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Prevalence of strong anticholinergic use in residents with and without cognitive impairment and frailty: Analysis from 106 nursing homes in 12 Asia-Pacific and European countries

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HIGHLIGHTS

- One in six residents of nursing homes use strong anticholinergic medications.
- There was a 20-fold variation in prevalence across the 12 countries.
- Antipsychotics and antidepressants were the most common strong anticholinergics.

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ABSTRACT

Purpose: There is a need to balance the benefits and risks associated with strong anticholinergic medications in older adults, particularly among those with frailty and cognitive impairment. This study explored the international prevalence of strong anticholinergic medication use in residents of nursing homes with and without cognitive impairment and frailty.

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Methods: Secondary, cross-sectional analyses of data from 5,800 residents of 106 nursing homes in Australia, China, Czech Republic, England, Finland, France, Germany, Israel, Italy, Japan, Netherlands, and Spain were conducted. Strong anticholinergic medications were defined as medications with a score of 2 or 3 on the Anticholinergic Cognitive Burden scale. Dementia or cognitive impairment was defined as a documented diagnosis or using a validated scale. Frailty was defined using the FRAIL-NH scale as 0–2 (non-frail), 3–6 (frail) and 7–14 (most-frail). Data were analyzed using descriptive statistics.

Results: Overall, 17.4 % (n = 1010) residents used ≥1 strong anticholinergic medication, ranging from 1.3 % (n = 2) in China to 27.1 % (n = 147) in Italy. The most prevalent strong anticholinergics were quetiapine (n = 290, 5.0 % of all residents), olanzapine (132, 2.3 %), carbamazepine (102, 1.8 %), paroxetine (88, 1.5 %) and amitriptyline (87, 1.5 %). Prevalence was higher among residents with cognitive impairment (n = 602, 17.9 %) compared to those without (n = 408, 16.8 %), and among residents who were most frail (n = 553, 17.9 %) compared to those who were frail (n = 286, 16.5 %) or non-frail (n = 171, 17.5 %).

Conclusions: One in six residents who were most frail and living with cognitive impairment used a strong anticholinergic. However, there was a 20-fold variation in prevalence across the 12 countries. Targeted deprescribing interventions may reduce potentially avoidable medication-harm.

1. Introduction

People with dementia and frailty are at high risk of medication-related harm. A 2021 meta-analysis showed more than half of all residents in nursing home have diagnosed dementia, ranging from 11 % in Mexico to 84 % in Norway (Fagundes et al., 2021, Matthews and Dening, 2002). Furthermore, between 28 % to 75 % of residents are considered 'most frail' (Liau et al., 2021). Older adults with dementia and high anticholinergic burden had a 15 % higher risk of death than older adults not taking anticholinergics (Taylor-Rowan et al., 2022). Four out of 10 studies reported anticholinergic burden was associated with cognitive decline and one out of four studies with reduced physical function (Taylor-Rowan et al., 2022). Similar mixed results have been reported for people with frailty, with four out of six studies showing anticholinergics were associated with weaker grip strength and three out of four studies with impaired activities of daily living (Mehdizadeh et al., 2021).

Previous studies have reported anticholinergic prevalence in nursing homes ranges from 24 % in the United States (Malagaris et al., 2020), to 35 % in Japan (Hamada et al., 2021), 46 % in Australia (Hillen et al., 2019) and 60 % in Europe (Oudewortel et al., 2021). In Finland, approximately half of all residents in nursing homes used anticholinergics, and this proportion remained similar from 2003 to 2017 (Aalto et al., 2020). Conversely, there was a corresponding decline in anticholinergic prevalence in the United States from 35 % to 24 % between 2011 and 2017 (Malagaris et al., 2020). The apparent variation in prevalence and mixed associations with adverse events may be partly due to differences in the definitions and tools used to measure anticholinergic burden (Michael et al., 2023). Most prevalence estimates include definite (strong) anticholinergics and possible (weak) anticholinergics (Lozano-Ortega et al., 2020). Strong anticholinergics include some first- and second-generation antipsychotics and anticonvulsants, all tricyclic antidepressants and bladder antimuscarinics. Strong anticholinergics are considered potentially inappropriate for older adults in most explicit 'drugs to avoid' criteria (O'Mahony et al., 2023, Panel, 2023). On the other hand, the benefit-to-risk ratio of medications with weak anticholinergic effects (e.g. atenolol, furosemide, metoprolol and warfarin) is less well established. Inclusion of both strong and weak anticholinergics may dilute the apparent associations with adverse events.

International consensus suggests that the decision to prescribe or deprescribe anticholinergics should be based on an individual assessment of benefits and risks (Liau et al., 2021). This individual assessment should include consideration of the resident's cognitive and frailty status (Liau et al., 2021). The impact of anticholinergic burden on frailty is understudied (Michael et al., 2023). Evidence for the association between strong anticholinergic medications and risk of adverse events is stronger than for multiple weak anticholinergics (Green et al., 2019, Coupland et al., 2019). The unfavorable risk-to-benefit ratio of strong anticholinergics may represent a clearer and more acceptable prompt for deprescribing (Stewart et al., 2021).

There is currently no international comparison of strong anticholinergic medication use in nursing homes. This is necessary, as analyzing data from countries with different clinical practice guidelines, prescribing cultures and aged care systems can help to inform future prescribing and deprescribing interventions. We hypothesized that the prevalence of strong anticholinergics would be lower in residents with cognitive impairment or dementia and frailty than among those without. The objective of this study was to explore the international prevalence of strong anticholinergic medication use in residents of nursing homes with and without cognitive impairment and frailty.

2. Methods

2.1. Study design and setting

We conducted secondary cross-sectional analyses of data from 106 nursing homes across 12 countries. Nursing homes, also known as long-term care facilities and residential aged care facilities, provide a domestic-styled environment and supported accommodation for adults with long-term needs (i.e. assistance with activities of daily living) (Sanford et al., 2015). Studies/countries were identified via professional contacts of the research team, and selected as they represented countries underrepresented in current literature regarding anticholinergic use in older adults. Data were obtained from six studies including;

- Frailty in Residential Sector over Time (FIRST) study, Australia (Jadczak et al., 2021). Cross-sectional analysis of baseline data collected in 2019 across 12 nursing homes operated by one aged care provider organization in South Australia, Australia.
- Services and Health for Elderly in Long TERm care (SHELTER) study (Onder et al., 2012). Data collected between 2009 and 2010 from 50 European facilities (10 in Czech Republic, 9 in England, 4 in Finland, 4 in France, 9 in Germany, 10 in Italy, and 4 in the Netherlands) and 7 facilities in Israel.
- Data collected in 2022 from 13 long-term care facilities, assisted living facilities and care homes in China (Liau et al., 2024).
- Data collected in 2019–2020 from 18 assisted living facilities in Finland (Roitto et al., 2023).
- Data collected in 2020 from four special nursing homes or '*Tokuyo*' (Japan Association of Geriatric Health Services Facilities, 2023) in Japan.
- Data collected in 2015 from two nursing homes in Spain (Gutiérrez-Valencia et al., 2018).

2.2. Data collection

In Australia and Japan data were retrieved from medical records, medication charts and electronic prescription records. In Australia the medication data reflected the medications that were actually administered in the records. In Japan, the medication data reflected the medications that were prescribed to residents. In China, Finland and Spain, data collection from medical records was supplemented with interviews with residents and nurses (China), residents or their closest proxy (Finland) or residents and the resident's legal guardian as appropriate (Spain). In the European SHELTER study, medication data were collected using the InterRAI-Long Term Care assessment tool (InterRAI-LTCF) completed by trained assessors (Onder et al., 2012).

2.3. Strong anticholinergic medications

Strong anticholinergic medications were defined as any medication with a score of 2 or 3 on the 2012 Anticholinergic Cognitive Burden (ACB) scale (Supplement 1), which represents medications with definite anticholinergic properties (Boustani et al., 2008, Campbell et al., 2013). Strong anticholinergic medications were categorized based on the Anatomical Therapeutic Chemical (ATC) Classification System codes recommended by the (World Health Organisation (WHO) 1982).

All available medication data collected as part of the six original studies were used to assess prevalence of strong anticholinergic medications. Four of those studies included regular medications only (Australia, China, Finland, Japan), two included regular and PRN medications (SHELTER, Spain) (Table 1).

2.4. Frailty

Frailty was defined using the FRAIL-NH scale in all 12 countries. The FRAIL-NH scale is a 7-item screening tool specifically designed for nursing homes (Kaehr et al., 2015). It included domains related to potentially reversible variables including: fatigue, resistance, ambulation, incontinence or illness, loss of weight, nutritional approach; and help with dressing (Kaehr et al., 2015). Each item was assigned a score of up to 2 points, generating a total score of between 0 and 14 (higher scores= more frail) (Kaehr et al., 2015). Frailty was categorized as 0–2 (non-frail), 3–6 (frail) and 7–14 (most frail). This categorization was consistent with previous studies (Liau et al., 2021). The FRAIL-NH Japanese version was used in Japan (Sakata et al., 2021). In Japan a score of 2 was assigned for residents for which it was not possible to assess fatigue. For all countries, the 'incontinence or illness' item of the scale was defined as incontinence.

2.5. Cognitive impairment or dementia

Cognitive impairment or dementia was defined as the presence of any form of dementia or moderate/severe cognitive impairment. The method of defining cognitive impairment or dementia differed between countries (Table 1) and included a dementia diagnosis recorded in medical records, or moderate-severe cognitive impairment based on a cognitive assessment tool (i.e. Dementia Severity Rating Scale (Moelter et al., 2015), Mini Mental State Examination (Folstein et al., 1975), Short Portal Mental Status Questionnaire (Pfeiffer, 1975)).

2.6. Missing data

In the SHELTER study, 30 (0.7 %) participants were excluded because FRAIL-NH scores could not be calculated. Further details have been published previously (Villani et al., 2021).

2.7. Data analysis

In order to avoid sharing of resident-level data, statistical analyses were conducted by investigators in their respective institutions/countries. Aggregate data from each country was reported on a standardized data collection tool developed and pilot tested with members of the research team. Descriptive statistics were used to describe demographics and prevalence of strong anticholinergic medications. Figures representing prevalence based on cognitive and frailty status were prepared using Microsoft Office Excel 2019.

Meta-analyses of the prevalence of strong anticholinergic medications by cognitive and frailty subgroups were performed using a random-effects model and presented as forest plots in STATA using *metan* and the DerSimonian-Laird (DL) estimator (StataCorp. 2019. STATA Statistical Software: Release 16. College Station, TX: StataCorp LLC). The degree of heterogeneity was measured by the I^2 statistic, where an I^2>75 % was considered indicative of considerable heterogeneity (Higgins et al., 2019).

2.8. Ethical considerations

Each study was approved by the respective Human Research Ethics Committee in their countries. In Australia, ethics approval was obtained from the University of Adelaide Human Research Ethics Committee (HREC-2018-247) and the study was registered with the Monash University Human Research Ethics Committee (23620). In China, the Institutional Review Board of the Shandong University (2022-R-024) approved the study. In Finland, the Helsinki University Hospital Ethics committee (HUS/2042/2016) approved the study. In Japan, the ethical review board of the Institute for Health Economics and Policy approved the study (R2-002). In Spain, the Institutional Research Ethics Committee of Hospital of Navarra, (CEIC 68/2013) approved the study. In the SHELTER study, ethical approval for the study was obtained in all countries according to country-specific agreements, on behalf of the ethical committee of the Catholic University of the Sacred Heart (P/220/CE/2009).

3. Results

In total, data were collected for 5830 residents from 106 nursing homes across 12 countries, ranging from 110 residents in Spain to 580 residents in Israel (Table 1). The mean/median age ranged from 79 years to 89 years, and 73.3 % were female (range 54.4 % to 79.7 %). The prevalence of cognitive impairment or dementia ranged from 20.1 % in China, to 79.7 % in Finland, and the prevalence of residents considered 'most-frail' ranged from 10.7 % in China, to 69.8 % in England.

3.1. Strong anticholinergic use

A total of 17.4 % (n = 1010/5800) residents used one or more strong anticholinergic medications (Table 2). The prevalence was highest in Italy (n = 147, 27.1 %) and Japan (n = 80, 24.0 %) and lowest in China (n = 2, 1.3 %). The most prevalent classes of strong anticholinergics, as reported using ATC therapeutic subgroups, were psycholeptics (NO5, n = 593, 10.2 %) and psychoanaleptics (N06, n = 211, 3.6 %). The 10 most prevalent anticholinergic medications used were quetiapine (n = 290, 5.0 % of all residents), olanzapine (132, 2.3 %), carbamazepine (102, 1.8 %), paroxetine (88, 1.5 %), amitriptyline (87, 1.5 %), hydroxyzine (55, 0.9 %), oxybutynin (39, 0.7 %), trihexyphenidyl (39, 0.7 %), promazine (31, 0.5 %), amantadine (24, 0.4 %).

Quetiapine was the in the top 3 most common strong anticholinergic medications for all countries, except China, France and Netherlands (Table 3). Antidepressants were the most common strong anticholinergic medication for three countries, Australia (amitriptyline), France (paroxetine) and Netherlands (paroxetine). Australia and Japan reported urinary anticholinergic medications in their top 3 most prevalent strong anticholinergics, oxybutynin in Australia and solifenacin in Japan.

3.2. Strong anticholinergic use according to cognitive impairment or dementia status

Overall, a higher proportion of residents with cognitive impairment

Table 1
Study details and participant demographics.

Country (state/ province), year of data collection	Number of facilities, Number of residents	Inclusion and exclusion criteria	Age, mean (SD) unless stated	Female sex, n (%)	Type of medication data collected and source of medication data	Frailty status† based on FRAIL-NH Scores, n (%)	Cognitive impairment or dementia prevalence, n (%) and method of defining
Australia (South Australia), 2019	12 facilities, 550 residents	*Inclusion*: Residents living in the nursing home for ≥8 weeks. *Exclusion*: residents deemed by clinical staff to be medically unstable (e.g. experiencing delirium), at the end of life (<3 months to live), or who had difficulty understanding English.	Median 89 (IQR 84–92)	403 (73.3)	*Type*: Administered, regular medications only. *Source*: medication charts and electronic prescription records	Non-frail: 68 (12.4 %) Frail: 231 (42.0 %) Most-frail: 251 (45.6 %)	417 (75.8), defined as a score of >11 on DSRS
China (Jinan, Shandong Province), 2022	13 facilities, 149 residents	*Inclusion*: Aged ≥60 years, residing in a nursing home for ≥2 months. *Exclusion*: hearing impairment, communication disorder, comatose, end-stage diseases; severe cognitive dysfunction as determined by a SPMSQ, and/or undergoing psychotherapy or taking psychotropic drugs (e.g. antidepressants).‡	79.0 (8.9)	81 (54.4)	*Type*: Prescribed, regular medications only *Source*: medical records, supplemented with interviews with residents and nurses	*Non-frail:* 74 (49.7 %) *Frail:*59 (39.6 %) *Most-frail:* 16 (10.7 %)	30 (20.1), a score of 5 or more using the SPMSQ§
Czech Republic, 2009–2010*	10 facilities, 500 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	81.3 (8.3)	362 (72.4)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	Non-frail: 102 (20.4 %) Frail: 129 (25.8 %) Most-frail: 269 (53.8 %)	240 (48.0), dementia status as per InterRAI-LTCF
England, 2009–2010*	9 facilities, 507 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	84.5 (9.5)	365 (72.0)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*Non-frail:* 61 (12.0 %) *Frail:* 92 (18.1 %) *Most-frail:* 354 (69.8 %)	188 (37.1), dementia status as per InterRAI-LTCF
Finland (Helsinki), 2019–2020	18 facilities, 532 residents	*Inclusion:* provided informed consent. *Exclusion*: N/A	Median: 84.5 (IQR 61–102)	424 (79.7)	*Type*: Prescribed, regular medications based on medical records *Source*: medical records, supplemented with interviews with residents or closest proxy	*Non-frail:* 15 (2.8 %) *Frail: 269* (50.6 %) *Most-frail:* 248 (46.7 %)	424 (79.7) based on diagnosis in medical records
Finland, 2009–2010*	4 facilities, 484 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	84.9 (7.9)	362 (74.8)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*(n = 464)* ‖ *Non-frail:* 52 (11.2 %) *Frail:* 147 (31.7 %) *Most-frail:* 265 (57.1 %)	323 (66.7), dementia status as per InterRAI-LTCF
France, 2009–2010*	4 facilities, 493 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	87.4 (7.8)	374 (75.9)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*(n = 489)* ‖ *Non-frail:* 93 (19.0 %) *Frail:* 95 (19.4 %) *Most-frail:* 301 (61.6 %)	284 (57.6), dementia status as per InterRAI-LTCF
Germany, 2009–2010*	9 facilities, 496 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	84.6 (8.3)	392 (79.0)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*Non-frail:* 125 (25.2 %) *Frail:* 177 (35.7 %) *Most-frail:* 194 (39.1 %)	259 (52.2), dementia status as per InterRAI-LTCF
Israel, 2009–2010*	7 facilities, 580 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	81.2 (11.0)	412 (71.0)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data	*Non-frail:* 99 (17.1 %) *Frail:* 130 (22.4 %) *Most-frail:*	393 (67.8), dementia status as per InterRAI-LTCF

(*continued on next page*)

Table 1 (*continued*)

Country (state/ province), year of data collection	Number of facilities, Number of residents	Inclusion and exclusion criteria	Age, mean (SD) unless stated	Female sex, n (%)	Type of medication data collected and source of medication data	Frailty status[†] based on FRAIL-NH Scores, n (%)	Cognitive impairment or dementia prevalence, n (%) and method of defining
					collection *Source*: InterRAI-LTCF	351 (60.5 %)	
Italy, 2009–2010*	10 facilities, 548 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	83.5 (9.3)	401 (73.2)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*(n = 542)* [‖] *Non-frail:* 97 (17.9 %) *Frail:* 114 (21.0 %) *Most-frail:* 331 (61.1 %)	303 (55.3), dementia status as per InterRAI-LTCF
Japan (Tokyo metropolitan area), 2020	4 facilities, 333 residents	*Inclusion:* informed consent from resident or their representative. *Exclusion:* residents who received medications from other hospitals/ clinics, and new residents for whom medications had not yet been charted.	Median 87 (IQR 83–91)	244 (73.3)	*Type*: Prescribed, regular medications only based on electronic records *Source*: electronic prescription records	*Non-frail:* 43 (12.9) *Frail:* 84 (25.2) *Most-frail:* 206 (61.9)	233 (70.0), based on diagnosis in medical records.
Netherlands, 2009–2010*	4 facilities, 548 residents	*Inclusion:* older adults living in the nursing home during 3-month enrolment period who provided informed consent. *Exclusion*: N/A	81.0 (10.4)	367 (67.0)	*Type*: Prescribed and/or administered regular medications and PRN medications administered in 3 days prior to data collection *Source*: InterRAI-LTCF	*Non-frail:* 114 (20.8 %) *Frail:* 175 (31.9 %) *Most-frail:* 259 (47.3 %)	238 (43.4), dementia status as per InterRAI-LTCF
Spain (Navarre), 2015	2 facilities, 110 residents	*Inclusion:* >65 years, living in the nursing home at baseline, provided informed consent. Randomly selected 110 residents (from 320). *Exclusion:* N/A	86.3 (7.3)	79 (71.8)	*Type*: All prescribed regular and when required medications, based on electronic records *Source*: medical records, supplemented with interviews with residents and their legal guardians	*Non-frail:* 35 (31.8 %) *Frail:* 29 (26.4 %) *Most-frail:* 46 (41.8 %)	58 (52.7), diagnosis of dementia in medical records or moderate-severe cognitive impairment according to MMSE.

Abbreviations: DSRS, dementia severity rating scale; InterRAI-LTCF, InterRAI-Long Term Care assessment tool; IQR, interquartile range; MMSE, mini-mental state examination; PRN, pro re nata or as-needed; SPMSQ, short portable mental status questionnaire.
*Country part of the SHELTER study
† Frailty based on FRAIL-NH where score 0–2= Non-frail, score 3–6= Frail, and score 7–14= Most frail.
‡ The exclusion criteria for psychotropic medicine was intended to exclude patients with parapsychological mental disorders, which may affect the accuracy of questionnaire answers. During the study only one resident was excluded due to mental disorder or taking psychotropic drugs.
§SPMSQ score of 5 or more based on literature (Malhotra et al., 2013).
|| FRAIL-NH scores could not be calculated for all residents

or dementia used a strong anticholinergic compared to residents without cognitive impairment or dementia (with: 17.9 %, without: 16.8 %, Fig. 1). Six of 12 countries (England, Finland [SHELTER], Germany, Israel, Italy and Japan) had higher proportions of residents with cognitive impairment or dementia using strong anticholinergics than those without. Overall the meta-analyses (Fig. 2) showed there was considerable heterogeneity across the countries in both the cognitive impairment or dementia and no cognitive impairment or dementia subgroup (I^2 90.6 % and 91.3 % respectively), but between group heterogeneity was non-significant (p = 0.995).

3.3. *Strong anticholinergic use according to frailty status*

Overall, strong anticholinergic medication use was more prevalent among residents who were most-frail (17.9 %) compared to residents who were frail (16.5 %) or non-frail (17.5 %) (Fig. 3). Four of 12 countries (Finland, France, Netherlands and Spain) had a higher prevalence of strong anticholinergic use among residents who were most-frail, compared to those who were non-frail or frail. Overall the meta-analyses (Fig. 4) showed there was considerable heterogeneity across the countries in the non-frail, frail and most-frail subgroups (I^2 87.5 %, 86.6 % and 82.5 % respectively), but between group heterogeneity was non-significant (p = 0.947).

3.4. *Strong anticholinergic use among residents who are most-frail and living with cognitive impairment or dementia*

Overall, 18.3 % (n = 381/2084) of residents who were most-frail and living with cognitive impairment or dementia used a strong anticholinergic medication. Prevalence among this sub-group ranged from 0 % in China through to 32.4 % in Italy, with 11 countries (91.7 %) reporting more than 10 % of their residents who were most-frail and living with cognitive impairment or dementia used at least one strong anticholinergic (Table 2).

4. Discussion

This was the largest international study comparing the prevalence of strong anticholinergic use in residents of nursing homes. More than one in six residents who were most frail and living with cognitive impairment or dementia used a strong anticholinergic. The most prevalent strong anticholinergics were second-generation antipsychotics (quetiapine and olanzapine), anticonvulsants (carbamazepine), tricyclic antidepressants (amitriptyline) and a selective-serotonin reuptake inhibitor (paroxetine).

There was up to 20-fold variation in the prevalence of strong anticholinergic medication use across the 12 countries. This geographic variation is consistent with the variation reported for other high-risk

Table 2
Prevalence of residents who use one or more strong anticholinergic medications (SAMs), by cognitive impairment or dementia and frailty status.

Country, N	Total residents using a SAM, n(%)	Residents taking a SAM who are non-frail without cognitive impairment/ dementia, n(%)	Residents taking a SAM who are frail without cognitive impairment/ dementia, n(%)	Residents taking a SAM who are most-frail without cognitive impairment/ dementia, n(%)	Residents taking a SAM who are non-frail with cognitive impairment/ dementia, n(%)	Residents taking a SAM who are frail with cognitive impairment/ dementia, n(%)	Residents taking a SAM who are most-frail with cognitive impairment/ dementia, n(%)
Australia (n = 550)	97 (17.6)	12 (23.1)	17 (22.4)	1 (20.0)	4 (25.0)	19 (12.3)	44 (17.9)
China (n = 149)	2 (1.3)	1 (1.6)	1 (2.2)	0 (0)	0 (0)	0 (0)	0 (0)
Czech Republic* (n = 500)	63 (12.6)	13 (16.3)	11 (13.3)	9 (9.3)	2 (9.1)	9 (19.6)	19 (11.0)
England* (n = 507)	106 (20.9)	9 (20.9)	14 (26.4)	37 (16.6)	6 (33.3)	8 (20.5)	32 (24.4)
Finland (n = 532)	80 (15.0)	0 (0)	14 (23.7)	13 (28.3)	1 (8.3)	18 (8.6)	34 (16.8)
Finland* (n = 464)	63 (13.6)	4 (15.4)	7 (14.9)	9 (11.0)	5 (19.2)	18 (18.0)	20 (10.9)
France* (n = 489)	95 (19.4)	11 (17.5)	9 (19.6)	29 (29.9)	6 (20.0)	8 (16.3)	32 (15.7)
Germany* (n = 496)	86 (17.3)	14 (16.9)	14 (16.3)	12 (17.6)	6 (14.3)	20 (22.0)	20 (15.9)
Israel* (n = 580)	97 (16.7)	13 (25.5)	8 (16.3)	10 (11.5)	12 (25.0)	16 (19.8)	38 (14.4)
Italy* (n = 542)	147 (27.1)	13 (18.3)	14 (21.5)	15 (14.2)	9 (34.6)	23 (46.9)	73 (32.4)
Japan (n = 333)	80 (24.0)	6 (31.6)	3 (10.0)	10 (19.6)	6 (25.0)	15 (27.8)	40 (25.8)
Netherlands* (n = 548)	78 (14.2)	8 (10.4)	13 (12.3)	25 (19.7)	4 (10.8)	5 (7.2)	23 (17.4)
Spain (n = 110)	16 (14.5)	6 (19.4)	1 (6.7)	2 (33.3)	0 (0)	1 (7.1)	6 (15.0)
TOTAL (n = 5800)	1010 (17.4)	110 (16.6)	126 (16.6)	172 (17.1)	61 (19.2)	160 (16.5)	381 (18.3)

SAM: strong anticholinergic medication. *Country part of the SHELTER study

medications such as benzodiazepines and z-drugs (Lukačišinová et al., 2021). However, unlike benzodiazepines that have seen a decrease in prescribing in countries such as Japan in recent years, antipsychotic prescribing rates have remained unchanged (Hamada et al., 2023). Higher anticholinergic prevalence in some countries may reflect a higher rate of polypharmacy in these countries (Naseralallah et al., 2023). Although some of the variation was also likely study specific, where difference in inclusion criteria may have led to underestimation of prevalence (e.g. residents with severe cognitive impairment were excluded in China). Understanding the drivers of anticholinergic prescribing in different countries will help develop global strategies to reduce avoidable medication-related harm.

Half the countries reported a higher prevalence of strong anticholinergic use among residents with cognitive impairment or dementia, including England, Finland [SHELTER], Germany, Israel, Italy and Japan. This finding was not unexpected given that changed behaviors represent a common reason for prescribing antipsychotics, including the off-label use of quetiapine and olanzapine which are both strong anticholinergics. Five of these countries were from the SHELTER study with data collected between 2009–2010, and it is possible that prescribing patterns have changed in these countries since 2010. Recently updated lists of potentially inappropriate medications such as the Beers Criteria (Panel, 2023), STOPP criteria (O'Mahony et al., 2023), and the EURO-FORTA list (Pazan et al., 2023), have reaffirmed the importance of avoiding strong anticholinergic medications in residents living with dementia. However, high rates of use in residents both with and without cognitive impairment or dementia suggest new models of care may be needed to support quicker, more effective translation of these guidelines, recommendations and emerging evidence into practice. Anticholinergic stewardship programs have produced promising results in the hospital setting (Masnoon and Lo, 2023). Tools that measure anticholinergic burden can be used to quantify and evaluate the impact of interventions such as stewardships (Nishtala et al., 2009). Given anticholinergic medications are prescribed for a range of indications and residents of nursing homes often experience multimorbidity, a more broad-spectrum polypharmacy stewardship may be required to address the overall complexities of medication use in this population (Daunt et al., 2023). Understanding the drivers for strong anticholinergic prescribing, and barriers to implementing guideline recommendations in different countries is important when designing new interventions to address high rates of strong anticholinergic use. Interventions need to be pragmatic and adaptable to local healthcare systems and not one-size-fits-all. The use of local opinion leaders, change champions, or knowledge brokers may be one implementation strategy that could help to ensure interventions are tailored to local nursing home context. Knowledge brokers are intermediaries that facilitate knowledge translation into practice, including translation of evidence and guidelines (Cross et al., 2023). Knowledge brokers are an emerging strategy in the nursing home setting (Bell et al., 2024), and could be utilized to help address system-level barriers to deprescribing in nursing homes such as lack of co-ordination between healthcare settings (Heinrich et al., 2022). Funding to support implementation of stewardships and knowledge brokers is required to ensure their uptake and sustainability.

Frailty status did not appear to impact the prescribing, with most-frail and non-frail residents having similar prevalence of strong anticholinergic medications. The recognition of frailty as a factor that can be used to guide prescribing in nursing homes is relatively new (Liau et al., 2021, Liau and Bell, 2021, Onder et al., 2018, Liau et al., 2024). Frailty can modify the effect of polypharmacy and multimorbidity on mortality risk among residents of nursing homes (Zazzara et al., 2023). Clinical guidelines increasingly recommend caution when prescribing for frail older adults. It is likely that translation of this recommendation into practice is ongoing. Strong anticholinergic medication use has been associated with poorer physical performance, increased risk of falls and

Table 3
Top three most prevalent strong anticholinergic medications used by residents in each country or data set.

Country	Most common strong anticholinergic medication	Second most common strong anticholinergic medication	Third most common strong anticholinergic medication
Australia (n = 550)	Amitriptyline (n = 26)	Quetiapine (n = 18)	Oxybutynin (n = 17)
Czech Republic* (n = 500)	Oxcarbazepine (n = 14)	Quetiapine (n = 12)	Levomepromazine (n = 9)
England* (n = 507)	Quetiapine (n = 39)	Amitriptyline (n = 14)	Carbamazepine (n = 10)
Finland (n = 532)	Quetiapine (n = 35)	Olanzapine (n = 29)	Carbamazepine (n = 10)
Finland* (n = 464)	Quetiapine (n = 24)	Olanzapine (n = 20)	Hydroxyzine (n = 6)
France* (n = 489)	Paroxetine (n = 38)	Hydroxyzine (n = 22)	Olanzapine (n = 10)
Germany* (n = 496)	Quetiapine (n = 23)	Carbamazepine (n = 13)	Amantadine (n = 7)
Israel* (n = 580)	Quetiapine (n = 26)	Trihexyphenidyl (n = 25)	Olanzapine (n = 16)
Italy* (n = 542)	Quetiapine (n = 62)	Promazine (n = 31)	Olanzapine (n = 24)
Japan (n = 333)	Quetiapine (n = 39)	Amantadine (n = 6)#	Solifenacin (n = 6)#
Netherlands* (n = 548)	Paroxetine (n = 23)	Amitriptyline (n = 15)	Carbamazepine (n = 11)
Spain (n = 110)	Quetiapine (n = 8)	N/A^	N/A^
Overall (n = 5800)	**Quetiapine (n = 290)**	**Olanzapine (n = 132)**	**Carbamazepine (n = 102)**

*Country part of the SHELTER study. # equivalent prevalence. ^ Medications were only reported where ≥5 residents took the medication.
China was not reported in this table as all medications were taken by <5 residents.

mortality (Mehdizadeh et al., 2021). These medication-related problems can then contribute to increased risk of developing higher levels of frailty in a cyclical fashion. There may be value in nursing homes implementing proactive measures for monitoring and detecting increasing frailty among residents. These measures could include establishing processes that trigger multidisciplinary medication reviews to individualize treatment decisions for frail and most-frail residents who use strong anticholinergic medications (Chen, 2016).

Strategies for anticholinergic deprescribing may need to be resident and medication specific. Second-generation antipsychotics, such as quetiapine and olanzapine, can often be targeted for dose tapering and cessation. Most clinical guidelines recommend against the routine use of antipsychotics for changed behaviors in dementia (Reus et al., 2016, The Guideline Development Group, 2023, Zuidema et al., 2015). Quetiapine and olanzapine are often used off-label for changed behaviors, and if a resident is assessed and found that a short-term antipsychotic is required, there may be a safer alternatives (e.g. risperidone). On the other hand, the evidence for antidepressant use in dementia is mixed (The Guideline Development Group, 2023), and interventions are needed to assist healthcare professionals to identify when an antidepressant is no longer needed, and when it may be appropriate to switch certain residents to less anticholinergic or non-medication alternatives (Pazan et al., 2023). Deprescribing medications for Parkinson's disease or urinary incontinence may be challenging due to the underlying nature of the disease. However, tapering is still recommended for residents where the harms outweigh the benefits. A Cochrane review on the effectiveness of anticholinergics for Parkinson's found occurrence of neuropsychiatric and cognitive adverse events was almost three times higher in those using anticholinergics versus placebo (Katzenschlager et al., 2003). For urinary incontinence, structured deprescribing recommendations involving dose tapering, cessation or switching to a safer alternative medication (e.g. mirabegron) have a demonstrated high rates of acceptance and implementation (Ha et al., 2022). Increased physician and pharmacist involvement in nursing homes in countries where physicians and pharmacists are not routinely employed onsite may facilitate multidisciplinary medication review and deprescribing (Haider et al., 2023, Lee et al., 2019, Thiruchelvam et al., 2017). Nursing and care staff could be supported to conduct active monitoring of signs and symptoms suggestive of adverse events (McInerney et al., 2023). This in turn may help address use of strong anticholinergics and ensure the ongoing safety and well-being of residents.

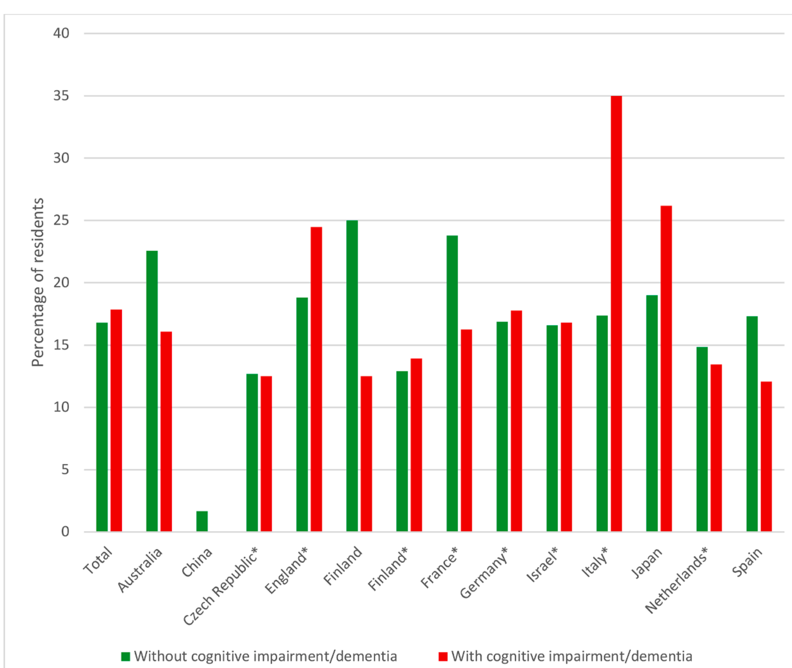

Fig. 1. Prevalence of strong anticholinergic use according to presence or absence of cognitive impairment or dementia.
* indicates country from SHELTER study.

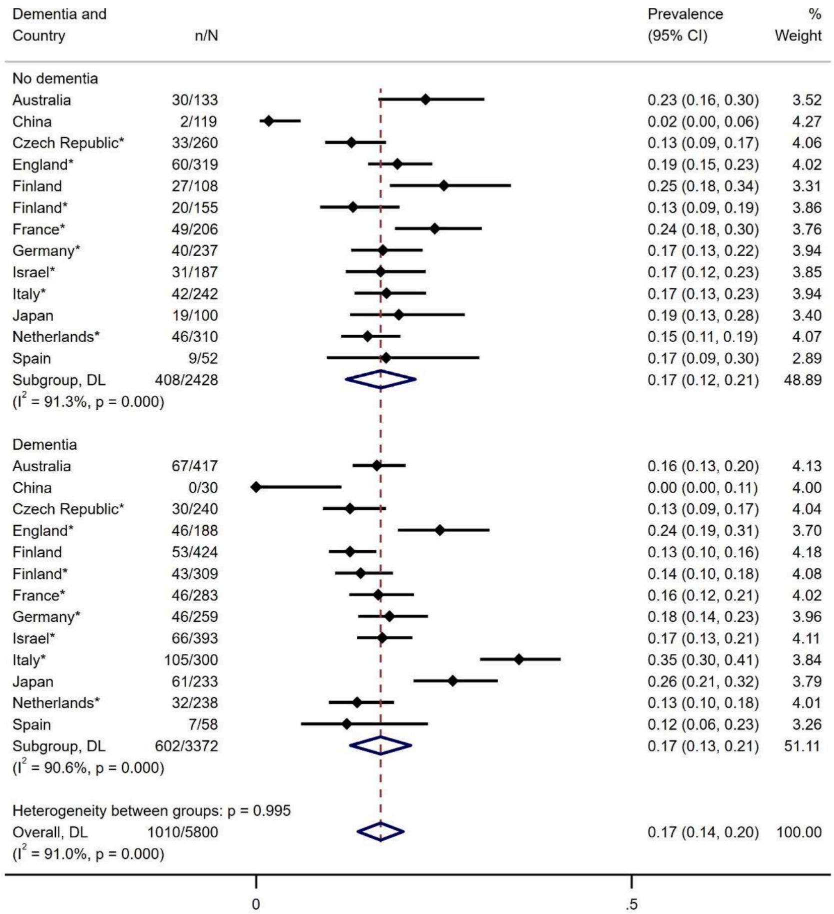

Fig. 2. Meta-analysis of prevalence of residents using strong anticholinergic medications, separated based on presence or absence of cognitive impairment or dementia.
* indicates country from SHELTER study. DL: DerSimonian-Laird estimator.

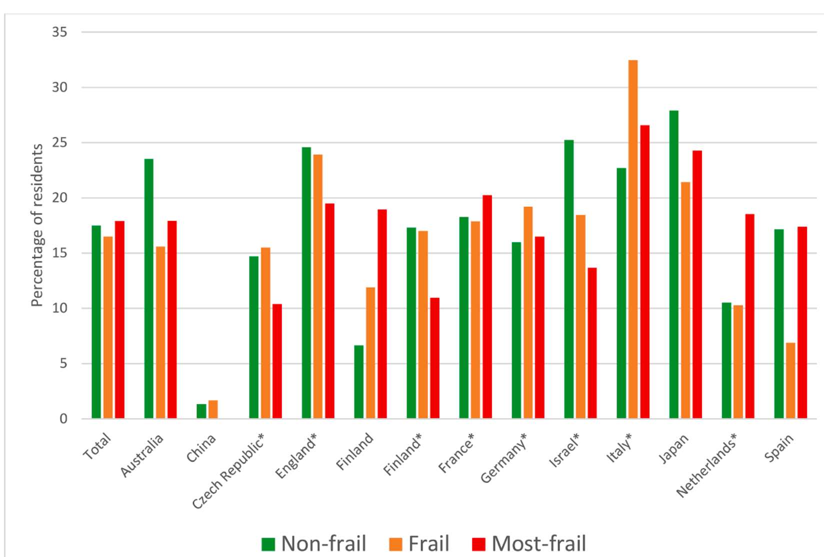

Fig. 3. Prevalence of strong anticholinergic use according to frailty status as measured using FRAIL-NH.
* indicates country from SHELTER study.

4.1. Strengths and limitations

This was the largest, cross-national comparison of strong anticholinergic medication use in nursing homes. However, the sample size of residents and nursing homes from each country was relatively small and this was not a prospectively planned comparison hence there

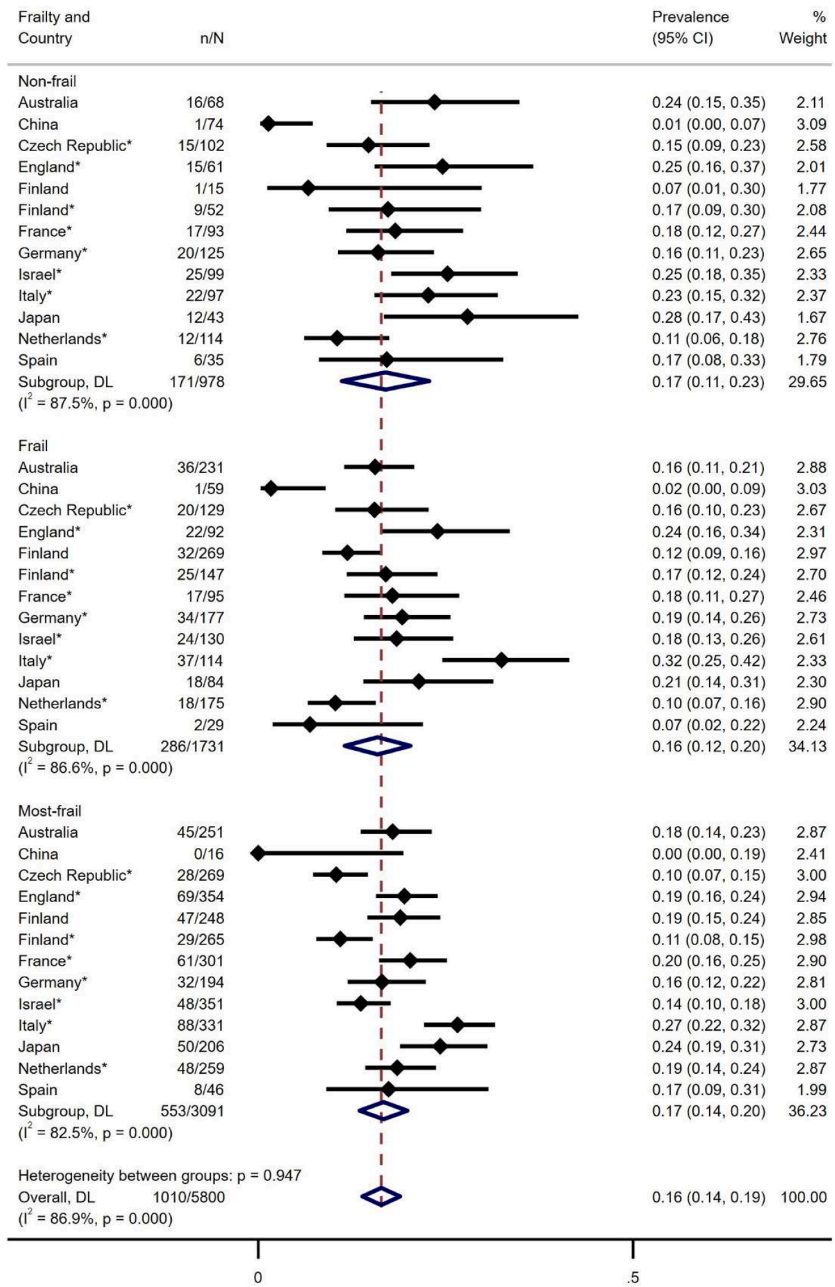

Fig. 4. Meta-analysis of prevalence of residents using strong anticholinergic medications, separated based on frailty sub-group (non-frail, frail and most-frail). * indicates country from SHELTER study. DL: DerSimonian-Laird estimator.

was no common protocol for selection or data collection between countries. The findings from each country may not be generalizable to overall prescribing patterns in each country. The overall prevalence may also have been different if other countries, such as the United States, had been included. We did not collect data on medication dose, duration or indication. Furthermore, we did not collect data on prescribing of non- or less-anticholinergic alternative medications nor the provision of non-pharmacological treatments. We conducted descriptive analyses to avoid needing to share resident level data. There were differences in inclusion and exclusion criteria for residents in different countries, and differences in how cognitive impairment, dementia and frailty were defined between countries. This may have contributed to some of the variation in prevalence, particularly in China where individuals with severe cognitive impairment were excluded and the criteria of 'most-frail' is rarely applied for residents in Chinese nursing homes. There were also differences in types of medication data collected (e.g. prescribed vs administered, regular vs regular and as-needed). For this reason, head-to-head between country comparisons need to be interpreted with caution. Furthermore, data were not collected during the same time period in all countries and changes in evidence and guidelines over time could have impacted anticholinergic prescribing. This is particularly noteworthy for the data obtained from the SHELTER study which was collected more than a decade ago in 2009–2010. This study defined strong anticholinergic medications using the 2012 ACB scale which is the most widely used and validated anticholinergic scale (Lisibach et al., 2021). Anticholinergic scales vary widely in which medications are classified as 'strong' and how many medications are considered to have anticholinergic properties. The use of a different scale, including a more recently developed scale, to define strong anticholinergic medications may have altered the prevalence rates observed in this study.

5. Conclusions and implications

More than one in six residents of nursing homes used a strong anticholinergic medication, including those living with cognitive impairment or dementia and who are most-frail. Substantial geographical heterogeneity does exist. Integrated resident- and system-level multidisciplinary interventions are needed, including individualized assessment of medication benefits and risks to identify any contraindications and support deprescribing, and targeted guideline implementation strategies that are tailored to the local settings to reduce potentially avoidable medication-related harm.

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CRediT authorship contribution statement

Amanda J. Cross: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Emanuele R. Villani:** Writing – review & editing, Methodology, Data curation. **Agathe D. Jadczak:** Writing – review & editing, Methodology, Data curation. **Kaisu Pitkälä:** Writing – review & editing, Methodology, Data curation. **Shota Hamada:** Writing – review & editing, Methodology, Data curation. **Meng Zhao:** Writing – review & editing, Methodology, Data curation. **Marta Gutiérrez-Valencia:** Writing – review & editing, Visualization, Methodology, Data curation. **Ulla Aalto:** Writing – review & editing, Methodology, Data curation. **Laura A. Dowd:** Writing – review & editing, Methodology, Data curation. **Li Li:** Writing – review & editing, Methodology, Data curation. **Shin J. Liau:** Writing – review & editing, Methodology, Data curation. **Rosa Liperoti:** Writing – review & editing, Methodology, Data curation. **Nicolás Martínez-Velilla:** Writing – review & editing, Methodology, Data curation. **Choon Ean Ooi:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Graziano Onder:** Writing – review & editing, Methodology, Data curation. **Kate Petrie:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Hanna M. Roitto:** Writing – review & editing, Methodology, Data curation. **Victoria Roncal-Belzunce:** Writing – review & editing, Methodology, Data curation. **Riitta Saarela:** . **Nobuo Sakata:** Writing – review & editing, Methodology, Data curation. **Renuka Visvanathan:** Writing – review & editing, Methodology, Data curation. **Tiange G. Zhang:** Writing – review & editing, Methodology, Data curation. **J. Simon Bell:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation.

Declaration of competing interest

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All other authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2024.105636.

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