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# Do medicines commonly used by older adults impact their nutrient status?

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ABSTRACT

*Background:* Chronic health conditions and polypharmacy are common among the older population and associated with increased risks of adverse events, medicine-interactions, geriatric syndromes, falls and mortality. Poor nutrition is also common in older people. Causal associations between medication use and older people's nutrient status is seldom discussed.

*Objectives:* The objectives of this review were to summarise the literature reporting associations between medicines commonly prescribed to older adults and nutrient deficiencies, and to discuss the clinical implications and management.

*Methods:* Medicine information resources ($n = 5$) were searched for information about nutrient deficiencies associated with common medicines used by older people and listed within the top 50 medicines prescribed by volume on the Australian Pharmaceutical Benefits Scheme. This was followed by a search for clinical studies published on PubMed from inception to April 2020. Data was extracted, tabulated and summarised with clinical information relevant to pharmacists and clinicians involved in the care of older people taking medicines.

*Results:* A total of 23 clinical studies were identified reporting medicine-induced nutrient deficiencies in older adults. Vitamin B12, sodium, magnesium were identified as the 3 main nutrients susceptible to deficiency by medicines used to treat cardiovascular disease, neurological conditions, gastrointestinal conditions, and diabetes. The coenzyme CoQ10 was depleted by statins.

Conclusion: Certain medicines commonly prescribed to older adults are associated with nutrient deficiencies that may be clinically significant. Given the high prevalence of comorbidities and polypharmacy it is possible that some of these individual drug-induced nutrient deficiencies are compounded, warranting both clinical and research attention.

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## 1. Introduction

The term 'older' is commonly used to describe populations aged ≥65 years.[1] An ageing population is a global phenomenon, with up to 703 million adults in the world reported as being ≥65 years of age in 2019.[2] This figure is expected to double to 1.5 billion in 2050.[2] Australians and New Zealanders older than 65 years of age are expected to live for an additional 21 more years.[2] This is consistent with findings from the 2020 Australian Institute of Health and Welfare (AIWH), which identified that 1 in every 6 Australians are ≥65 years.[3]

Chronic health conditions are common among the older population, with many taking regular medicines for a range of health issues including cardiovascular, neurological and gastrointestinal conditions.[4] Given the complexity of these conditions and higher likelihood of multiple comorbidities, it is not surprising that an older person may be prescribed several medicines. The practice of polypharmacy (defined as ≥5 medicines) is common, and associated with increased risks of adverse events, medicine-interactions, multiple geriatric syndromes, falls and mortality.[4]

In addition to multiple comorbidities and the number of medicines used by older adults, a 2020 AIHW report found that 91.8% of older adult Australians do not meet the recommended daily intake of fruits and vegetables.[3] It is therefore unsurprising that micronutrient deficiencies are common in older adults.[5] A systematic and meta-analysis involving 37 studies (≥ 28,000 aged ≥65 years) reported that community-dwelling older adults have a higher risk of inadequate intakes of vitamin D, thiamine, riboflavin, calcium, magnesium and selenium.[6] The same study also reported that ≥30% were at risk of inadequate dietary intakes of calcium, magnesium and selenium.[6]

Factors contributing to nutrient deficiencies in older adults include age-related decline in physiological function, poor oral hygiene and dental health, gastrointestinal disorders and loss of cognitive function.[7] These factors may result in a loss of appetite, reduction in food intake and compromised nutrient absorption.[7] Collectively these factors, combined with polypharmacy, may lead to increased risks of other nutrition related non-communicable chronic diseases.[3,7]

To reduce the risk of medicine interactions associated with multiple medicines use, healthcare professionals (HCPs) have access to a wide range of reputable medicine information resources to help inform clinical decisions about appropriate concurrent medication use. Information on the indications and adverse effects are relatively consistent across these databases. This information is based on evidence obtained from pharmacokinetic, pharmacodynamic and physiochemical interaction studies that report changes to the way a medicine works when taken with another medicine, food or dietary supplement.[8,9] However, the effects of medicines on nutrient status has largely fallen outside the classification of these three main pharmacological interactions. Within the context of this study, the minerals commonly referred to as electrolytes (calcium, sodium, potassium, magnesium) will be referred to as essential nutrients obtained through dietary sources.

In 2011, a controversial collaboration between Australian stakeholders who promoted the companion 'prescribing' of certain medicines and dietary supplements was heavily criticised as being non-evidence based and not in the interest of public health.[10] Fast forward a decade, and it is still relatively undiscussed, as to whether sufficient evidence exists to support recommending specific nutritional supplements with certain medications.

Given the complex health care needs (including nutrition and medicines use) of older adults, there is a need for an evidence-based information resource in this area that informs clinical care. Such information would contribute to the goals of the World Health Organisation (WHO) "Global Strategy and Action Plan on Ageing and Health" to promote healthy ageing among older adults.[11,12]

Therefore, the objectives of this review were to summarise the literature reporting medicine induced nutrient deficiencies in older adults and discuss what is known about the clinical implications and management.

## 2. Method

### 2.1. Common medicines used by older Australians

To identify the most common medicines used by older Australians, medicines listed in the Australian Top 50 Pharmaceutical Benefit Scheme (PBS) for 2018–2019 (by volume) were cross checked against the total burden of diseases among older adults population reported in AIHW 2020.[3,13] Of the top 50 PBS listed medicines, only oral contraceptive medications were excluded from further searches. Medicines listed in the top 50 PBS list (Appendix A) were then divided into 9 main categories in accordance with the PBS drug classification which is based on the Anatomical Therapeutic Chemical (ATC) classification index. These categories include medicines used to treat (1) cardiovascular disease and associated risk factors; (2) neurological conditions; (3) gastrointestinal conditions; (4) diabetes; (5) pain; (6) infections; (7) corticosteroids; (8) respiratory conditions and (9) thyroid disorders.

### 2.2. Identifying medicine-nutrient deficiencies

To identify which medicines were commonly associated with medicine-nutrient deficiencies, the top 50 PBS drugs were searched in databases commonly accessed by Australian HCPs. These databases include the Australian

Medicines Handbook (AMH),[14] Australian Pharmaceutical Formulary and Handbook 24 edition (APF24)[15] and MIMSonline.[16] Two additional databases specifically focusing on interactions between complementary medicines/dietary supplements and prescription medicines, namely Integrative Medicine Gateway Interaction Database (IMGateway)[17] and Natural Medicines Database[18] were also searched. Where a specific nutrient deficiency was reported across the majority databases i.e., 3 or more databases, a search of the primary literature was conducted. Authors RC, JH, IG and BC developed the search strategy that was conducted by RC. The National Library of Medicine database PubMed[19] was employed to access literature published from inception to October 2020 using the keywords: "medicine class" or "medicine name" and "nutrient name" and "medical terminology"; for example, "thiazide diuretics" OR "hydrochlorothiazide" AND "sodium" AND "hyponatraemia". The searches conducted are outlined in Appendix C.

Inclusion criteria were as follows: Full text papers reporting the results of clinical studies involving adults ≥65 years of age including case reports, case series, clinical trials, and systematic reviews with meta-analysis written in English. Exclusion criteria were in-vitro and animal studies and review papers without meta-analysis. An additional search of google scholar using the same keywords for each medicine class and nutrient was conducted to capture any additional articles not identified in the PubMed search.

After removing duplicates, titles and abstracts were screened for suitability by RC and JH for inclusion. Studies not meeting the inclusion criteria were removed. The remaining papers were reviewed by RC and JH, and relevant data were extracted and tabulated. Bibliographies of relevant articles were also reviewed for any potentially relevant studies not identified in the search. Where there were any disagreements about the inclusion of the articles, IG and BC were consulted until consensus was reached. Fig. 1 illustrates the PRISMA flow process for article identification, screening and inclusion.

## 3. Results

Across the five medicine information databases available to health care professionals, we identified seven medicine categories which were consistently reported to be associated with one or multiple nutrient deficiencies (Appendix B). These include medicines used to treat (1) cardiovascular disease and associated risk factors: thiazide diuretics (hydrochlorothiazide (HCTZ)), statins (rosuvastatin, atorvastatin, simvastatin); (2) neurological conditions: antidepressants (sertraline, escitalopram, fluoxetine, citalopram, venlafaxine, duloxetine, amitriptyline); (3) gastrointestinal conditions: proton pump inhibitor (PPI) (esomeprazole, pantoprazole, rabeprazole, omeprazole), (4) diabetes: biguanide (metformin); (6) medicine for corticosteroids (prednisolone) and (7) respiratory conditions (salbutamol). Among the seven medicine categories, three nutrients were identified as susceptible to deficiency. These include: (1) sodium (thiazide diuretics, antidepressant), (2) vitamin B12 (metformin and PPI), (3) magnesium (PPI) and the coenzyme Q10 (CoQ10) (statin). As presented in Table 1, the search of Pubmed, identified a total of 23 papers meeting the inclusion criteria to support potentially clinically significant nutrient deficiencies associated with specific medicines used by older adults. These results are presented across five medicine classes. The sample size of the studies included for each nutrient deficiency induced by the specific medicine were substantial, with total participants ranging from 576 to 357,566.

### 3.1. Medicine-induced hyponatraemia

Table 1 show studies reporting medicine-induced hyponatraemia (MIHN) associated with thiazide diuretics and antidepressants respectively. In a large population-based cohort study utilising data from a primary care database involving 60,405 patients ≥65 years, older patients taking selective serotonin reuptake inhibitors (SSRIs) (escitalopram, citalopram, fluoxetine) showed a significant increase ($p < 0.001$) in risk of primary hyponatraemia compared to control group.[20] In a separate study, a more granulated assessment of these associations reported that only the use of tricyclic antidepressants (TCAs) significantly increased the risk of recurrent hyponatraemia among antidepressant users ($p < 0.05$) by adjusting for baseline and comorbid conditions.[21] The differences in study designs, definition of hyponatraemia used, and outcome measures may explain the differences in types of antidepressants found to increase the risk of hyponatraemia.

Certain population groups were reported to have higher risks of hyponatremia. These include advanced age, female, those with low sodium baseline levels, mild hypokalaemia and people with psychosis.[22,23] In thiazide-induced hyponatraemia (TIHN), a meta-analysis involving 4164 patients (mean age = 75 years) reported that the onset was at a mean of 19 days.[22] Other reports suggested TIHN may occur at any point after initiating diuretics.[24] Whereas the risk was highest for antidepressant-induced hyponatraemia (AD-Na) at 28 days after commencing any TCAs or SSRIs, and a shorter onset of action developed within three to five days of venlafaxine initiation.[20,25]

### 3.2. Medicines-induced B12 deficiency

The studies of vitamin B12 deficiency in older adults associated with PPI and metformin use respectively are presented in Table 1. Certain population groups were reported to have higher risk of vitamin B12 deficiency, such as older, people with diabetes taking high-dose metformin (≥2 g/d) and chronic use of metformin (≥ 3 years).[26]

### 3.3. Medicine-induced hypomagnesaemia: PPIs

Table 1 show studies of hypomagnesaemia associated with PPI use. This appears to be a class effect as it was reported to be associated with all PPIs as shown in Table 4. Certain groups of people are at higher risk of hypomagnesaemia induced by PPI such as high-dose and chronic (≥12 months) use of PPIs.[27] However, a systematic review of 18 studies involving 36 cases showed no significant risk factors were identified as PPI-induced hypomagnesaemia (PPI-HM) ($p > 0.05$).[28] This may be explained by the difficulty of recognising PPI-HM as the onset of PPI-HM can range from 14 days to 13 years as reported in a systematic review.[28] Having said that, these conflicting findings are likely due to the limited number of cases ($n = 16$) included in this review.[28]

### 3.4. Medicine-induced Coenzyme Q10 deficiency: Statins

Table 1 show studies of CoQ10 reduction induced by statins.[29–32] However, the reduction in serum CoQ10 levels was not found to be linked to the common side effects of statins, also known as statin-associated muscle symptoms (SAMS).[33]

### 3.5. Other medicine-induced nutrient deficiencies

Hypokalaemia was reported across several studies among older adults using HCTZ[34–36] and salbutamol.[37–43] Two Angiotensin Converting Enzyme - inhibitors (ACE-inhibitors), captopril and enalapril have been reported to be associated with zinc deficiency. However, these ACE-inhibitor drugs did not feature in the top 50 PBS medicines.

## 4. Discussion

### 4.1. Drug-induced sodium depletion

This review identified studies reporting sodium depletion associated with thiazide diuretic and antidepressant medication use in older people. These findings are also supported by a medicines safety update published by the Australian Therapeutic Goods Administration (TGA).[44] Sodium is a primary cation involved in regulating extracellular fluid volume and

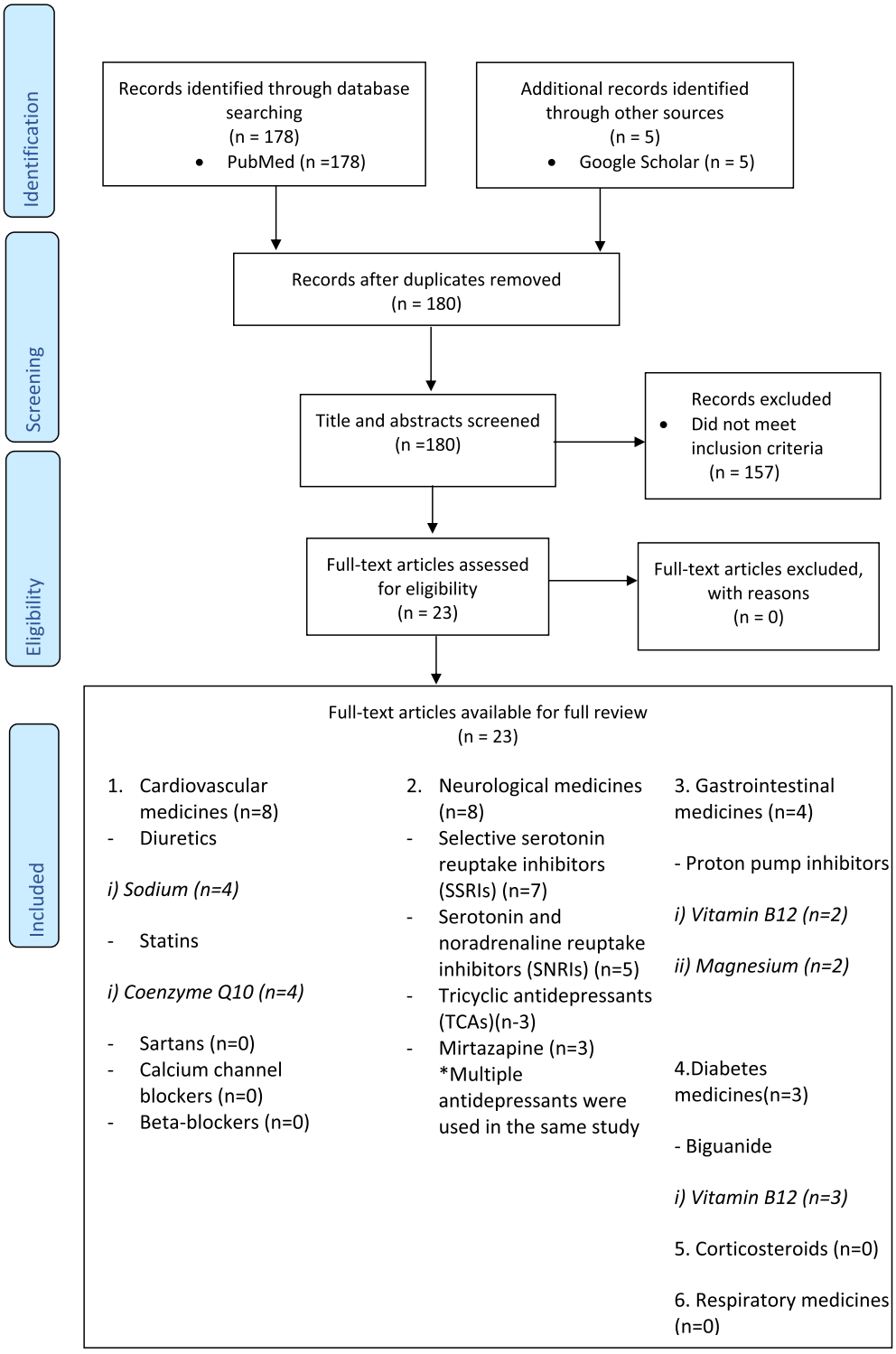


**Fig. 1.** Literature search strategy.

cellular membrane potential in humans.[22] As excessive sodium intake is commonly associated with increased risks of cardiovascular disease, particularly hypertension, the effects of low sodium levels, hyponatraemia, are often overlooked.[22] Clinical presentations of hyponatraemia are often non-specific, however, mild hyponatraemia can contribute to severe adverse clinical effects such as cognitive impairment, bone demineralisation, neurological symptoms, unconsciousness and seizures, particularly in older adults.[20–23,25,45–47]

### *4.2. Mechanism of action for medicine-induced hyponatraemia*

#### *4.2.1. Cardiovascular medicines: Thiazide diuretics*

Thiazide-induced hyponatraemia is categorised by hypovolaemia hyponatraemia, which is a clinically detectable decrease in extracellular fluid volume associated with high urinary sodium levels.[48] Patients with clinical presentations of volume depletion, namely vomiting, diarrhoea, decreased skin turgor, dry mucous membranes, increased pulse rate, and

**Table 1**
Clinical studies that evaluated nutrient levels in older people taking medications.

| Drugs class | Author (Year) | Type of studies | Study design | | | | | Risk estimate (95%, CI) or *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Aim/ characteristic | Age (years) | Drugs; duration, dose (if known) | Outcome | |
| Thiazide diuretics | Hyponatraemia | | | | | | | |
| | Jun et al. (2020)[21] | Cross-sectional study and nested case-control study | Case Vs Control 154/913 (16.9%) Vs 2383/18260 (13.1%) | i) To evaluate the use of HIMs before and after treatment for symptomatic or severe hyponatraemia and;<br><br>ii) Investigate the impact of HIMs on the recurrence of symptomatic or severe hyponatraemia in elderly already diagnosed with hyponatraemia | ≥ 65 (100%) | Thiazide and thiazide-like diuretics | Prescription rate of thiazide and thiazide-like diuretics decreased significantly 3 months before and after treatment of hyponatraemia<br><br>Risk of hyponatraemia recurrence with thiazide diuretic use<br><br>Post hoc analysis:<br>The combination use of thiazide diuretic and any HIMs (except SNRIs) showed significant association with recurrence of symptomatic or severe hyponatraemia | P < 0.001<br><br>aOR 1.51 (1.25–1.82)<br><br>aOR 1.69 (1.34–2.14) |
| | Ramirez et al. (2019)[46] | 10-year results of a prospective pharmacovigilance program | Number of patients: 387 | Detect and report on drug-induced severe hyponatraemia (<116 nM) adverse drug reaction-serum sodium (ADR-Na), whether hospital acquired, or community acquired | ≥65 (73.6%) | Thiazide (HCTZ) and thiazide-like diuretics (indapamide, chlorthalidone) | TIHN attributed to 178/786 cases (22.6% of cases) | P < 0.05 |
| | Barber et al. (2015)[22] | Meta-analysis of t | 102 articles (49 single case reports, 52 case series ranging from 2 to 1802 patients)<br><br>Total patients: 4164 | Summarise and reflect on the observation literature regarding the clinical and laboratory 42 characteristic of TIHN | Mean age = 75 (pooled estimated, 95% CI 73–77, based on 36 studies and 2840 patients) | Thiazide or thiazide-like diuretics<br><br>HCTZ<br>HCTZ + amiloride<br>HCTZ + triamterene<br>Bendroflumethiazide<br>Indapamide<br>Chlortalidone | Patients with TIHN were characterised by advanced age, female gender, inappropriate saliuresis and mild hypokalaemia<br><br>TIHN was first detected at mean 19 days | Pooled estimate Mean: 95%, CI<br><br>Advanced age: 75 (73–77)years (based on 36 studies, 2840 patients)<br><br>Female: 79% women (74–82%) (based on 43 studies, 3269 patients)<br><br>Urinary sodium concentration: 64 mM (47-81 mM) (based on 13 studies, 98 patients)<br><br>Mild hypokalaemia: 3.3 mM (3.0–3.5 mM) (based on 28 studies, 902 patients)<br><br>19 days: (8–30) $I^2$ = 97% based on 19 studies and 466 patients |

*(continued on next page)*

**Table 1** (*continued*)

| Drugs class | Author (Year) | Type of studies | Study design | | | | | Risk estimate (95%, CI) or *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Aim/ characteristic | Age (years) | Drugs; duration, dose (if known) | Outcome | |
| Statins | Coenzyme Q10 | | | | | | | |
| | Chitose et al. (2014)[29] | Prospective, randomized, open-label, clinical trial | Total ($n$ = 75)<br>Rosuvastatin ($n$ = 38)<br><br>Atorvastatin ($n$ = 37) | Compare the effects of hydrophilic (rosuvastatin) and hydrophobic (atorvastatin) statins on patients with ST-elevated myocardial infarction (STEMI) who had received emergency reperfusion therapy. | Mean age:<br><br>Rosuvastatin group = 64<br><br>Atorvastatin group = 65<br><br>$P$ = 0.54 | 6 months treatment of:<br>Rosuvastatin (5 mg/day)<br>Atorvastatin (10 mg/day) | Serum CoQ10 levels significantly lower after 6 months treatment with rosuvastatin and atorvastatin | P < 0.001 |
| | McMurray et al. (2010)[30] | Clinical trial | 1191 | To determine whether CoQ10 is an independent predictor of prognosis in heart failure in patients with ischemic systolic heart failure enrolled in CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) | Mean age = 73<br>(≥ 60 years were included in this study) | 3 months of:<br>Rosuvastatin (10 mg/d) or placebo | Rosuvastatin significantly reduced serum CoQ10 concentration (but no interaction was found between CoQ10 and the effects of rosuvastatin) | $P$ < 0.0001 |
| | Mabuchi et al. (2005)[31] | Clinical trial | 14 | Japanese hypercholesterolemic (≥ 220 mg/dL) patients | Mean age = 66 | 8 weeks of:<br>Atorvastatin (10 mg/d) | Atorvastatin significantly reduced the total CoQ10 levels in all patients. | P < 0.0001 |
| | Rundek et al. (2004)[32] | Prospective double-blinded, placebo control study | 34 | To test the hypothesis that<br><br>i) short-term exposure of atorvastatin for 30 days might significantly decrease plasma CoQ10 levels compared with pre-treatment levels.<br><br>ii) decrease plasma CoQ10 levels might be rapid and already detectable 2 weeks after initiation of treatment<br><br>in patients with hypercholesterolemic | Mean age = 70<br>(≥ 45 years were included in this study) | 14 days and 30 days of:<br>Atorvastatin calcium (80 mg/d) | Atorvastatin significantly reduced plasma CoQ10 concentration at 14 days and 30 days | 14 days: $P$ < 0.001<br>30 days: $p$ < 0.001 |
| | Oranje et al. (2001)[109] | Double-blind randomized placebo-controlled study | 19 | To investigate whether atorvastatin has a favourable effect on LDL oxidation in normocholesterolemic in patients with type 2 diabetes | Atorvastatin group = 64<br><br>Placebo group = 63 | 3 months of:<br>Atorvastatin (10 mg/d) | Atorvastatin significantly reduced plasma CoQ10 | $P$ = 0.009 |
| Antidepressant | Hyponatraemia | | | | | | | |
| | Jun et al.[21] | Cross-sectional study and nested case-control study | Case vs Control<br><br>SNRI:<br>22/913 (2.4%) vs 322/18260 (1.8%)<br><br>SSRIs<br>48/913 (5.3%) vs 995/18260 (5.5%)<br><br>TCAs<br>59/913 (6.5%) vs 932/18260 (5.1%) | i) Investigate the impact of HIMs on the recurrence of symptomatic or severe hyponatraemia in elderly already diagnosed with hyponatraemia | ≥ 65<br>(100%) | SNRIs<br>SSRIs<br>TCAs | After adjusting for baseline comorbid conditions, only the use of TCAs significantly increased the risk of recurrent hyponatraemia<br><br>Post hoc analysis:<br>The combination use of thiazide diuretic and any HIMs (except SNRIs) showed significant association with recurrence of symptomatic or severe hyponatraemia | aOR<br>TCAs<br>1.36 (1.03–1.81)<br><br>aOR<br>1.69 (1.34–2.14) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gandhi et al. (2017)[110] | A retrospective population-based, matched-cohort study | 450/138246 (0.33%) | To investigate the 30-day risk for hospitalisation with hyponatraemia in elderly who were newly dispensed a second-generation antidepressant in a non-hospitalised setting | Mean age = 76 (100% ≥ 65) | User group<br>1 of the 9 s-generation antidepressants<br><br>(citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, venlafaxine, duloxetine, mirtazapine or sertraline) | Primary outcome:<br>5-fold increase in 30-day risk for hospitalisation with hyponatraemia compared to non-use (all second-generation study antidepressants except venlafaxine)<br><br>Subpopulation with serum sodium (≤132 mmol/L) showed consistent association with primary findings<br><br>Absolute increase in 30-day incidence of hyponatraemia is low | RR<br>5.46 (4.32–6.91)<br><br>RR<br>4.23 (2.50–7.19) |
| Manness et al. (2013)[23] | Cross-sectional study with prospectively collected data | 32/345 (9.3%) | To describe the characteristic of hyponatraemia in elderly users of antidepressants, to determine the prevalence and risk factors for hyponatraemia, and to identify the underlying mechanisms | Mean age = 76 (≥ 60 were included in this study) | ≥ 4 days to 6 months of:<br><br>TCA<br>SSRIs<br>Venlafaxine<br>Mirtazapine<br>Monoamine oxidase[111] inhibitors | The prevalence of hyponatraemia to all type of study antidepressant-induced was 9.3%, independent of the duration and type of study antidepressant used<br><br>Risk factors: | AR<br>1.31% (0.87%–1.75%)<br>9.3% ($P$ = 0.85)<br>(11.5% TCA<br>10.2% SSRI<br>8.6% venlafaxine<br>5.6% mirtazapine)<br><br>aOR:<br>History of hyponatraemia<br>11.17 (2.56–40.41)<br>Weight < 60 kg<br>3.47 (1.19–10.13)<br>Psychosis<br>3.62 (1.12–11.73) |
| Coupland et al. (2011)[20] | Cohort study (using a large primary care database) | 1114/60405 (1.84%) | To establish the relative safety and balance of risks for antidepressant drugs in older people, hyponatraemia was one of the 13 outcome measures | ≥ 65 (100%) | TCA (amitriptyline, dosulepin, lofepramine, trazodone)<br><br>SSRI (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)<br><br>Venlafaxine<br><br>Mirtazapine | Overall, the risk of hyponatraemia was significant associated only with use of SSRIs<br><br>Risk of hyponatraemia increased significantly after adjusting potential confounding variables | aHR<br>1.52 (1.33–1.75); $p$ < 0.001<br><br>aHR<br>Escitalopram<br>2.08 (1.40–3.09); $p$ < 0.01<br>Fluoxetine<br>1.70 (1.38–2.09); p < 0.01<br>Citalopram<br>1.65 (1.38–1.97); p < 0.01 |
| Roxanas et al. (2007)[25] | Prospective practice-based study | 10/58 (17.2%) | To determine the incidence of hyponatraemia induced by venlafaxine, mechanism of action, and to evaluate a simple management | Mean age = 76 (100% ≥ 65) | Venlafaxine | Hyponatraemia was developed within 3–5 days after initiation of venlafaxine | 17.2% |

(continued on next page)

**Table 1** (*continued*)

| Drugs class | Author (Year) | Type of studies | Study design | | | | | Risk estimate (95%, CI) or *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Aim/ characteristic | Age (years) | Drugs; duration, dose (if known) | Outcome | |
| | Kirby et al. (2002)[112] | Retrospective controlled analysis | Treated group/ control group 74/125<br><br>Case vs Control 29/74 (39%) vs 13/125 (10%) | To determine the prevalence of hyponatraemia associated with SSRI and venlafaxine use in elderly psychiatric patients compared to non-user | Mean age = 74 (ranging from 60 to 100) | SSRI (paroxetine, sertraline, fluoxetine, fluvoxamine) venlafaxine | Risk of hyponatraemia was 5.6 times higher in SSRI/venlafaxine users in elderly compared to non-user<br><br>Risk of hyponatraemia in SSRI users (when venlafaxine was reclassified as non-SSRI) was 2.7 times that of non-user | OR 5.6 (2.6–11.6); $p < 0.001$ (29% Sertraline, 32% paroxetine, 71% venlafaxine) |
| | Movig et al. (2002)[45] | A case-control study | Elderly: 49/107 (46%)<br><br>Of these 49, Case vs control 19/29 (65%) vs 30/78 (38%) | To estimate in psychiatric in- and out-patients, the risk of hyponatraemia associated with the use of SSRIs compared with the use of other antidepressants, and to identify risk factors of hyponatraemia | Mean = 68 (Only 46% were aged ≥65, however we included this study due to stratified analysis and statistical tests for interaction were performed in elderly ≥65 years) | SSRIs | Daily clinical practise older (≥65 years) psychiatric in- and outpatients using SSRIs more frequently developed hyponatraemia then users of other classes of antidepressant drugs<br><br>Risk factor:<br>Elderly (≥ 65 years) had more than 6-fold increased risk for SSRI-induced hyponatraemia than younger patients<br><br>Concurrent use of SSRIs and diuretics in elderly (≥65 years) compared to non-use | OR 3.3 (1.3–8.6)<br><br>aOR 6.3 (1.0–41)<br><br>OR 13.5 (1.8–101) |
| | Wilkinson et al. (1999)[113] | Retrospective descriptive and case control study | 14/845<br><br>Fluoxetine (11/14)<br>Paroxetine (3/14) | To establish the incidence, risk factors and time course of the development of hyponatraemia induced by fluoxetine/paroxetine | Mean age = 81 (100% ≥65) | 501 people were taking over 3.5 years of fluoxetine<br><br>344 people were taking 2.5 years of paroxetine | The incidence of hyponatraemia induced by fluoxetine/paroxetine<br><br>Risk factors:<br><br>Mean of hyponatraemia detected at day | 4.7/1000 people treated/year (Fluoxetine: 6.3/1000 Paroxetine: 3.5/1000)<br><br>ORs*<br>Low body weight (<60 kg) 0.92 (0.86–0.99); $p = 0.04$<br>Older age 1.10 (1.23–0.99) $p = 0.09$<br><br>19 (range 4–64)<br>79% occurred within the first 3 weeks |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Proton pump inhibitors | Vitamin B12 deficiency | | | | | | | |
| | Rozgony et al. (2010)[114] | Clinical study | Case/Control 11/16 (69%) vs 2/18 (11%) | i) To determine the association between institutionalised older adults with PPI use and non-PPI user;<br><br>ii) the frequency of vitamin B12 deficiency after a cyanocobalamin nasal spray treatment in PPI user compared to non-user | Mean age = 82 (ranging from 63 to 89) | Omeprazole<br>Esomeprazole<br>lansoprazole<br>(≥12 months) | Significant difference between the frequency of vitamin B12 deficiency between PPI(≥12 months) and non-PPI groups<br><br>Significant difference in the frequency of vitamin B12 deficiency after 8 weeks of cyanocobalamin (500 μg/week) nasal spray treatment in PPI (≥12 months) user | $P = 0.006$<br><br>$P = 0.012$ |
| | Dharmarajan et al. (2008)[115] | Cross-sectional study | Total ($n = 542$ of PPI or H2RA)<br><br>PPI: 141/524 | To examine the relationship between serum vitamin B12 levels in older adults on H2RA or PPI use over 6 years | 81 (ranging from 60 to 102 years) | PPI | Significant decreased of serum B12 levels with increasing duration of PPI use (but not prolonged use of H2RA)<br><br>Concomitant use of oral B12 supplementation (7-50μg/day) slowed but did not prevent the decline in B12 status during prolonged PPI use | $p < 0.00005$<br><br>$p = 0.0125$ |
| | Hypomagnesemia | | | | | | | |
| | Srinutta et al. (2019)[27] | Meta-analysis | 16 observational studies; 131,507 patients in 13 cross-sectional studies, 2 case-control studies, and 1 cohort study | To evaluate all observational studies to determine whether there was an association between PPI dose or treatment duration and the development of hypomagnesemia | Pooled mean age = 64 (mean age ranging from 48 to 80)<br><br>No sub-analyses in ≥65 | Omeprazole<br>Pantoprazole<br>Lansoprazole<br>Esomeprazole<br>Rabeprazole<br>dexlansoprazole | Risk of hypomagnesemia with PPI use among PPI users relative to non-users<br><br>Association between high-dose PPI use and hypomagnesemia relative to low-dose PPI use<br><br>Association between low-dose PPI use and hypomagnesemia relative to non-PPI use | Pooled unadjusted OR 1.83 (1.26–2.67); $p = 0.002$<br><br>Pooled adjusted OR 1.71 (1.33–2.19); $p < 0.001$<br><br>Pooled adjusted OR 2.13 (1.26–3.59); $p = 0.005$<br><br>Pooled adjusted OR 2.61 (1.44–4.71) $p = 0.001$ |
| | Hess et al. (2012)[28] | Systematic review of case reports | 36 cases | i)To investigate serum magnesium dynamics in trials drug withdrawal and re-challenge;<br><br>ii)Profile 'patient at risk' of PPI-induced hypomagnesemia | 67 (ranging from 30 to 83) | Omeprazole<br>Esomeprazole<br>Pantoprazole<br>Lansoprazole<br>Rabeprzole | Primary endpoint:<br><br>Normalisation of serum magnesium by withdrawal of the PPI and/or other changes in treatment<br><br>Secondary endpoint:<br><br>Specific risk profile in patients with hypomagnesemia (hypertensive, diuretics users, non-diuretics users, women and men) | Primary endpoint:<br><br>PPI-induced hypomagnesemia occurred after 5.5 years (median) of PPI use, (ranging from 14 days to 13 years);<br>Discontinuation of PPIs resulted in fast recovery from PPI in 4 days and re-challenge led to reoccurrence within 4 days.<br>*Secondary endpoint:*<br>$P > 0.05$. |

*(continued on next page)*

**Table 1** (*continued*)

| Drugs class | Author (Year) | Type of studies | Study design | | | | | Risk estimate (95%, CI) or *P*-value |
|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Aim/ characteristic | Age (years) | Drugs; duration, dose (if known) | Outcome | |
| Anti-diabetics | Vitamin B12 deficiency | | | | | | | |
| | Yang et al. (2019)[26] | Meta-analysis | 31 studies were included in the meta-analyses | To perform a meta-analyses of all available studies on associations between metformin use and vitamin B12 levels, anaemia, and neuropathy in patients with diabetes. | NR (Age-based sub-analysis >60) | Metformin | Risk of B12 deficiency in patients with diabetes taking metformin compared to non-metformin user | Pooled risk ratios 2.09 (1.49–2.93); $p < 0.0001$ ($I^2 = 64\%$) |
| | | | | | | | Risk of B12 deficiency in patients with diabetes taking metformin (mean duration ≥3 years) compared to non-metformin user | Pooled risk ratios 2.88 (1.95–4.26); $p < 0.00001$ ($I^2 = 0\%$) |
| | | | | | | | Risk of B12 deficiency in patients with diabetes taking metformin (mean daily dose ≥2000 mg) compared to non-metformin user | Pooled mean differences −85.47 (−106.92 to −64.03); p < 0.00001 ($I^2 = 83\%$) |
| | | | | | | | Age-based sub-analysis: ≥ 60 years showed a significant serum B12 concentrations than <60 years | Pooled risk ratios 3.26 (1.78–5.97); $p = 0.0001$ ($I^2 = 0\%$) |
| | Wong et al. (2018)[116] | Retrospective study | 94/174 | Evaluate the association between metformin use and vitamin B12 deficiency in elderly living in the long term care institutions. | 80 | Metformin | Vitamin B12 deficiency associated with metformin use compared to non-metformin use; non-diabetes | 53.2% in patients with diabetes compared to 31% non-metformin use (p < 0.001); 33.3% non-diabetes (p < 0.001) |
| | | | | | | | Association between vitamin B12 deficiency and metformin dose use of ≥1500 mg/day compared to <1000 mg/day | Adjusted odds ratio 2.72 (1.11–6.7); $p = 0.029$ |
| | | | | | | | Association between vitamin B12 deficiency and metformin duration of >4 years compared to <2 years | Adjusted odds ratio 3 (1.35–6.68); $p = 0.007$ |
| | Aroda et al. (2016)[117] | RCT | Metformin/ Placebo<br><br>DPPOS Year 1 = 859/856<br><br>DPPOS Year 9 = 753/736 | To assess the risk of B12 deficiency with metformin use in the DPP/DPPOS | DPP baseline = 51<br>DPPOS Year 1 = 57<br>DPPOS Year 9 = 66 | Metformin | Vitamin B12 deficiency per year of total metformin use compared to placebo | Adjusted OR 1.13 (1.06–1.20) |
| | | | | | | | Prevalence of B12 deficiency of Metformin Vs placebo at 5 years (but not at 13 years) | 4.3% vs 2.3%; p = 0.02 (7.4 vs 5.4%; $p = 0.12$) |

orthostatic decrease in blood pressure, should be considered as hypovolemic.[48] Thiazide diuretics work by reducing sodium reabsorption in the kidneys and decreasing fluid retention by inhibiting $Na^+/Cl^-$ channels in the proximal segment of the distal convoluted tubule (DCT).[49] This increases sodium delivery to the late DCT and collecting duct.[49]

#### 4.2.2. Neurological medicines: Antidepressants

Euvolaemia hyponatraemia occurs in AD-Na.[50] When plasma osmolality rises above the normal range (290–300 mmol/kg), antidiuretic hormone (ADH) will be released to activate water channels in the kidney to enhance water reabsorption, which then restores the plasma osmolality.[25] Conversely, ADH release is suppressed when plasma osmolality falls below 285 mmol/kg.[25] In euvolaemia hyponatraemia, ADH release is not suppressed even when plasma osmolality levels fall below said levels. This condition is more commonly known as syndrome of inappropriate antidiuretic hormone (SIADH).[25,50]

Beside SIADH, a separate study investigating the relationship between ADH and osmolality postulated a different mechanism for AD-Na, known as nephrogenic syndrome of inappropriate antidiuresis.[23]This mechanism was characterised by an increase in water channels expression, which increases the sensitivity of the kidney to ADH even when ADH secretion is normal.[23] Findings from this study would then impact the choice of treatment, as vasopressin receptor antagonists would be ineffective given they only work in the presence of unsuppressed ADH (SIADH).[23]

#### 4.2.3. Screening and monitoring of medicine-induced hyponatraemia

The normal range of serum sodium concentration ([Na+]) for adults aged ≥18 years is 135-145 mmol/L.[51] Mild hyponatraemia is a condition where [Na+] falls below 135 mmol/L, whereby individuals are generally asymptomatic.[50] Severe hyponatraemia is characterised by a decrease in [Na+] to levels below 120 mmol/L, with individuals often presenting with cerebral symptoms such as confusion and lethargy.[50] Current practice guidelines recommend serum [Na+] evaluation in individuals with high risk of TIHN on day four and day ten; otherwise, check within 2 weeks after initiation of thiazide therapy.[52] For antidepressants, the Adverse Drug Reactions Advisory Committee (ADRAC) within the TGA recommends routine monitoring of older patients at risk of hyponatraemia, particularly those presenting with neuropsychological symptoms within the first month of SSRI use or within three to five days of venlafaxine commencement.[25,53,54] Due to the variations in timing for the onset of hyponatraemia, monitoring for symptoms at a range of time points would be prudent.

#### 4.2.4. Management of medicine-induced hyponatraemia

Effective clinical management of hyponatraemia is important as it has been shown to lead to a reduction in overall mortality, notably in older adults.[55] Management is determined by the cause, clinical context and severity of the condition. The conventional treatment is to eliminate other apparent causes and withdraw the implicated medicine where safe and appropriate to so.[24,50] In acute (<48 h), severe and symptomatic conditions, intravenous (IV) 3% sodium chloride solution is generally needed.[56,57] However, rapid infusion should be avoided as it may cause osmotic demyelination which can result in detrimental effects to the central nervous system.[50] Different management approaches for categories of hyponatraemia are outlined in a number of guidelines, including Australian[50], American[57] and European[56] guidelines.

The Screening Tool of Older People's Prescriptions (STOPP) criteria in 2015 recommends avoiding thiazide diuretics or SSRIs in patients with [Na+] <130 mmol/L as said medicines increase the risk of hyponatraemia more than sixfold.[58] This is consistent with a previous study which reported that concurrent use of diuretics and SSRIs in older adults resulted in an additive effect on hyponatraemia, with an odds ratio of 13.5 in stratified and interaction analyses.[45] Another study evaluating national insurance claim databases confirmed an association between the use of ≥2 MIHN (especially thiazide diuretics) and increased risks of recurrent hyponatraemia, independent of the primary causes of hyponatraemia.[21]

#### 4.2.5. Drug-induced Vitamin B12 depletion

This review identified studies reporting metformin and proton pump inhibitors were associated with vitamin 12 deficiencies in older people. Vitamin B12, also known as cyanocobalamin, is a water-soluble vitamin.[59] Humans obtain vitamin B12 primarily from animal sources such as meat, eggs and dairy products.[59] Adequate vitamin B12 is essential because it plays a vital role in erythrocyte production, synthesis of fatty acids in myelin and DNA synthesis, all which are essential for normal blood and neurological function.[60,61] However, recognising and diagnosing vitamin B12 deficiency can be challenging as symptoms are diverse and may take up to 10 years to manifest due to the storage of vitamin B12 in the liver.[26,62] Vitamin B12 deficiency can result in haematological, neuropsychiatric and digestive disorders.[63] Haematopoietic changes such as skin pallor, low energy, low exercise tolerance, shortness of breath and palpitations are primary indicators in the diagnosis of vitamin B12 deficiency, as the signs are more apparent when compared to neurological disorders.[64] Neuropsychiatric symptoms associated with vitamin B12 deficiency include paraesthesia, gait abnormalities, autonomic dysfunction, depression, psychosis and confusion.[64] In older adults, it is also associated with a significant risk of brain atrophy and decline in cognitive performance, and neurological symptoms such as irreversible peripheral neuropathy.[65] Despite these significant clinical implications, vitamin B12 deficiency may be asymptomatic with some patients only presenting with low serum levels.[65] Conversely, neurological symptoms may be present despite serum vitamin B12 being over 150 pmol/L.[63] It is important to note that vitamin B12 deficiency is often linked to folate deficiency.[65] This 'co-deficient' state is associated with an increased risk of hyperhomocysteinemia, and cardiovascular disease.[65]

### 4.3. Mechanism of action of medicine-induced vitamin B12 deficiency

#### 4.3.1. Gastrointestinal medicines: PPIs

Proton pump inhibitors reduce the secretion of hydrochloric acid and pepsin in the stomach, which impairs vitamin B12 absorption.[66] Gastric acid is required to release the protein bounded vitamin B12, which will subsequently bind to intrinsic factors to form an IF-B12 complex.[66] Subsequently, the IF-B12 complex binds to the ileal cubilin receptors, which then initiates calcium-dependent endocytosis leading to uptake of vitamin B12.[64,67] Synthetic forms of vitamin B12 added to fortified foods and dietary supplement are already in free bioavailable form, therefore the aforementioned step does not occur.[61]

#### 4.3.2. Diabetes medicines: metformin

Metformin displaces calcium cations by repulsive forces.[67] This inhibits the calcium-dependent IF-B12 complex from binding to the ileal cubilin receptor, thus inhibiting the endocytosis process. This was found in a calcium supplementation study conducted among people with type 2 diabetes mellitus on metformin (for 3 months), where participants were given 1.2 g oral calcium carbonate daily for one month.[68]

Another proposed mechanism is the overgrowth of bacteria caused by increased pH in the stomach induced by PPIs.[67] This creates competition for vitamin B12, further reducing vitamin B12 bioavaibility.[67]

#### 4.3.3. Screening and monitoring of medicines-induced vitamin B12 deficiency

There is no 'gold standard' for the diagnosis of vitamin B12 deficiency. Common clinical presentations are usually a combination of low serum vitamin B12 with elevated serum homocysteine and/or serum/urine methylmalonic acid (MMA).[63] Serum vitamin B12 of >200 pmol/L is considered the normal range of serum vitamin B12.[69] However, local laboratory guidelines should be referred to for accurate reference of vitamin B12 to inform diagnosis of deficiency. According to reports from the WHO in 2008, vitamin B12 deficiency is classified by plasma levels below 150 pmol/L (203 pg/mL).[70] However, some studies suggested a higher cut-off value of 220-258 pmol/L in older adults, in conjunction with elevated serum homocysteine and/or MMA levels.[65]

In addition to MMA and homocysteine, a decrease in serum holotranscolobalamin level is also considered to be an early marker for vitamin B12 deficiency. However, it is not commonly used in practice due to cost and test availability concerns.[63]

To date, the Australian Health Department has not published guidelines for the clinical management of vitamin B12 with the majority of literature referring to American and British guidelines and recommendations. Interestingly, a recent study in 2019 found that only 44% of physicians are familiar with the current guidelines of the American Diabetic Association (ADA) with regards to vitamin B12 Screening.[71] The ADA recommends periodic vitamin B12 screening in patients on long-term metformin, particularly in older adults, and those with anaemia or peripheral neuropathy.[72] This is supported by a recent meta-analysis which recommends annual assessments of vitamin B12 levels in patients taking metformin.[26] Vitamin B12 supplementation should be considered in all cases as mentioned above.[72] Table 2 shows the reference values to be considered as vitamin B12 deficiency that commonly used in clinical practice.

#### 4.3.4. Management of medicine-induced vitamin B12 deficiency

Conventional treatment for vitamin B12 deficiency involves intramuscular (IM) administration of cyanocobalamin and hydroxocobalamin, especially in individuals with pernicious anaemia, malabsorption or neurological symptoms.[65,73] It is recommended to correct vitamin B12 within 6–12 months of cognitive impairment to achieve optimal response.[65] Initial IM administration of both cyanocobalamin and hydroxocobalamin is typically 1 mg on alternate days for 2 weeks.[50] As the conversion of hydroxocobalamin to active enzymes is easier compared to cyanocobalamin and retained in the body longer, the maintenance dose of the former is every 3 months instead of every month of the latter.[65]

There is inconclusive evidence of using oral vitamin B12 to treat vitamin B12 deficiency.[73,74] In fact, current clinical practice in Australia and England requires giving IM vitamin B12 for initial treatment; and oral vitamin B12 can be considered for maintenance or correction of mild/moderate cases which are asymptomatic.[73,74] Therefore, an individual's ability to absorb vitamin B12, and the severity of the deficiency should be taken into consideration when determining the route of administration of vitamin B12 supplementation.[75]

#### 4.3.5. Magnesium

This review identified magnesium deficiency associated with proton-pump inhibitor use in older people. Magnesium is a cofactor for more than 300 enzymatic reactions in human physiology including protein synthesis, muscle and nerve function.[76,77] Magnesium is vital in regulating the active transport of calcium and potassium ions across cell membranes that are involved in nerve conduction, muscle contractions and the rhythm of the heart.[77] Magnesium is abundant in both plant and animal foods such as unrefined grains, green leafy vegetables, eggs and meats.[76] Healthy adults typically have 25 g magnesium stored in the body, most of which is present in bones, muscle and soft tissue.[78] Mild hypomagnesaemia is typically asymptomatic.[50] However, severe hypomagnesaemia can result in hypokalaemia and hypocalcaemia due to the disruption of mineral homeostasis, which can lead to life-threatening consequences such as arrythmias, tetany and seizures.[79]

#### 4.3.6. Mechanism of action of PPIs-induced hypomagnesaemia

Magnesium status is regulated in the body through a balance between gastrointestinal absorption and renal excretion.[80] However, magnesium excretion or 'magnesium wasting' was not demonstrated in a study measuring urinary magnesium over 24 h, in fact, low urinary magnesium was found.[80] Here, researchers have suggested that reduced gastrointestinal absorption is responsible for PPI-HM due to decreased activity of transient receptor potential melastatin (TRMP) 6.[28,80]

TRMP 6 is a protein with high affinity for magnesium, acting as a gatekeeper of magnesium absorption.[80] Increasing the pH of the lumen by PPIs leads to a decrease in TRPM 6 activity, negatively impacting magnesium absorption.[80] This was further supported by an in-vitro study which demonstrated that cations such as $Mg^{2+}$ are transported through layers of colonic cells and this activity is reduced in PPI users.[81]

#### 4.3.7. Screening and monitoring of PPI-induced hypomagnesaemia

The normal range of serum magnesium levels ([Mg2+]) for adults aged ≥18 years is 0.80–1.10 mmol/L.[50] Levels below 0.8 mmol/L indicate mild magnesium deficiency, whereas levels below 0.4 mmol/L indicate severe deficiency.[50] However, employing serum [Mg2+] in the diagnosis of hypomagnesaemia is not recommended in clinical practice due to low extracellular [$Mg^{2+}$](≤1%), which does not accurately indicate total body magnesium stores.[80] In Australia the National Prescribing Service (NPS) recommends monitoring for hypomagnesaemia in patients with other factors predisposing them to hypomagnesaemia.[82] This aligns with the 'Expert Review and Best Practice Advice from 2017 American Gastroenterological Association (AGA)' that suggests that routine screening and monitoring of serum [$Mg^{2+}$] in all patients taking PPIs on a long-term basis is not needed.[83] This is also consistent with findings from a 2019 meta-analysis study (131,507 participants, pooled mean age of 64 years), which concluded that monitoring serum [$Mg^{2+}$] in long-term or high-dose PPI users is not required.[27] If monitoring is warranted, urinary magnesium measurements should also be taken to assure renal magnesium retention, as urinary magnesium declines prior to serum [$Mg^{2+}$], act as an early indicator of PPI-HM.[28] Overall, recommendations on the appropriateness of [$Mg^{2+}$] monitoring is conflicting. Both the TGA[84] and the Food and Drug Administration (FDA)[85] highlighted the importance of awareness on risks of long-term PPI use and its adverse effects, notably hypomagnesaemia. Here, the FDA recommends checking serum [$Mg^{2+}$] before PPI initiation in patients who are expected to be on these medications for long term.[85]

#### 4.3.8. Management of PPI-induced hypomagnesaemia

There are currently no standard practice guidelines on managing patients with PPI-HM. However, both the TGA and FDA recommend discontinuation of PPI and the initiation of magnesium supplementation in individuals with PPI-HM.[84,85] This is supported by a systematic review (mean age = 67 years) which reported that PPI discontinuation resulted in rapid recovery from PPI-HM in 4 days, and re-challenging led to

**Table 2**
Summary of reference ranges for vitamin B12 deficiency.

| Assays for vitamin B12 deficiency | Total serum level of Vitamin B12 | MMA | HCy |
|---|---|---|---|
| Normal range | 200-900 pmol/L | <400 nmol/L | Male: 6–15 nmol/mL<br>Female: 5–12 nmol/mL |
| Cut-off values considered as deficient | 220-258 pmol/L (46) | >3 standard deviations above the mean in normal subjects has a sensitivity of 98.4% in diagnosis of B12 deficiency (46) | >65 years in folate-fortified: 16 nmol/mL (117)<br>>65 years in non-folate-fortified communities: 20 nmol/mL(117)<br>>3 standard deviations above the mean in normal subjects has a sensitivity of 95.9% in diagnosis of B12 deficiency(46) |

Abbreviation: MMA = Methylmalonic acid; HCy = Homocysteine.

reoccurrence within 4 days.[28] Therefore, HCPs should be aware of the potential risk of hypomagnesaemia whenever PPI is prescribed to the patient, as withdrawal of PPI may help in the diagnosis of the underlying condition. Others have recommended considering histamine H2 receptor antagonist (H2RA) instead of PPI to prevent hypomagnesaemia.[28] If the acid-suppressive effect is insufficient, alternate day dosing of PPI in combination with a H2RA and magnesium supplementation may be helpful.[28,86]

#### 4.3.9. Coenzyme Q10

Coenzyme Q10 (CoQ10) is technically not a nutrient, rather a fat-soluble 'vitamin-like' molecule present in all cellular membranes within the human body.[87] It is obtained from dietary intake and endogenous synthesis.[87] CoQ10 is essential for energy metabolism and stabilisation of muscle cell membranes.[88,89]

#### 4.3.10. Mechanism of action of CoQ10 reduction induced by statins

Statins reduce serum CoQ10 levels by inhibiting the enzyme 3-hydro-3-methylglutaryl Coenzyme-A (HMG-CoA) reductase, a rate-limiting step in the process of cholesterol biosynthesis.[90] This then inhibits the conversion of mevalonate to CoQ10.[90] The reduction in serum CoQ10 levels and the role of CoQ10 in mitochondrial energy production prompted the hypothesis that statin-induced CoQ10 deficiency is associated with SAMS.[91]

#### 4.3.11. Screening and monitoring of coenzyme Q10 deficiency

As mentioned, the association between serum CoQ10 and SAMS is inconclusive, which may be reflected in CoQ10 not being routinely measured in clinical practice.[91] However, creatine kinase and transaminases levels should be measured at baseline and when patient are presenting with SAMS.[92] In fact, creatine kinase levels are generally used as an indicator to assess SAMS in clinical practice.[93]

#### 4.3.12. Management of statin-related muscle symptoms

In contrast to magnesium, vitamin B12 and sodium, the current evidence does not support that supplementation with CoQ10 is of benefit in managing a statin induced depletion.[94] This is supported by current guidelines, outlining the lack of evidence of benefit for CoQ10 supplementation in SAMS.[95,96] However, a 2018 meta-analysis[97] conducted on 575 participants (age ranging from 43 to 65 years) concluded that CoQ10 supplementation showed improvement in SAMS, which contradicts with findings from the more recent meta-analysis.[94] Therefore, large high quality randomized controlled trials are required to resolve these conflicting results regarding the benefits of supplementing CoQ10 in patients with SAMS. To help inform clinical decisions about the management of SAMS, HCPs can refer to clinical tools such as the NPS Medicinewise.[93]

Other medicine induced deficiencies.

While not making the Top 50 PBS drugs used by Australians, furosemide is one of the highest subsidised prescriptions in Australia and also associated with several nutrient depletions including hypokalaemia, hyponatraemia, hypomagnesaemia and hypocalcaemia.[14] Both HCTZ and salbutamol have been in use for greater than 20 years and the mechanism of thiazide diuretics induced hypokalaemia is well understood.[49] The inhibition of $Na^+/Cl^-$ co-transporter by thiazide diuretics at the early DCT causes more $Na^+$ to reach the $Na^+/K^+$ exchanger at the late DCT and the collecting duct. This increases the reabsorption of $Na^+$, which leads to excretion of $K^+$ at the late DCT.[49]

For salbutamol, all subjects in seven studies found in the primary literature were aged $<40$ years. Salbutamol-induced hypokalaemia could be explained to be a result of stimulation of membrane-bound beta-2 adrenoceptor linked $Na^+/K^+$ ATPase in skeletal muscle, leading to an influx of $K^+$ into cells.[40] The lack of older patients included in these studies may have been due to the serious adverse events (sudden death, increased cardiac arrythmias) associated with hypokalaemia as reported in previous studies.[36] Given that thiazide diuretics are first-line treatments for uncomplicated hypertension in older ($\geq 65$ years), it is important to understand and investigate the implications for older populations potassium status.[98–100]

The ACE-inhibitors perindopril and captopril were on the top 50 PBS medicines but no studies reporting zinc deficiency in an older population have been reported to include in this review. Only captopril has been reported to be associated with zinc deficiency in other populations.[101–103] This could be explained by the variations in chemical structures of ACE-inhibitors. Captopril is a sulfhydryl-containing ACE-inhibitors whereas perindopril and ramipril are both dicarboxyl-containing ACE-inhibitors.[101] The thiol-radical group in captopril can chelate serum zinc, inducing zincuria.[102,103] This reduces plasma zinc levels, which then leads to a shift of intracellular zinc out of body cells, further enhancing the zincuric effect.[104] Individuals using ACE-inhibitors (specifically captopril) and thiazide diuretics concurrently may be more prone to zinc depletion due to reduced zinc reabsorption in distal tubules.[105] Concurrent use of ACE-inhibitors and thiazide diuretics is a common first line approach in a hypertensive population.[106] Comorbidities such as diabetes and chronic heart failure further increase the risk of zinc depletion.[107] While we may speculate that this is relevant to older people, participants involved in these aforementioned studies were aged $<65$ years.[108]

### 4.4. Limitations

Due to the rigorous inclusion criteria, potentially relevant studies could have been omitted in the search process. By limiting our inclusion to adults $\geq 65$ years, generating a smaller number of studies than those published on this topic in younger age groups, we may not have captured the full extent of these nutrient deficiencies. However, some studies retrieved and included a range of age groups including those $\geq 65$ years. In those cases, it was decided that where a mean age of a cohort was greater than 65 years of age, the data were included in the review. Importantly, when including results from studies with a range of ages including people as young as 30 years of age, overall, this did not change the association between the medicine-nutrient deficiencies reported here for older adults.

Secondly, a risk of notoriety bias may have been introduced by our focussed search of secondary information resources, followed by specific follow-up searches of the primary literature. Having said that, a search of primary literature without an initial search on secondary sources is logistically impractical given a huge majority of the results are extraneous.

Thirdly, as this was not a systematic review a meta-analysis, risk of bias and quality assessment were not conducted on studies included in this review due to the heterogeneity of study designs and variation of definitions used in each study. However, the size of the studies included for each nutrient deficiency induced by the specific medicine were substantial, with total participants ranging from 576 to 357,566.

Furthermore, the medicines of interest are PBS medicines used by Australians but subjects in studies retrieved may not necessarily be conducted in the Australian context and dietary intake may be a confounding factor associated with a susceptibility to developing a drug induced nutrient deficiency between different demographic locations. Importantly, the top 50 PBS medications that formed the basis of this review were not specific to an older population, rather to the general Australian population. As such, some medications more frequently prescribed to older Australians may not have been included in this review.

## 5. Conclusion

In conclusion, medicines used to manage conditions of the cardiovascular, neurological, and gastrointestinal systems and diabetes in older adults are associated with specific nutrient deficiencies and/or depletion. Given the high prevalence of comorbidities and polypharmacy by older people, it is possible that some of these individual drug-induced nutrient deficiencies are compounded, warranting both clinical and research attention. Of these, medicine-induced depletion of vitamin B12, sodium and magnesium have important clinical implications. Given the high prevalence of polypharmacy in this patient population, findings from this study will not only help inform prescribing decisions, but also promote the quality use

of medicines, nutritional counselling, and appropriate dietary supplement use among the older population.

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## Declaration of Competing Interest

Author JH is an academic at The University of Sydney's Faculty of Medicine and Health Pharmacy School where she teaches and conducts research in the field of traditional, complementary, and integrative medicine (TCIM). She has received research funds from universities, organisations, and/or industry for TCIM research and education and have received payments for providing expert advice about TCIM to industry, government bodies and/or non-government organisations.

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N/A

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rcsop.2021.100067.

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