

Appendix 1 STOPP version 2 criteria that could not be applied

Section A: Indication of medication

1. Any drug prescribed without an evidence-based clinical indication.

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).
11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).

Section C: Antiplatelet/Anticoagulant Drugs

3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)
8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).

Section D: Central Nervous System and Psychotropic Drugs

4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na⁺ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).

9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m² (risk of digoxin toxicity if plasma levels not measured).
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m² (risk of bleeding).
3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m² (risk of bleeding).
4. NSAID's if eGFR < 50 ml/min/1.73m² (risk of deterioration in renal function).
5. Colchicine if eGFR < 10 ml/min/1.73m² (risk of colchicine toxicity).
6. Metformin if eGFR < 30 ml/min/1.73m² (risk of lactic acidosis).

Section F: Gastrointestinal System

3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where nonconstipating alternatives are available (risk of exacerbation of constipation).

Section G: Respiratory System

5. Benzodiazepines with acute or chronic respiratory failure i.e. pO₂ < 8.0 kPa ± pCO₂ > 6.5 kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H₂ antagonist (risk of peptic ulcer relapse).
5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

Section I: Urogenital System

2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J. Endocrine System

3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that predictably increase the risk of falls in older people

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure $\geq 20\text{mmHg}$ (risk of syncope, falls).
4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Appendix 2 Description of the 45 STOPP 2 criteria applied

Criteria description	Patients at risk of PIP	Patients with PIP in each year	Previous information taken into account
Indication of medication			
1. Any drug prescribed beyond the recommended duration, where treatment duration is well defined			
Zolpidem & Zopiclone (up to 4 weeks)	Have a prescription for Zolpidem or Zopiclone	Prescribed doses for > 4 weeks ⁽¹⁾	Prescriptions 4 weeks prior to period analysed
Chloral hydrate (up to 3 weeks)	Have a prescription for Chloral hydrate	Prescribed doses for > 3 weeks ⁽¹⁾	Prescriptions 3 weeks prior to period analysed
Melatonin (up to 13 weeks)	Have a prescription for Melatonin	Prescribed doses for > 13 weeks ⁽¹⁾	Prescriptions 13 weeks prior to period analysed
NSAIDs (up to 3 months)	Have a prescription for NSAID	Prescribed doses for > 3 months ⁽¹⁾	Prescriptions 3 months prior to period analysed
Duplication of drug class therapy			
2. Any duplicate drug class prescription	Have a prescription for at least one of the drugs in the list.	Prescribed drug from same drug class within 2 weeks.	Prescriptions 2 weeks prior to period analysed
List of drugs: Stimulant laxatives Thiazide diuretics Loop diuretics Beta-blockers ACE inhibitors Angiotensin II Receptor antagonists Calcium-channel blockers Oral anticoagulants Statins Benzodiazepines Z-drugs hypnotics TCAs SSRIs Opioid analgesics NSAIDs.			
Cardiovascular system			
3. Beta-blocker in combination with verapamil or diltiazem	• Have a prescription for Beta-blocker	• Prescribed verapamil or diltiazem within 2 weeks.	Prescriptions 2 weeks prior to period analysed
	• Have a prescription for verapamil or diltiazem	• Prescribed beta-blocker within 2 weeks	
4. Amiodarone as first-line antiarrhythmic therapy in	Have the first amiodarone prescription in the year analysed	Not prescribed antiarrhythmic / beta-blockers in the 3 months	Previous information related to prescriptions.

supraventricular tachyarrhythmias		preceding their first amiodarone prescription.	
5. Loop diuretic as first-line treatment for hypertension	Coded as having hypertension and subsequently having a first prescription for a loop diuretic analysed	Not prescribed an antihypertensive (beta blocker, ACE, ARB, CCB) in the 3 months preceding their first loop diuretic prescription	Previous information related to diagnosis and prescriptions.
6. Thiazide diuretic with a history of gout	Have gout diagnosis code or be regular users of drugs for gout ⁽²⁾	Prescribed thiazide diuretic after diagnosis date (any thiazide diuretic prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
7. Phosphodiesterase type-5 inhibitors with concurrent nitrate therapy for angina in severe heart failure	Have angina diagnosis code or be regular users of drugs for angina ⁽³⁾	Prescribed phosphodiesterase type-5 inhibitors and nitrates after diagnosis date (any prescription of both medications in the year, for patients considered regular user)	Previous information related to diagnosis.
Antiplatelet/Anticoagulant drugs			
8. Long-term aspirin at doses greater than 150mg per day	Long term users of aspirin ⁽⁴⁾	Prescribed doses greater than 150 mg	
9. Ticlopidine in any circumstances	All patients	Prescribed ticlopidine	
10. Aspirin with a past history of peptic ulcer disease without concomitant PPI	Have peptic ulcer diagnosis code and prescribed aspirin afterwards	Not prescribed PPI within 4 weeks of aspirin prescription	Prescriptions 4 weeks prior to period analysed and all available information related to diagnosis
11. NSAID and anticoagulant (vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors) in combination	• Have a prescription for NSAID	• Prescribed anticoagulant within 2 weeks	Prescriptions 2 weeks prior to period analysed
	• Have a prescription for anticoagulant	• Prescribed NSAID within 2 weeks	
12. Antiplatelet agents with anticoagulant (vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors) in patients with coronary/cerebrovascular/arterial disease	• Have atherosclerosis diagnosis code and regular users of antiplatelet afterwards ⁽⁵⁾	• Prescribed anticoagulant within 4 weeks of antiplatelet prescription	Prescriptions 4 weeks prior to period analysed and all available information related to diagnosis
	• Have atherosclerosis diagnosis code and regular users of anticoagulant afterwards ⁽⁶⁾	• Prescribed antiplatelet within 4 weeks of anticoagulant prescription	

13. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	Have a prescription for antiplatelet agent and prescribed NSAID within 2 weeks	Not prescribed PPI within 4 weeks of antiplatelet prescription	Prescriptions 4 weeks prior to period analysed
Central nervous system and psychotropic drugs			
14. Tricyclic antidepressants (TCAs) with any of the below conditions:			
Dementia	Have dementia diagnosis code or be regular users of antidementia drugs ⁽⁷⁾	Prescribed TCA after diagnosis date (any TCA prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Narrow angle glaucoma	Have narrow angle glaucoma diagnosis code or be regular users of antiglaucoma drugs ⁽⁸⁾	Prescribed TCA after diagnosis date (any TCA prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Cardiac conduction abnormalities	Have cardiac conduction abnormalities diagnosis code	Prescribed TCA after diagnosis date	Previous information related to diagnosis.
Prostatism and urinary retention (BPH)	Have BPH diagnosis code or be regular users of drugs for BPH ⁽⁹⁾	Prescribed TCA after diagnosis date (any TCA prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
15. Neuroleptics with moderate-marked antimuscarinic / anticholinergic effects with a history of prostatism or previous urinary retention	Have BPH diagnosis code or be regular users of drugs for BPH ⁽⁹⁾	Prescribed neuroleptics after diagnosis date (any neuroleptics prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
16. Benzodiazepines for ≥4 weeks	Have a prescription for Benzodiazepines	Prescribed doses for ≥ 4 weeks ⁽¹⁾	Prescriptions 4 weeks prior to period analysed
17. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism	Have parkinsonism diagnosis code or be regular users of antiparkinson drugs ⁽¹⁰⁾	Prescribed antipsychotics after diagnosis date (any antipsychotics prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
18. Anticholinergics / antimuscarinics in patients with dementia / delirium	Have dementia/delirium diagnosis code or be regular users of antidementia drugs ⁽⁷⁾	Prescribed anticholinergics / antimuscarinics after diagnosis date (any anticholinergics /	Previous information related to diagnosis.

		antimuscarinics prescription in the year, for patients considered regular user)	
19. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment	Have a first TCA prescription in the year analysed	Not prescribing any other antidepressant in the 3 months preceding their first TCA prescription.	Previous information related to prescriptions.
20. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications	Have a prescription for neuroleptic medications	Prescribed Anticholinergics/antimuscarinics within 4 weeks	
21. Anticholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	Have a prescription of drug to reduce heart rate	Prescribed anticholinesterase within 2 weeks	
22. Phenothiazines as first-line antipsychotic treatment	Have a first phenothiazine prescription in the year analysed	Not prescribing any other antipsychotic in the 3 months preceding their first phenothiazine prescription.	Previous information related to prescriptions.
23. First-generation antihistamines	All patients	Prescribed first-generation antihistamines	
Gastro-Intestinal system			
24. Prochlorperazine or metoclopramide with Parkinsonism	Have parkinsonism diagnosis code or be regular users of antiparkinson drugs ⁽¹⁰⁾	Prescribed prochlorperazine or metoclopramide after diagnosis date (any prochlorperazine or metoclopramide prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
25. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	Have a prescription for PPI ⁽¹¹⁾	Prescribed doses for > 8 weeks ⁽¹⁾	Prescriptions 8 weeks prior to period analysed

26. Oral elemental iron doses greater than 200 mg daily	Have a prescription for oral elemental iron	Prescribed doses greater than 200 mg daily	
Respiratory system			
27. Theophylline as monotherapy for Chronic obstructive pulmonary disease (COPD)	Coded as having COPD and subsequently having a first prescription for theophylline	Not prescribed any other COPD treatment	Previous information related to diagnosis.
28. Non-selective beta-blocker (oral/topical) with history of asthma requiring treatment	Have asthma diagnosis code and prescribed asthma treatment afterwards	Prescribed for non-selective beta-blocker after either diagnosis date or asthma prescription	Previous information related to diagnosis and asthma prescription.
29. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	Coded as having COPD and subsequently having at least two prescription for systemic steroids	Not prescribed inhaled steroids	Previous information related to diagnosis
30. Antimuscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of the below conditions:			
Narrow-angle glaucoma	Have narrow-angle glaucoma diagnosis code or be regular users of antiglaucoma drugs ⁽⁸⁾	Prescribed antimuscarinic bronchodilators after diagnosis date (any antimuscarinic bronchodilators prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Bladder outflow obstruction	Have BPH diagnosis code or be regular users of drugs for BPH ⁽⁹⁾	Prescribed antimuscarinic bronchodilators after diagnosis date (any antimuscarinic bronchodilators prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
31. NSAID with severe hypertension or severe heart failure			
Severe hypertension	Have hypertension diagnosis code and prescribed 3 or more antihypertensive classes afterwards	Prescribed NSAID after diagnosis date	Previous information related to diagnosis and hypertension prescription.

Severe heart failure	Have heart failure diagnosis code and prescribed 3 or more antihypertensive classes afterwards	Prescribed NSAID after diagnosis date	Previous information related to diagnosis and hypertension prescription.
32. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	Long term user of NSAID (> 3 months)	Not prescribing paracetamol in the 3 months preceding their first NSAID prescription.	Prescriptions 3 months prior to period analysed
33. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis	Have rheumatoid arthritis diagnosis code and prescribed corticosteroids for more than 3 months afterwards	Not prescribed disease modifying antirheumatic drug (DMARD)	Previous information related to diagnosis, DMARD prescriptions, and corticosteroids prescriptions 3 months prior to period analysed
34. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor	Have gout diagnosis code or be regular users of drugs for gout ⁽²⁾ , and prescribed NSAID or colchicine for more than 3 months afterwards	Not prescribed xanthine-oxidase inhibitor	Previous information related to diagnosis, xanthine-oxidase inhibitor prescriptions, and NSAID prescriptions 3 months prior to period analysed
35. COX-2 selective NSAIDs with concurrent cardiovascular disease	Have cardiovascular disease diagnosis code or be regular users of drugs for cardiovascular disease ⁽¹²⁾	Prescribed COX-2 selective NSAIDs after diagnosis date (any COX-2 selective NSAIDs prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
36. NSAID with concurrent corticosteroids without PPI prophylaxis	<ul style="list-style-type: none"> Long term users of NSAID (>3 months) and prescribed corticosteroids at the same time (within 2 weeks) 	<ul style="list-style-type: none"> Not prescribed PPI within 4 weeks of corticosteroids 	Prescriptions 3 months prior to period analysed
	<ul style="list-style-type: none"> Long term users of corticosteroids (>3 months) and prescribed NSAID at the same time (within 2 weeks) 	<ul style="list-style-type: none"> Not prescribed PPI within 4 weeks of NSAID 	
37. Oral bisphosphonates in patients with a current/recent history of upper gastrointestinal (GI) disease, or upper GI bleeding)	Have GI disease diagnosis code or be regular users of GI disease drugs ⁽¹³⁾	Prescribed oral bisphosphonates after diagnosis date (any oral bisphosphonates prescription in	Previous information related to diagnosis.

		the year, for patients considered regular user)	
Urogenital system			
38. Antimuscarinic drugs with any of the below conditions:			
Dementia, or chronic cognitive impairment	Have dementia diagnosis code or be regular users of antidementia drugs ⁽⁷⁾	Prescribed antimuscarinic after diagnosis date (any antimuscarinic prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Narrow-angle glaucoma	Have narrow-angle glaucoma diagnosis code or be regular users of antiglaucoma drugs ⁽⁸⁾	Prescribed antimuscarinic after diagnosis date (any antimuscarinic prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Chronic prostatism	Have chronic prostatism diagnosis code or be regular users of drugs for BPH ⁽⁹⁾	Prescribed antimuscarinic after diagnosis date (any antimuscarinic prescription in the year, for patients considered regular user)	Previous information related to diagnosis.
Endocrine system			
39. Sulphonylureas with a long duration of action with type 2 diabetes mellitus	All patients	Prescribed Sulphonylureas	
40. Thiazolidenediones in patients with heart failure	Have heart failure diagnosis code or be regular users of drugs for heart failure ⁽³⁾	Prescribed thiazolidenediones after diagnosis date (any prescription of thiazolidenediones in the year, for patients considered regular user)	Previous information related to diagnosis.
41. Oestrogens with a history of breast cancer or venous thromboembolism			
Breast cancer	Have breast cancer diagnosis code	Prescribed oestrogens after diagnosis date	Previous information related to diagnosis.
Venous thromboembolism	Have venous thromboembolism diagnosis code	Prescribed oestrogens after diagnosis date	Previous information related to diagnosis.

Analgesic drugs			
42. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain	Have the first oral or transdermal strong opioids prescription in the year analysed ⁽¹⁴⁾	Not prescribed pain medications in the 3 months preceding their first oral or transdermal strong opioid prescription.	Previous information related to prescriptions.
43. Use of regular (as distinct from PRN) opioids without concomitant laxative	Regular users of opioids ⁽¹⁵⁾	Not prescribed laxative within 6 months of opioids	Laxative prescriptions 6 months prior to period analysed
44. Long-acting opioids without short-acting opioids for break-through pain	Have a long-acting opioids prescription	Not prescribed short-acting opioids within 1 month of long-acting opioids	Short-acting opioids prescriptions 1 month prior to period analysed
Antimuscarinic/Anticholinergic drug burden			
45. Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	• Have a prescription for TCA	• Prescribed first generation antihistamines or antimuscarinics or anticholinergics within 2 weeks	Prescriptions 2 weeks prior to period analysed
	• Have a prescription for first generation antihistamines	• Prescribed TCA or antimuscarinics or anticholinergics within 2 weeks	Prescriptions 2 weeks prior to period analysed
	• Have a prescription for antimuscarinics	• Prescribed TCA or first generation antihistamines or anticholinergics within 2 weeks	Prescriptions 2 weeks prior to period analysed
	• Have a prescription for anticholinergics	• Prescribed TCA or first generation antihistamines or antimuscarinics within 2 weeks	Prescriptions 2 weeks prior to period analysed

(1) Prescribed treatment that exceed the recommended duration or second prescription of this medication within the recommended duration, and in total, the number of days of treatment exceed the recommended duration.

- (2) Regular user of drugs for gout: patients who have at least one prescription of gout treatment (allopurinol, tisopurine, febuxostat, colchicine, and uricosuric agents) during the first 5 months, one prescription during the last 7 months or only one prescription with at least two issues in the year analysed.
- (3) Regular user of drugs for angina: patients who have at least one prescription of loop diuretics and ACE inhibitor during the first 5 months and one prescription of loop diuretics and ACE inhibitor during the last 7 months in the year analysed.
- (4) Long term users of aspirin: patients prescribed aspirin during the first 5 months and during the last 7 months in the year analysed.
- (5) Regular users of antiplatelet: to rule out cases of switching from an antiplatelet to an anticoagulant, patients had to have a further antiplatelet prescription in the 4 weeks following their antiticoagulant prescription
- (6) Regular users of anticoagulant: to rule out cases of switching from an anticoagulant to an antiplatelet, patients had to have a further anticoagulant prescription in the 4 weeks following their antiplatelet prescription
- (7) Regular user of antedementia drugs: patients who have at least one prescription of antedementia drug during the first 5 months, one prescription of antedementia drug during the last 7 months or one prescription with at least two issues in the year analysed.
- (8) Regular user of antiglaucoma drugs: patients who have at least one prescription of antiglaucoma drug during the first 5 months, one prescription of antiglaucoma drug during the last 7 months or one prescription with at least two issues in the year analysed.
- (9) Regular user of drugs for BPH: patients who have at least one prescription for BPH during the first 5 months, one prescription for BPH during the last 7 months or one prescription with at least two issues in the year analysed.
- (10) Regular user of antiparkinson drugs: patients who have at least one prescription of antiparkinson drug during the first 5 months, one prescription of antiparkinson drug during the last 7 months or one prescription with at least two issues in the year analysed.
- (11) Patients with Zollinger Ellison syndrome and Barrett's oesophagus were excluded.
- (12) Regular user of drugs for cardiovascular disease: patients who have at least one prescription of drugs for cardiovascular disease during the first 5 months, one prescription of drugs for cardiovascular disease during the last 7 months or one prescription with at least two issues in the year analysed.
- (13) Regular user of drugs for GI disease: patients who have at least one prescription of drugs for GI disease during the first 5 months, one prescription of drugs for GI disease during the last 7 months or one prescription with at least two issues in the year analysed.
- (14) Patients with methadone were excluded.
- (15) Regular users of opioids: patients who have at least 3 prescriptions of opioids during the first half of the year and 3 prescriptions of opioids during the second half, or a prescription with at least 3 issues in the first half and a prescription with at least 3 issues in the second half.

Appendix 3. Prevalence of PIP by year according to the STOPP Version 2 criteria

Criteria description	Year			
	2012 (n=30753)	2013 (n=30789)	2014 (n=30231)	2015 (n=29077)
	N (% prevalence)			
Indication of medication				
1. Any drug prescribed beyond the recommended duration, where treatment duration is well defined ^a	3905 (12.7)	4065 (13.2)	4047 (13.4)	3988 (13.7)
Zolpidem & Zopiclone (up to 4 weeks)	2913 (9.4)	3108 (10.1)	3187 (10.5)	3103 (10.6)
Chloral hydrate (up to 3 weeks)	0 (0)	0 (0)	0 (0)	0 (0)
Melatonin (up to 13 weeks)	2 (0.006)	5 (0.01)	4 (0.01)	6 (0.02)
NSAIDs (up to 3 months)	1211 (3.94)	1157 (3.76)	1053 (3.48)	1091 (3.75)
Duplication of drug class therapy				
2. Any duplicate drug class prescription ^a	1273 (4.13)	1289 (4.18)	1298 (4.29)	1217 (4.18)
Stimulant laxatives	83 (0.27)	87 (0.28)	81 (0.27)	56 (0.19)
Thiazide diuretics	6 (0.02)	5 (0.01)	4 (0.01)	5 (0.017)
Loop diuretics	30 (0.10)	25 (0.08)	46 (0.15)	46 (0.16)
Beta-blockers	39 (0.12)	34 (0.11)	42 (0.13)	36 (0.12)
ACE inhibitors	18 (0.06)	11 (0.03)	11 (0.03)	6 (0.02)
Angiotensin II receptor antagonists	7 (0.02)	12 (0.03)	7 (0.02)	5 (0.02)
Calcium-channel blockers	55 (0.17)	61 (0.19)	72 (0.23)	63 (0.21)
Oral anticoagulants	9 (0.02)	24 (0.07)	11 (0.03)	9 (0.03)
Statins	39 (0.12)	28 (0.09)	27 (0.09)	30 (0.13)

Benzodiazepines	465 (1.51)	458 (1.48)	461 (1.52)	430 (1.47)
Z-drugs hypnotics	42 (0.14)	39 (0.12)	36 (0.12)	31 (0.10)
TCAs	8 (0.03)	7 (0.02)	8 (0.02)	5 (0.017)
SSRIs	24 (0.08)	14 (0.04)	19 (0.06)	15 (0.05)
Opioid analgesics	265 (0.86)	293 (0.95)	322 (1.06)	249 (1.20)
NSAIDs	262 (0.85)	261 (0.84)	237 (0.78)	218 (0.75)
Cardiovascular system				
3. Beta-blocker in combination with verapamil or diltiazem	186 (0.60)	166 (0.54)	170 (0.56)	166 (0.57)
4. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	39 (0.12)	38 (0.12)	29 (0.10)	26 (0.09)
5. Loop diuretic as first-line treatment for hypertension	59 (0.19)	56 (0.18)	63 (0.21)	46 (0.16)
6. Thiazide diuretic with a history of gout	111 (0.36)	111 (0.36)	129 (0.43)	137 (0.47)
7. Phosphodiesterase type-5 inhibitors in severe heart failure characterised by hypotension, or with concurrent nitrate therapy for angina	7 (0.02)	7 (0.02)	6 (0.02)	17 (0.06)
Antiplatelet/Anticoagulant drugs				
8. Long-term aspirin at doses greater than 150mg per day	115 (0.37)	99 (0.32)	83 (0.27)	58 (0.20)
9. Ticlopidine in any circumstances	0 (0)	0 (0)	0 (0)	0 (0)
10. Aspirin with a past history of peptic ulcer disease without concomitant PPI	68 (0.22)	76 (0.25)	84 (0.28)	71 (0.24)
11. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	133 (0.43)	156 (0.50)	168 (0.56)	178 (0.61)
12. Antiplatelet agents with vitamin K antagonist, coronary/cerebrovascular/arterial disease	81 (0.26)	90 (0.29)	100 (0.33)	109 (0.37)
13. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	541 (1.76)	526 (1.70)	497 (1.64)	399 (1.37)
Central nervous system and psychotropic drugs				
14. Tricyclic antidepressants (TCAs) with any of the below conditions: ^a	146 (0.47)	159 (0.51)	173 (0.57)	192 (0.66)
Dementia	43 (0.14)	42 (0.13)	45 (0.14)	43 (0.14)

Narrow angle glaucoma	45 (0.14)	52 (0.16)	62 (0.20)	45 (0.14)
Cardiac conduction abnormalities	0 (0)	0 (0)	0 (0)	0 (0)
BPH	71 (0.23)	77 (0.25)	75 (0.24)	82 (0.28)
15. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects with a history of prostatism or urinary retention	7 (0.02)	10 (0.03)	9 (0.03)	10 (0.03)
16. Benzodiazepines for ≥4 weeks	5653 (18.4)	5765 (18.7)	5763 (19.1)	5562 (19.1)
17. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease	162 (0.52)	159 (0.51)	154 (0.51)	156 (0.53)
18. Anticholinergics / antimuscarinics in patients with dementia / delirium	140 (0.45)	180 (0.58)	174 (0.58)	178 (0.61)
19. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment	292 (0.94)	260 (0.84)	252 (0.83)	262 (0.90)
20. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications	274 (0.89)	273 (0.88)	262 (0.87)	259 (0.89)
21. Anticholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate	317 (1.00)	341 (1.10)	340 (1.12)	322 (1.10)
22. Phenothiazines as first-line anti-psychotic treatment	8 (0.02)	0 (0)	8 (0.03)	1 (0.003)
23. First-generation antihistamines	630 (2.04)	664 (2.15)	726 (2.40)	725 (2.49)
Gastro-Intestinal system				
24. Prochlorperazine or metoclopramide with Parkinsonism	34 (0.11)	29 (0.09)	30 (0.10)	30 (0.10)
25. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	5854 (19.0)	6903 (22.4)	7421 (24.5)	7836 (26.9)
26. Oral elemental iron doses greater than 200 mg daily	484 (1.57)	561 (1.82)	522 (1.73)	507 (1.74)
Respiratory system				
27. Theophylline as monotherapy for Chronic obstructive pulmonary disease (COPD)	0 (0)	0 (0)	0 (0)	0 (0)
28. Non-selective beta-blocker (oral/topical) with history of asthma requiring treatment	30 (0.09)	42 (0.13)	50 (0.17)	57 (0.19)
29. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	239 (0.77)	275 (0.89)	352 (1.16)	314 (1.08)
30. Antimuscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of the below conditions: ^a	284 (0.92)	317 (1.03)	343 (1.10)	354 (1.21)
Narrow-angle glaucoma	95 (0.31)	106 (0.34)	110 (0.36)	113 (0.33)

Bladder outflow obstruction	210 (0.68)	231 (0.75)	255 (0.84)	263 (0.90)
Musculoskeletal system				
31. NSAID with severe hypertension or severe heart failure ^a	1683 (5.47)	1911 (6.20)	1988 (6.57)	1900 (6.53)
Severe hypertension	1659 (5.39)	1892 (6.14)	1960 (6.48)	1879 (6.46)
Severe heart failure	53 (0.17)	57 (0.17)	84 (0.27)	78 (0.26)
32. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	694 (2.26)	656 (2.13)	556 (1.83)	567 (1.94)
33. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis	10 (0.03)	8 (0.02)	7 (0.02)	6 (0.002)
34. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor	23 (0.07)	23 (0.07)	27 (0.09)	28 (0.09)
35. COX-2 selective NSAIDs with concurrent cardiovascular disease	330 (1.07)	387 (1.25)	426 (1.41)	417 (1.43)
36. NSAID with concurrent corticosteroids without PPI prophylaxis	73 (0.23)	67 (0.21)	87 (0.29)	73 (0.25)
37. Oral bisphosphonates in patients with a current/recent history of upper gastrointestinal (GI) disease, or upper GI bleeding)	1509 (4.91)	1461 (4.74)	1436 (4.75)	1314 (4.52)
Urogenital system				
38. Antimuscarinic drugs with any of the below conditions: ^a	345 (1.12)	412 (1.33)	389 (1.29)	388 (1.33)
Dementia, or chronic cognitive impairment	132 (0.43)	170 (0.55)	162 (0.54)	168 (0.57)
Narrow-angle glaucoma	72 (0.23)	83 (0.27)	69 (0.23)	68 (0.23)
Chronic prostatism	178 (0.57)	207 (0.67)	208 (0.68)	200 (0.68)
Endocrine system				
39. Sulphonylureas with a long duration of action with type 2 diabetes mellitus	47 (0.15)	42 (0.13)	32 (0.10)	25 (0.08)
40. Thiazolidenediones in patients with heart failure	0 (0.0)	2 (0.006)	2 (0.00)	2 (0.00)
41. Oestrogens with a history of breast cancer or venous thromboembolism ^a	12 (0.04)	18 (0.05)	18 (0.05)	24 (0.05)
Breast cancer	9 (0.03)	7 (0.02)	10 (0.03)	10 (0.03)
Venous thromboembolism	4 (0.01)	11 (0.03)	8 (0.03)	16 (0.08)
Analgesic drugs				

42. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain	617 (2.01)	536 (1.74)	489 (1.61)	426 (1.46)
43. Use of regular (as distinct from PRN) opioids without concomitant laxative	520 (1.69)	548 (1.78)	554 (1.83)	542 (1.86)
44. Long-acting opioids without short-acting opioids for break-through pain	297 (0.96)	323 (1.05)	354 (1.17)	357 (1.22)
Antimuscarinic/Anticholinergic drug burden				
45. Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (bladder antispasmodics, intestinal antispasmodics, TCAs, first generation antihistamines)	223 (0.72)	216 (0.70)	269 (0.89)	264 (0.91)
Total	13940 (45.3)	14751 (48.0)	14962 (49.5)	14823 (51.0)

^a Indicator includes multiple subgroups which may not be mutually exclusive and therefore prevalence of subgroups may not sum to prevalence of overall indicator.

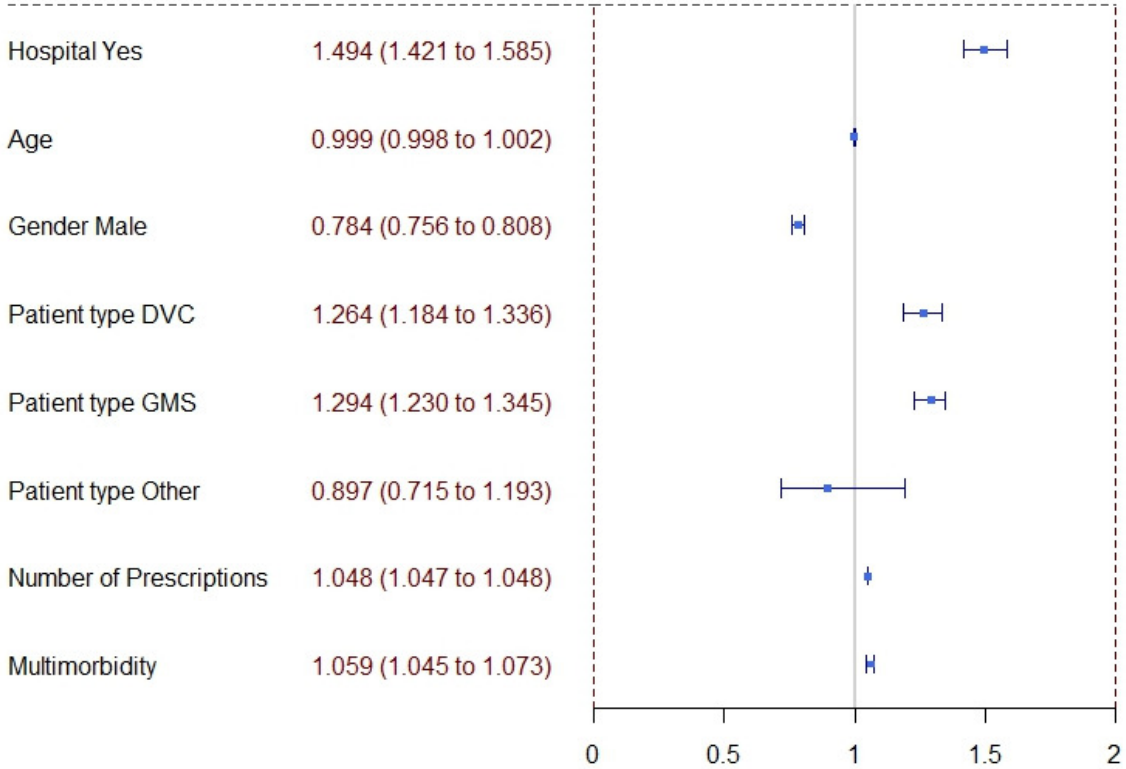
Appendix 4. Estimated odds ratios for the presence of PIP among all participants, with 95% credible intervals.

The reference groups used are no hospital admission, female gender, and private patient (health cover type)

2012-2015

n=28831

Logistic Model Odds Ratio (CI95%)



Appendix 5. Sensitivity analyses fitting models by calendar year

Figure A. Estimated hazard ratios for recurrent PIP among all participants, with 95% confidence intervals

The reference groups used are no hospital admission, female gender, and private patient (health cover type)

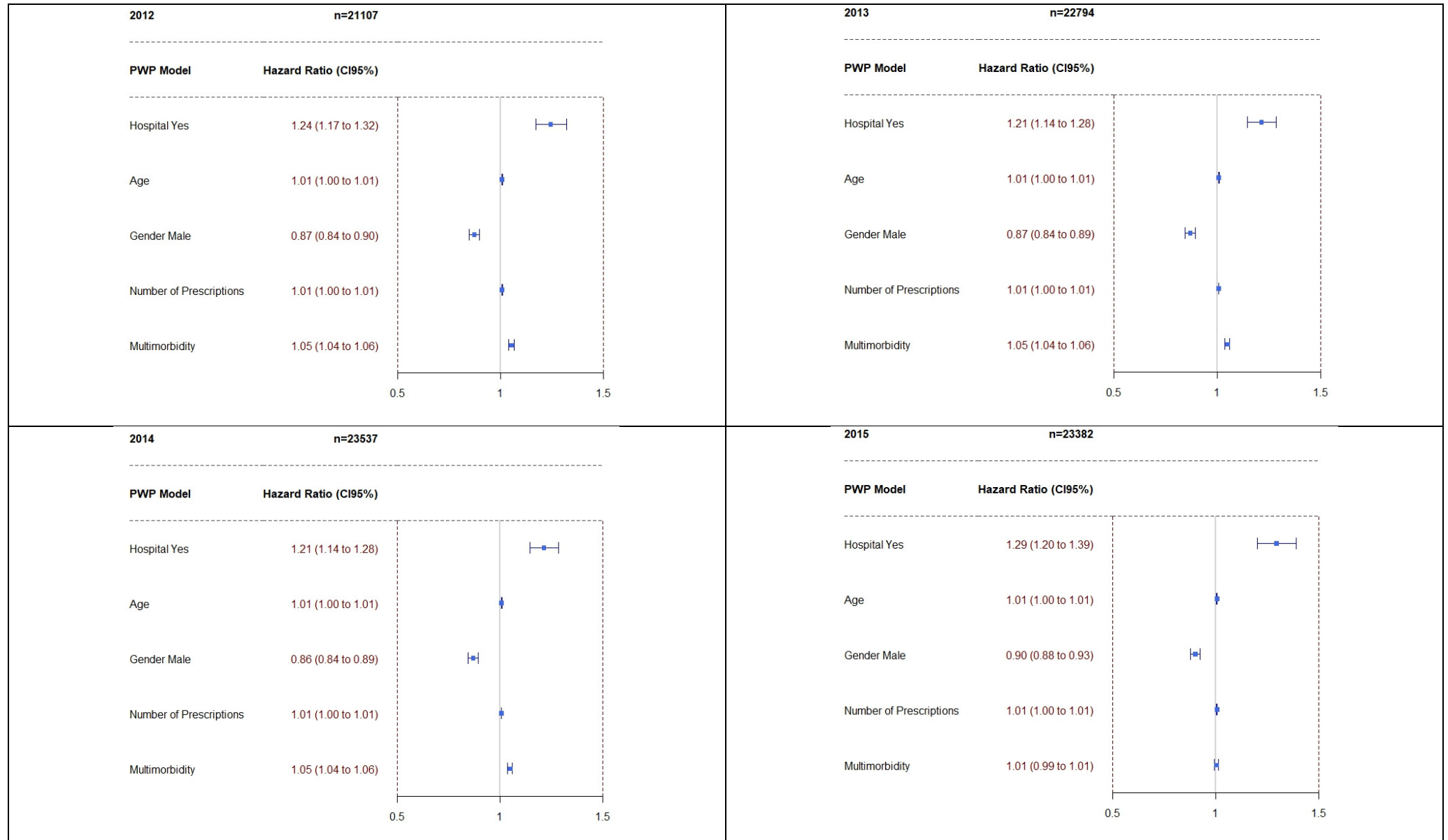


Figure B. Estimated odds ratios for the presence of PIP among hospitalised participants only, with 95% credible intervals and presented by year.

The reference groups are before hospitalisation and female gender. Also adjusted for patient health cover type, which did not show any significant association

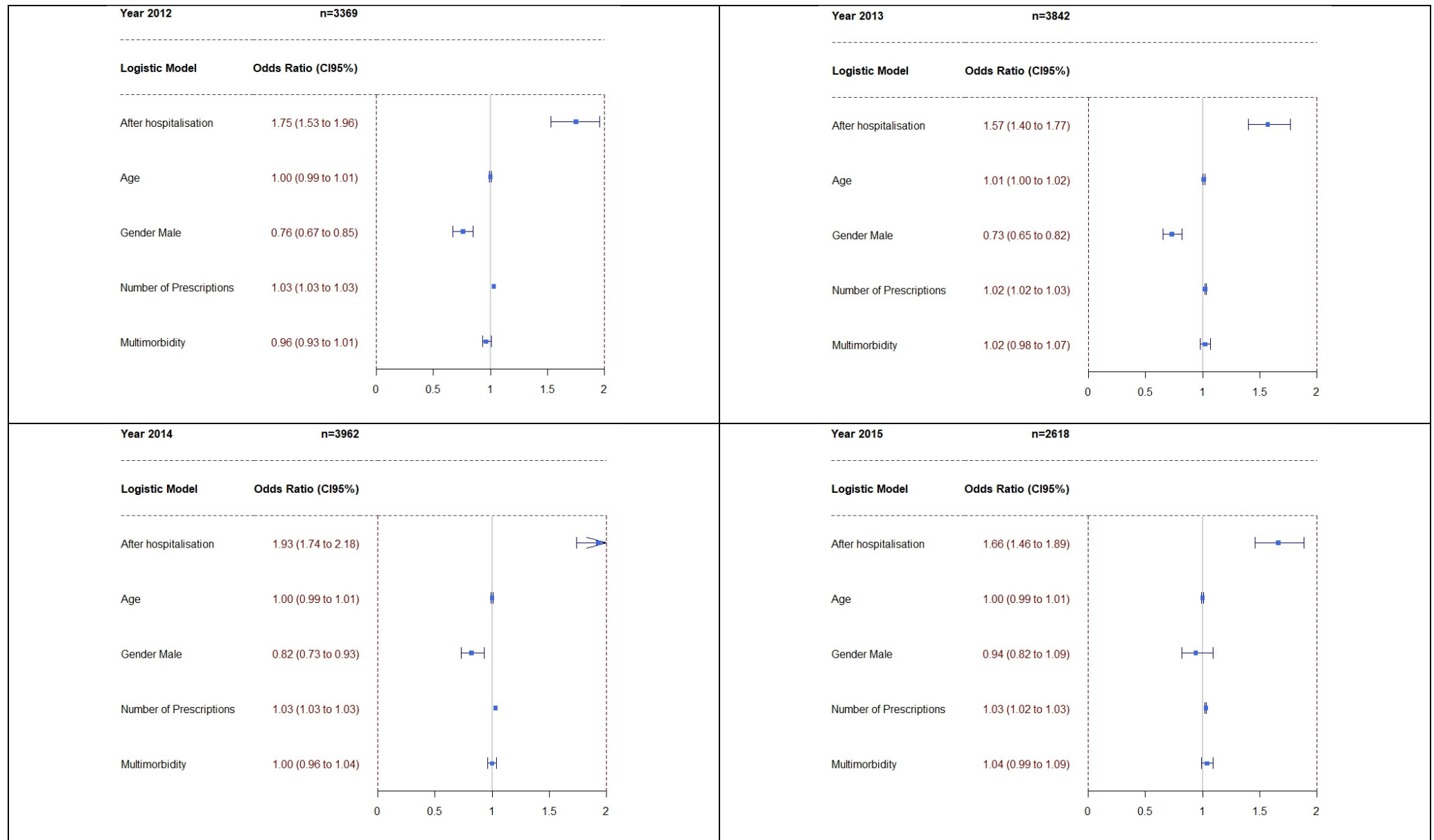
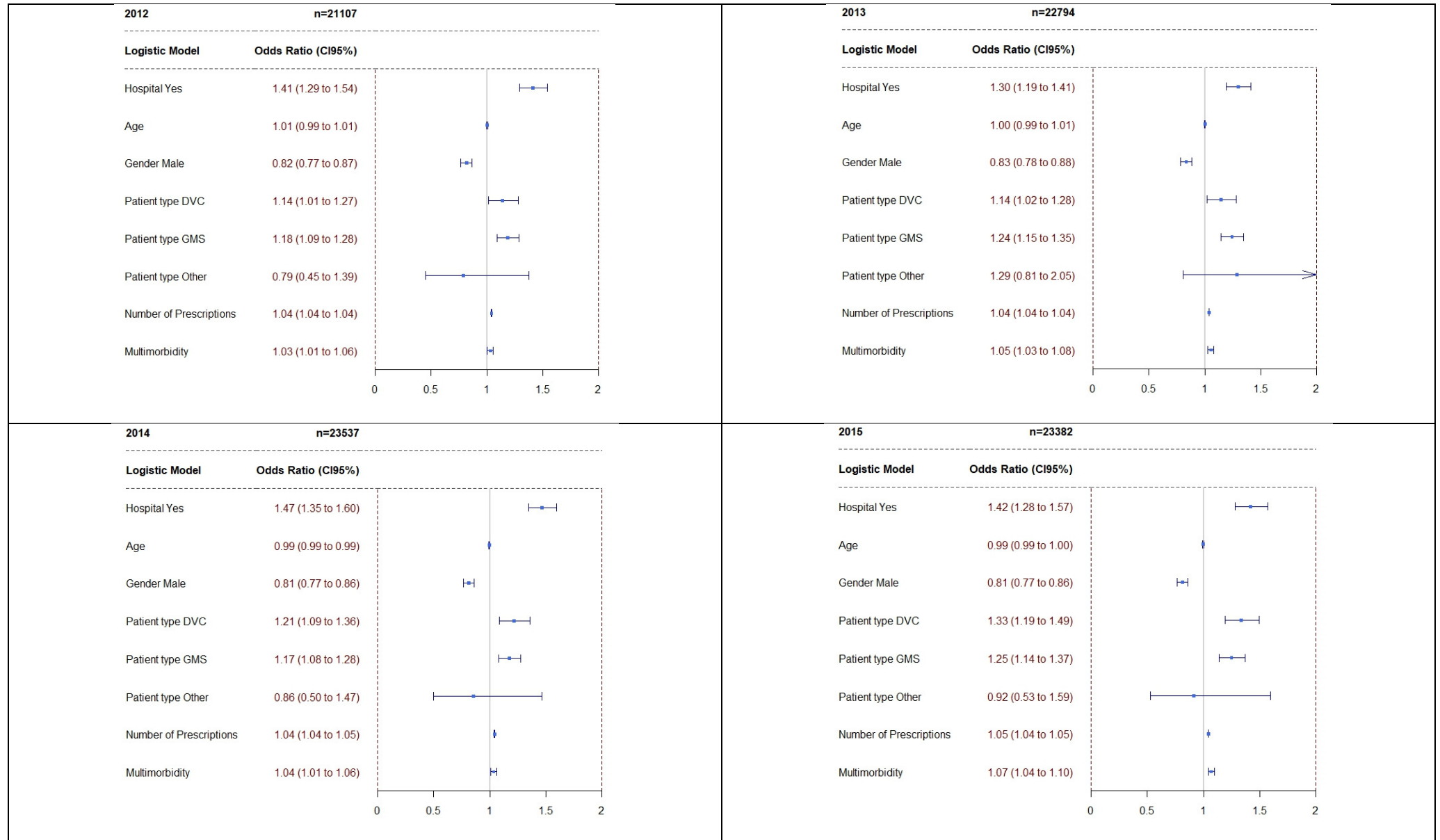


Figure C. Estimated odds ratios for the presence of PIP among all participants, with 95% confidence intervals and presented by year.

The reference groups used are no hospital admission, female gender, and private patient (health cover type)



Appendix 6. Propensity score-matched sensitivity analysis to estimate odds ratios for the presence of PIP, with 95% credible intervals.

The reference groups used are no hospital admission, female gender, and private patient (health cover type)

Propensity analysis

n=16582

Logistic Model Odds Ratio (CI95%)

Hospital Yes	1.480 (1.375 to 1.576)
Age	1.001 (0.997 to 1.005)
Gender Male	0.746 (0.697 to 0.803)
Patient type DVC	1.229 (1.023 to 1.439)
Patient type GMS	1.343 (1.214 to 1.462)
Patient type Other	1.374 (0.853 to 2.296)
Number of Prescriptions	1.035 (1.034 to 1.036)
Multimorbidity	1.061 (1.035 to 1.087)

