of evidence

Result

Figure 1. Flowchart of the study selection.
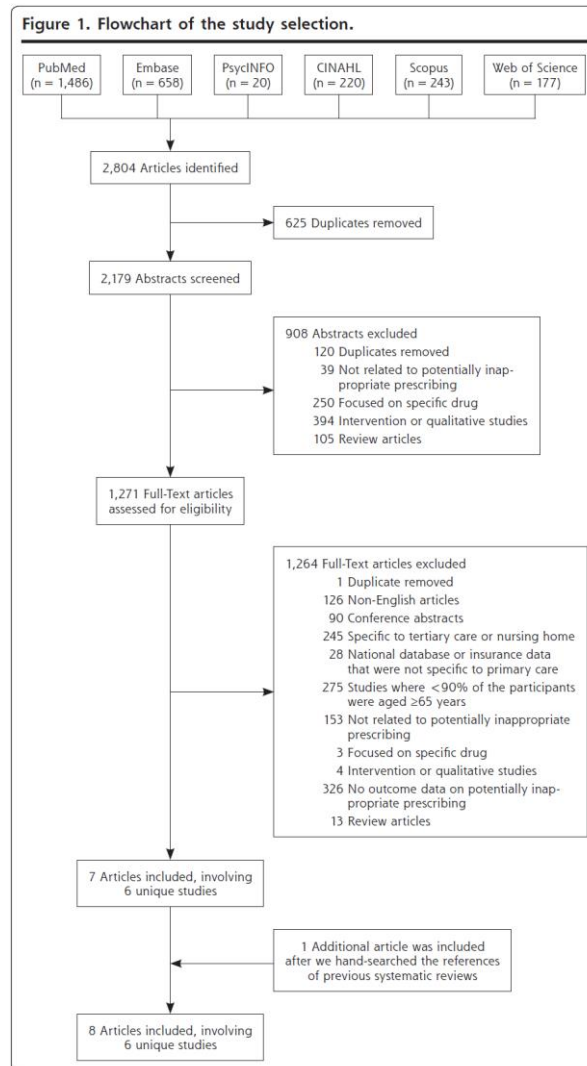
- 8 Articles included, involving 6 unique studies (all were cohort studies)

- Total of 77,624 participants

- Mean follow-up duration of 2.0 years

- All the included studies had low risk of bias and achieved max or near-max scores on the NOS

Result (Key characteristic of included studies)

Table 1. Key Characteristics of the Studies Included in the Systematic Review

Author (Year)	Sampling Method	Sample Size	Age, Years	% Female	Follow-Up Duration in Years	Data Source of PIP	Criteria of PIP	Data Source of Outcomes
Barnett et al,[27] 2011	Whole population registry	70,299	Mean 75.2 SD 6.8	57.0	2.0	Dispensed prescribing database	Beers Criteria 2003	Mortality: Death certification database
Cahir et al,[23] 2014 Cahir et al,[24] 2014	Stratified random sampling	931	Mean 78.0 SD 5.4	54.0	0.5	Pharmacy claim database	Beers Criteria 2012 STOPP	ADEs, hospitalizations, and A&E visits: Structured interview and medical records
								Functional decline: VES scale
								HRQoL: EQ-5D scale
Hanlon et al,[25] 2002 Fillenbaum et al,[26] 2004	Stratified probability sampling	3,234	65-74 years: 49.1% 75-84 years: 41.1% ≥85 years: 9.8%	64.8	3.0	Structured interview	Beers Criteria 1997 DUR	Mortality: National Death Index
								Functional decline: Combination of Katz ADL, OARS Instrumental ADLs, and abbreviated Rosow-Breslau scale
								Hospitalizations: Medicare and Medicaid database
								Outpatient visits and nursing home entry: self- or proxy report
Moriarty et al,[28] 2016	Stratified random sampling	1,753	Mean 76.5 SD 6.0	54.4	1.0	Pharmacy claim database	STOPP START	A&E visits, GP visits: Structured interview
								Functional decline: Difficulty in doing 6 named ADLs
								HRQoL: CASP-R12 scale
Wallace et al,[29] 2017	Stratified random sampling	904	Median 77 IQR 74-81	54.0	2.0	Pharmacy claim databases	Beers Criteria 2012 STOPP	ADEs: Patient interview and medical records
								A&E visits and hospitalizations: Medical records
								HRQoL: EQ-5D scale
Wauters et al,[30] 2016	Whole GP registry and consecutive sampling	503	Mean 84.4	61.2	1.5	Secured record	STOPP START	Mortality: Secured record
								Hospitalizations: Secured record

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Result (Meta-analysis: Beers Criteria)

Figure 2. Forest plots for the adverse outcomes of potentially inappropriate prescribing based on the Beers Criteria.
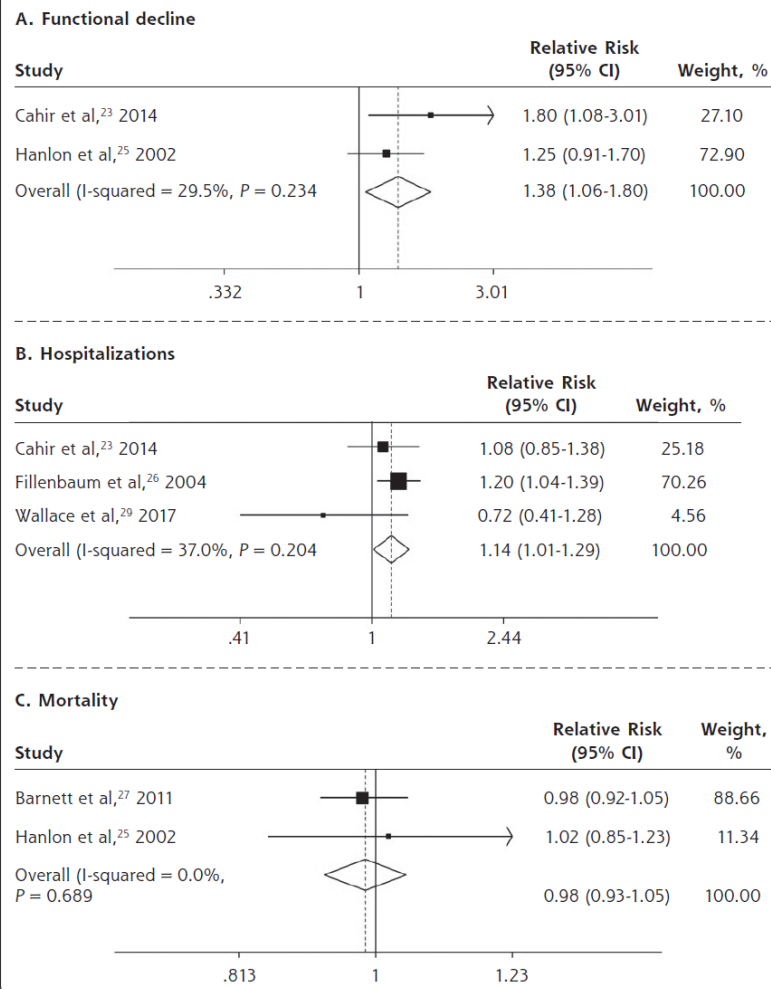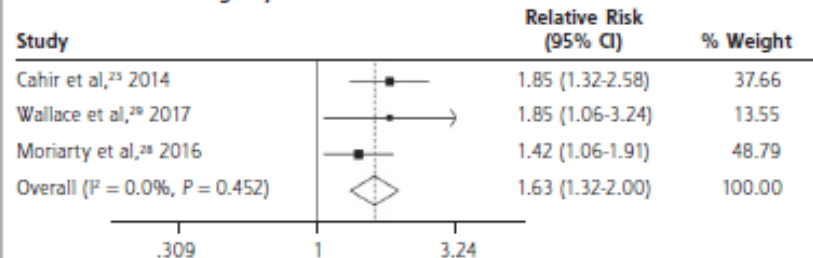
- Figure 2 shows the forest plots for the adverse outcomes of PIP based on the Beers Criteria

- PIP significantly associated with:
  - Functional decline (pooled RR 1.38; 95% CI, 1.06-1.80) and
  - Hospitalizations (pooled RR 1.14; 95% CI, 1.01-1.29)
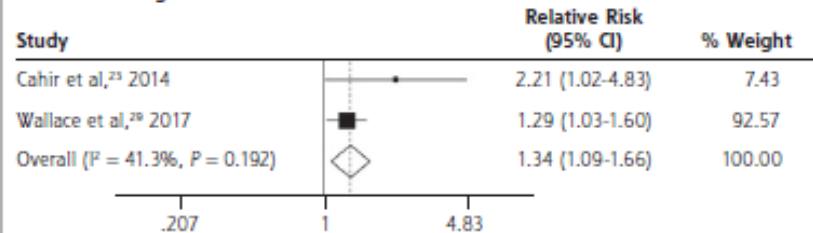 - Not with Mortality (pooled RR 0.98; 95% CI, 0.93-1.05).

Result (Meta-analysis: STOPP criteria)

Figure 3. Forest plots for the adverse outcomes of potentially inappropriate prescribing based on the STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) criteria.
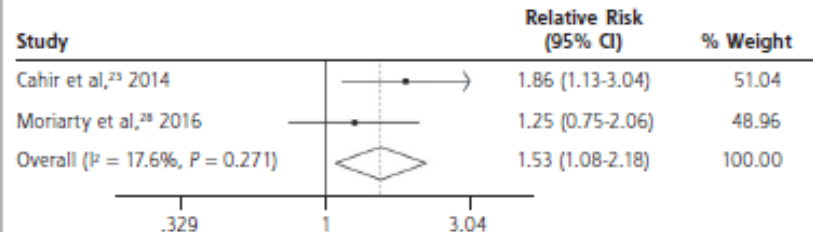
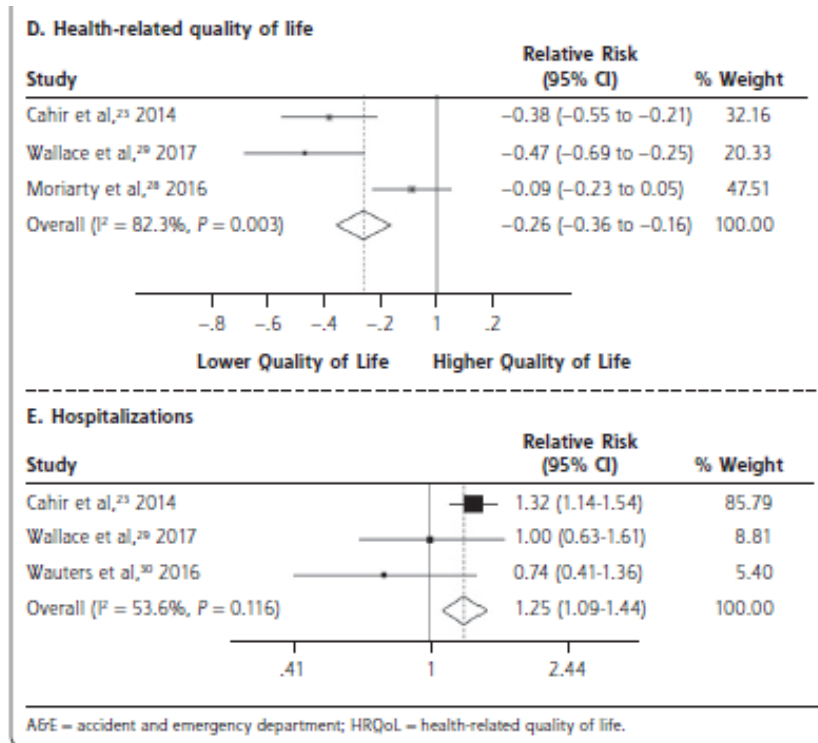- Figure 3 shows the forest plots for the adverse outcomes of PIP based on the STOPP criteria

- PIP significantly associated with:
  - ➤ A&E visits (pooled RR 1.63; 95% CI, 1.32-2.00)
  - ➤ ADEs (pooled RR 1.34; 95% CI, 1.09-1.66)
  - ➤ functional decline (pooled RR 1.53; 95% CI, 1.08-2.18)

Result (Meta-analysis: STOPP criteria)

Figure 3 (Cont.)

D. Health-related quality of life

Study	Relative Risk (95% CI)	% Weight
Cahir et al,[23] 2014	−0.38 (−0.55 to −0.21)	32.16
Wallace et al,[29] 2017	−0.47 (−0.69 to −0.25)	20.33
Moriarty et al,[28] 2016	−0.09 (−0.23 to 0.05)	47.51
Overall (I^2 = 82.3%, P = 0.003)	−0.26 (−0.36 to −0.16)	100.00

Lower Quality of Life   Higher Quality of Life

E. Hospitalizations

Study	Relative Risk (95% CI)	% Weight
Cahir et al,[23] 2014	1.32 (1.14-1.54)	85.79
Wallace et al,[29] 2017	1.00 (0.63-1.61)	8.81
Wauters et al,[30] 2016	0.74 (0.41-1.36)	5.40
Overall (I^2 = 53.6%, P = 0.116)	1.25 (1.09-1.44)	100.00

A&E = accident and emergency department; HRQoL = health-related quality of life.

- PIP significantly associated with:
  - HRQoL (pooled SMD –0.26; 95% CI, –0.36 to –0.16)
  - hospitalizations (pooled RR 1.25; 95% CI, 1.09-1.44).

Result (GRADE assessment)

Table 3. Summary of Key Findings and GRADE Assessment

Outcomes	Number of Participants	Pooled Effect Size (95% CI)	Certainty of Evidence (GRADE)	Risk of Bias[a]	Inconsistency[b]	Imprecision[c]/Publication Bias[d]/Indirectness[e]	Large Effect[f]/Dose Response
PIP based on the Beers Criteria							
Functional decline	4,165	RR 1.38 (1.06-1.80)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 29.5%, P = .234)	No downgrade	No upgrade
Hospitalizations	5,069	RR 1.14 (1.01-1.29)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 37.0%, P = .204)	No downgrade	No upgrade
Mortality	73,533	RR 0.98 (0.93-1.05)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 0.0%, P = .689)	No downgrade	No upgrade
PIP based on the STOPP criteria							
A&E visits	3,588	RR 1.63 (1.32-2.00)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 0.0%, P = .452)	No downgrade	No upgrade
ADEs	1,835	RR 1.34 (1.09-1.66)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 41.3%, P = .192)	No downgrade	No upgrade
Functional decline	2,684	RR 1.53 (1.08-2.18)	●●○○○ Low	No downgrade (NOS = 9)	No downgrade (I^2 = 17.6%, P = .271)	No downgrade	No upgrade
HRQoL	3,588	SMD −0.26 (−0.36 to −0.16)	●○○○○ Very low	No downgrade (NOS = 9)	Downgrade (I^2 = 82.3%, P = .003)	No downgrade	No upgrade
Hospitalizations	2,338	RR 1.25 (1.09-1.44)	●●○○○ Low	No downgrade (NOS = 8)	No downgrade (I^2 = 53.6%, P = .116)	No downgrade	No upgrade

- Apart from HRQoL, the rest of the outcomes maintained "low" certainty of evidence consistent with meta-analytic results based on observational studies, with no further downgrades or upgrades in the GRADE assessment.

- HRQoL was downgraded to "very low" certainty of evidence because of the high heterogeneity.

Clinical Implication

- This study demonstrated the associations between PIP and a wide range of **adverse outcomes** and highlighted the **relevance** of PIP among older persons in primary care.

- The findings showed that the construct of PIP is more than just a consensus of good clinical practice, and they underscored the need to **focus on PIP in primary care to improve patient outcomes**
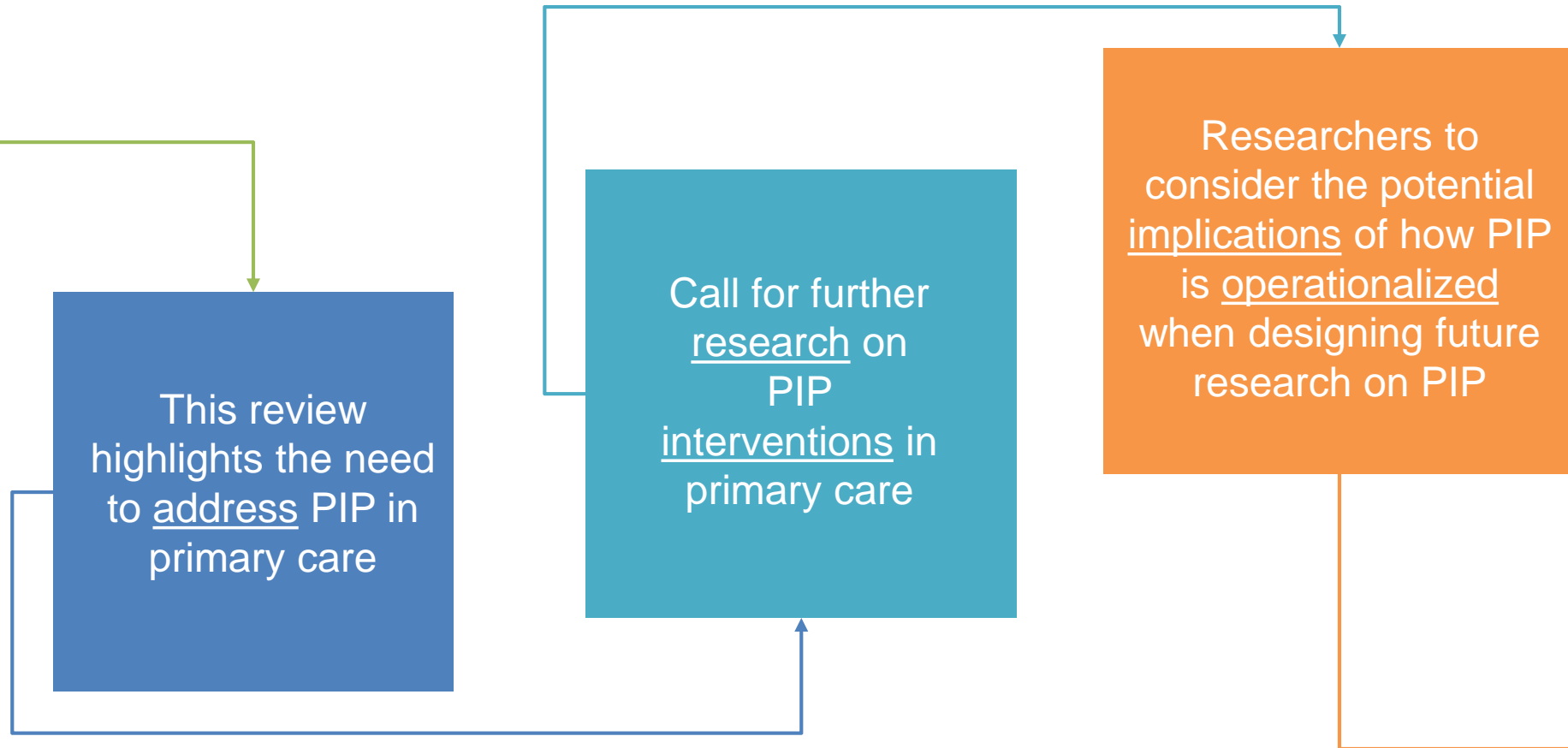
Clinical Implication

- A variety of **interventions** (RCTs) have been evaluated to address PIP among community dwelling older persons

Intervention	Description	Example
Organizational	Focus on changing the delivery of health care services	Medication reviews by pharmacists
Professional	Aim to improve the practice of health care professionals	Education, computerized clinical decision support systems (CCDSSs)
Multifaceted	Combinations of organizational or professional interventions	Combination of multiple interventions

Implication for future research

- Prior RCTs have infrequently reported on the clinical outcomes of interventions, with mostly reported only reduction of PIP

- Need further research to confirm that the **reduction of PIP** can have a direct effect in **improving outcomes** and that PIP has a **direct causal relationship** with the adverse outcomes

- Future RCTs should be adequately powered and have a sufficiently long follow-up period so that any difference in the outcomes can be captured sensitively

Conclusion

This review highlights the need to address PIP in primary care

Call for further research on PIP interventions in primary care

Researchers to consider the potential implications of how PIP is operationalized when designing future research on PIP

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