Trends of polypharmacy among older people in Asia, Australia, and the United Kingdom: a multinational population-based study

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CONFLICT OF INTERESTS

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ABSTRACT

Background: Polypharmacy among older people represents a global challenge due to its association with adverse drug events. The reported prevalence of polypharmacy varies widely across countries, and is particularly high in Asian countries. However, there is no multinational study using standardized measurements exploring variations in prescribing trends.

Objective: To compare polypharmacy trends in older people in Asia, Australia, and the United Kingdom (UK).

Design: Multinational, retrospective, time-trend, observational study using a common study protocol.

Setting: Outpatient and community settings.

Subjects: All individuals aged ≥65 years between 2013 and 2016

Methods: We defined polypharmacy as the concomitant use of ≥5 medications for ≥45 days per year. We estimated the annual prevalence of polypharmacy and calculated average annual percentage change (AAPC) to assess the time trends.

Results: A total of 1.62 million individuals were included in this study. The highest prevalence of polypharmacy was observed in Hong Kong (46.4%), followed by Taiwan (38.8%), South Korea (32.0%), the UK (23.5%), and Australia (20.1%) in 2016. For the time trend, the Asian region showed a steady increase, particularly in Hong Kong and South Korea (AAPC: Hong Kong, 2.7%; South Korea, 1.8%; Taiwan, 1.0%). However, Australia and the UK showed a decreasing trend (Australia, -4.9%; the UK, -1.1%).

Conclusions: Polypharmacy prevalence in older people was higher in Hong Kong, Taiwan, and South Korea, with an increasing trend over time, compared to Australia and the UK. Our findings underline the necessity to monitor polypharmacy among older people in Asia by conducting government-level interventions and introducing medicine-optimization strategies.

KEYWORDS: Polypharmacy, Drug utilization, Multinational study, Older people

INTRODUCTION

Polypharmacy in older people has become a global challenge in recent years, especially with increased multimorbidity [1]. Older people are vulnerable to adverse drug events due to physiological changes associated with aging (i.e., impairment of metabolism, drug excretion) [2], which could induce drug-drug or drug-disease interactions. Previous studies reported a substantial burden of adverse drug reactions across countries [3-6], and more than 2-fold risks of neurocognitive disorder, fracture, and mortality were associated with polypharmacy [7-9]. Therefore, the World Health Organization (WHO) launched the 5-year project "Medication Without Harm" as part of the Third Global Patient Safety Challenge in 2017 [10].

Cross-country comparison of trends is important to give insight into how to reduce inappropriate polypharmacy as we know that the differences in international polypharmacy trends are related to different strategic initiatives or policies. Indeed, there is substantial variability in the reported prevalence of polypharmacy across countries (e.g., 50% in Ireland and Sweden; less than 40% in the United States, Australia, and New Zealand) [11-17], with a particularly high prevalence observed in the Asian countries (e.g., over 80% in South Korea and Taiwan) [18-20]. However, it is challenging to compare results from published studies due to different study populations, polypharmacy definitions, data sources and medication reimbursement systems [21]. To date, there has been no multinational study using a common study protocol. Thus, we aimed to compare the prevalence and trend of polypharmacy using healthcare data with standardized measurement across five participating sites.

METHODS

Study design, data sources, and study population

We conducted a multinational, retrospective, time-trend, observational study in the outpatient or community settings of Australia, Hong Kong, Taiwan, South Korea, and the United

Kingdom (UK) using the five databases (Table 1). The study period was between 2013 and 2016, and the study population was patients aged 65 or older not diagnosed with cancer or using medications suggestive of cancer. This approach was adopted to avoid potential overestimation or underestimation of polypharmacy. Each site received ethical approval by the institutional review board (Australia: Monash University Human Research Ethics Committee, 22877; Hong Kong: UW 20-796; South Korea: SKKU 2020-01-007; Taiwan: BER107012; the UK: 20SRC045). The analysis plan was approved and the manuscript noted by Services Australia.

Polypharmacy definition

We focused on chronic polypharmacy to investigate polypharmacy arising from multimorbidity rather than short-term treatment of acute medical conditions. We defined polypharmacy as the use of ≥5 distinct medications concomitantly for a period of ≥45 days per calendar year, which considered both single prescription- and duration-based definitions simultaneously (Supplementary figure 1). This definition was selected after reviewing previous literature on polypharmacy definitions applied in research and practice [22, 23].

Statistical analysis

We calculated the annual prevalence of polypharmacy using the number of individuals who experienced polypharmacy at least once as the numerator and the total study population as the denominator, with 95% confidence intervals. We conducted sex- and age-standardization to address the difference in demographic distribution across study sites using the World Population Prospects 2019 [24]. Changes in trends were evaluated with average annual percentage change (AAPC) using a Poisson regression model, and we conducted sensitivity analyses with different thresholds (≥30 days, ≥60 days) to define polypharmacy. A two-tailed

$p<0.05$ indicates statistical significance, and all analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Our study cohort included 1.62 million individuals aged ≥65 years with a higher proportion of females (Table 1). We observed a difference in the age distribution across the study sites, and more than 30% of the study population was aged ≥80 years in Hong Kong and the UK. In 2016, after the age- and sex standardization, the highest overall polypharmacy prevalence was observed in Hong Kong (46.4%), followed by Taiwan (38.8%), South Korea (32.0%), the UK (23.5%), and Australia (20.1%) (Figure 1). Moreover, we observed a different change in polypharmacy trends across the study sites. There was a steady increase in polypharmacy prevalence in the Asian region, particularly in Hong Kong and South Korea (AAPC: Hong Kong, 2.7%; South Korea, 1.8%; Taiwan, 1.0%). In Australia and the UK, the trend decreased continuously (AAPC: Australia, -4.9%; the UK, -1.1%)).

DISCUSSION

We found polypharmacy prevalence was higher and increasing over time in Hong Kong, South Korea, and Taiwan. Conversely, polypharmacy prevalence decreased in Australia and the UK. We found polypharmacy prevalence was lower than in a range of previous studies [11, 12, 18-20]. Our findings may be affected by our instrumental definition of polypharmacy. While other studies focused on the number of medications use only, we additionally considered the continuing duration of multiple drug use to emphasize the burden of medication. Thus, our results should be interpreted in the context of chronic polypharmacy. Consistent with the previous findings [20, 25, 26], our study reaffirms the increasing trends in polypharmacy in Hong Kong, South Korea, and Taiwan. Meanwhile, in Australia, a decrease in polypharmacy

was reported in 2016 [12], which corresponded with our findings. For the UK, an increasing trend of polypharmacy was reported from a survey study between 1991 and 2011 [11] and our study found a slightly decreasing trend during the study period. This finding suggests that chronic polypharmacy in older people might have been sustained over the recent years, although there are some differences in the study setting (e.g., study period [1991-2011 vs. 2013-2016], database [interview vs. claims data-based], and study region [3 regions in England vs. all regions in the UK]).

Polypharmacy should be evaluated in view of its appropriateness within the clinical context of which the medications were prescribed [27]. Australia and the UK have implemented policy initiatives that may have contributed to decreasing polypharmacy prevalence. Australia now has a National Strategic Action Plan to Reduce Inappropriate Polypharmacy that has been endorsed by bodies including NPS MedicineWise and the Australian Deprescribing Network [28]. Moreover, the Australian Government has funded general practitioners and pharmacists to conduct clinical medication reviews since 2001, with reviews targeted to high risk patients including those who use five or more medications [29]. Indeed, a substantial decrease in the prevalence of polypharmacy in Australia was observed in 2016, and the previous study suggested that this decrease was induced by PBS policies influencing a pattern not to prescribe widely used low-cost medications [12]. However, a further study should be conducted on whether this impact was temporary or not. In the UK, a nationwide consultation service provided by community pharmacists was introduced in 2011 for patients starting a new medicine for chronic disease to prevent inappropriate medication use and enhance adherence [30]. However, our findings cannot be simply interpreted by the aforementioned policy initiatives as other factors (e.g., healthcare accessibility, social inequality) also could influence independently or interactively. In 2017, the UK organized the National Health Service Clinical Commissioners to provide the safest and most effective treatment to patients by establishing

the evidence on the clinical- and cost-effectiveness of medications [31]. In addition, the UK started the Discharge Medicine Service initiative in 2021 to prevent avoidable harm induced by medication and to provide guidance/materials to support pharmacy contractors [32], showing a continuing and practical effort at the governmental level.

Despite the awareness and efforts to reduce inappropriate polypharmacy, overall increasing trends were observed over a 10-year study period in Hong Kong, Taiwan, and South Korea. Of note, Hong Kong had the highest prevalence of chronic polypharmacy (44.9% in 2015) among the five study sites with 5.1% annual percentage increase over the study period. Hong Kong has a very well-developed publicly-funded secondary care healthcare system but a relatively poor-developed publicly-funded primary care system. High polypharmacy in Hong Kong may be partially attributable to patients consulting with multiple specialist doctors in secondary care without a key primary care doctor as a major care provider to coordinate care and prescribing [33, 34]. Furthermore, there is a lack of collaborative models for a medication review.

South Korea, Hong Kong, and Taiwan have developed lists of potentially inappropriate medications (PIMs) for older people since early 2010 [34-36]. Taiwan and Hong Kong developed country-specific PIM lists to address the differences in their approved medications, clinical practice, and medication accessibility under each healthcare system in 2018 and 2019, respectively [34, 36]. Moreover, South Korea has implemented a pilot project to provide a medication consultation service for patients with multimorbidity, receiving 5 or more medications based on a collaborative model among physicians, pharmacists, and nurses from 2019 [34]. Thus, further studies evaluating the comprehensive impact of these ongoing policy initiatives is warranted.

This study has several limitations. First, we did not consider other important factors, such as education level or socio-economic characteristics, indicating further trials are needed

to address these factors by stratification or standardization. Second, our findings may have been influenced by the definition of polypharmacy used in our study. However, we observed similar trends in several sensitivity analyses with different thresholds in terms of duration (Supplementary Fig 2, 3). Third, we measured polypharmacy using dichotomous cut-offs in our study, indicating that quantitative comparison of the number of medications is inappropriate across participating sites. Fourth, the prevalence of polypharmacy could be influenced by the number of medications included in each participating sites. However, all participating sites have adopted the positive list system based on an economic evaluation with risks and benefits when selecting reimbursed medications. Therefore, we believe that there is no substantial difference in the types of therapeutic areas or individual ingredients across our study sites. Lastly, we did not consider the appropriateness of polypharmacy and a high prevalence of polypharmacy does not necessarily indicate poor practice.

In conclusion, polypharmacy prevalence was higher and increasing over time in Hong Kong, South Korea, and Taiwan, compared to Australia and the UK. Our findings underline the necessity to monitor polypharmacy among older people in Asia by conducting government-level interventions and introducing medicine-optimization strategies.

REFERENCES

1. Whitty CJM, MacEwen C, Goddard A, Alderson D, Marshall M, Calderwood C, et al. Rising to the challenge of multimorbidity. BMJ (Clinical research ed). 2020 Jan 6;368:l6964.

2. Carroll C, Hassanin A. Polypharmacy in the Elderly-When Good Drugs Lead to Bad Outcomes: A Teachable Moment. JAMA Intern Med. 2017 Jun 1;177(6):871.

3. Chiatti C, Bustacchini S Fau - Furneri G, Furneri G Fau - Mantovani L, Mantovani L Fau - Cristiani M, Cristiani M Fau - Misuraca C, Misuraca C Fau - Lattanzio F, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people: a systematic review. (1179-1942 (Electronic)).

4. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. (0976-500X (Print)).

5. Parekh NA-O, Ali K, Stevenson JM, Davies JG, Schiff R, Van der Cammen T, et al. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. (1365-2125 (Electronic)).

6. Pirmohamed M, James S Fau - Meakin S, Meakin S Fau - Green C, Green C Fau - Scott AK, Scott Ak Fau - Walley TJ, Walley Tj Fau - Farrar K, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. (1756-1833 (Electronic)).

7. Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The Association between Polypharmacy and Dementia: A Nested Case-Control Study Based on a 12-Year Longitudinal Cohort Database in South Korea. PloS one. 2017;12(1):e0169463.

8. Pan HH, Li CY, Chen TJ, Su TP, Wang KY. Association of polypharmacy with fall-related fractures in older Taiwanese people: age- and gender-specific analyses. BMJ Open. 2014 Mar 28;4(3):e004428.

9. Morandi A, Bellelli G, Vasilevskis EE, Turco R, Guerini F, Torpilliesi T, et al.

Predictors of rehospitalization among elderly patients admitted to a rehabilitation hospital: the role of polypharmacy, functional status, and length of stay. Journal of the American Medical Directors Association. 2013 Oct;14(10):761-7.

10. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny M-P, Sheikh A. Medication Without Harm: WHO's Third Global Patient Safety Challenge. The Lancet. 2017;389(10080):1680-1.

11. Gao L, Maidment I, Matthews FE, Robinson L, Brayne C, on behalf of the Medical Research Council Cognitive F, et al. Medication usage change in older people (65+) in England over 20 years: findings from CFAS I and CFAS II. Age and Ageing. 2018;47(2):220-5.

12. Page AT, Falster MO, Litchfield M, Pearson S-A, Etherton-Beer C. Polypharmacy among older Australians, 2006–2017: a population-based study. Medical Journal of Australia. [https://doi.org/10.5694/mja2.50244]. 2019 2019/07/01;211(2):71-5.

13. Moriarty F, Hardy C, Bennett K, Smith SM, Fahey T. Trends and interaction of polypharmacy and potentially inappropriate prescribing in primary care over 15 years in Ireland: a repeated cross-sectional study. BMJ Open. 2015 Sep 18;5(9):e008656.

14. Morin L, Johnell K, Laroche ML, Fastbom J, Wastesson JW. The epidemiology of polypharmacy in older adults: register-based prospective cohort study. Clinical epidemiology. 2018;10:289-98.

15. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy Among Adults Aged 65 Years and Older in the United States: 1988-2010. The journals of gerontology Series A, Biological sciences and medical sciences. 2015 Aug;70(8):989-95.

16. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. Clinical pharmacology and therapeutics. 2012 Mar;91(3):521-8.

17. Nishtala PS, Salahudeen MS. Temporal Trends in Polypharmacy and

Hyperpolypharmacy in Older New Zealanders over a 9-Year Period: 2005–2013. Gerontology. 2015;61(3):195-202.

18. Chan DC, Hao YT, Wu SC. Characteristics of outpatient prescriptions for frail Taiwanese elders with long-term care needs. Pharmacoepidemiology and drug safety. 2009 Apr;18(4):327-34.

19. Kim HA, Shin JY, Kim MH, Park BJ. Prevalence and predictors of polypharmacy among Korean elderly. PloS one. 2014;9(6):e98043.

20. Lam DPY, Mak CF, Chan SMC, Yao RWY, Leung SSY, You JHS. Polypharmacy and inappropriate prescribing in elderly Hong Kong Chinese pateints. Journal of the American Geriatrics Society. [https://doi.org/10.1111/j.1532-5415.2009.02656.x]. 2010 2010/01/01;58(1):203-5.

21. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. Journal of the American Medical Directors Association. 2015 Jun 1;16(6):535.e1-12.

22. Pazan F, Wehling M. Polypharmacy in older adults: a narrative review of definitions, epidemiology and consequences. Eur Geriatr Med. 2021;12(3):443-52.

23. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230-.

24. Unites Nations Department of Economics and Social Affairs Population Division. World Population Prospects 2019. 2019.

25. National Health Insurance Service. Prevalence of polypharmacy between 2016 and 2019 in South Korea. Korea Pharmaceutical Association News; 2021 [10 March 2022]; Available from: https://www.kpanews.co.kr/article/show.asp?category=C&idx=223206.

26. Lai S-W, Liao K-F, Lin C-L, Lin C-C, Lin C-H. Longitudinal data of multimorbidity and polypharmacy in older adults in Taiwan from 2000 to 2013. Biomedicine (Taipei).

2020;10(2):1-4.

27. Cadogan CA, Ryan C, Francis JJ, Gormley GJ, Passmore P, Kerse N, et al. Improving appropriate polypharmacy for older people in primary care: selecting components of an evidence-based intervention to target prescribing and dispensing. Implementation Science. 2015 2015/11/16;10(1):161.

28. NHMRC Cognitive Decline Partnership Centre UoS, in Collaboration with the Australian Deprescribing Network and NPS MedicineWise. Quality use of Medicines to Optimise Ageing in Older Australians: Recommendations for a National Strategic Action Plan to Reduce Inappropriate Polypharmacy. 2018.

29. Jokanovic N, Tan EC, van den Bosch D, Kirkpatrick CM, Dooley MJ, Bell JS. Clinical medication review in Australia: A systematic review. Res Social Adm Pharm. 2016 May-Jun;12(3):384-418.

30. Elliott RA, Boyd MJ, Salema N-E, Davies J, Barber N, Mehta RL, et al. Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. BMJ Quality & Safety. 2016;25(10):747.

31. NHS England. Items which should not be routinely prescribed in primary care. NHS England; 2017 [28 October 2022].

32. NHS England. NHS Discharge Medicines Service. NHS England; 2021 [28 October 2022]; Available from: https://www.england.nhs.uk/primary-care/pharmacy/nhs-discharge-medicines-service/.

32. Hospital Authority. Strategic Plan 2017–2022: Innovating for Better Care. 2017;24,27. Available from: http://www.ha.org.hk/haho/ho/ap/HA-SP_1.pdf.

33. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, Hanlon JT. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet.

2007 Jul 14;370(9582):173-184.

34. Chang CB, Lai HY, Hwang SJ, Yang SY, Wu RS, Chang LY, et al. The updated PIM-Taiwan criteria: a list of potentially inappropriate medications in older people. Ther Adv Chronic Dis. 2019;10:2040622319879602.

35. Kim DS, Heo SI, Lee SH. Development of a list of potentially inappropriate drugs for the korean elderly using the delphi method. Healthc Inform Res. 2010 Dec;16(4):231-52.

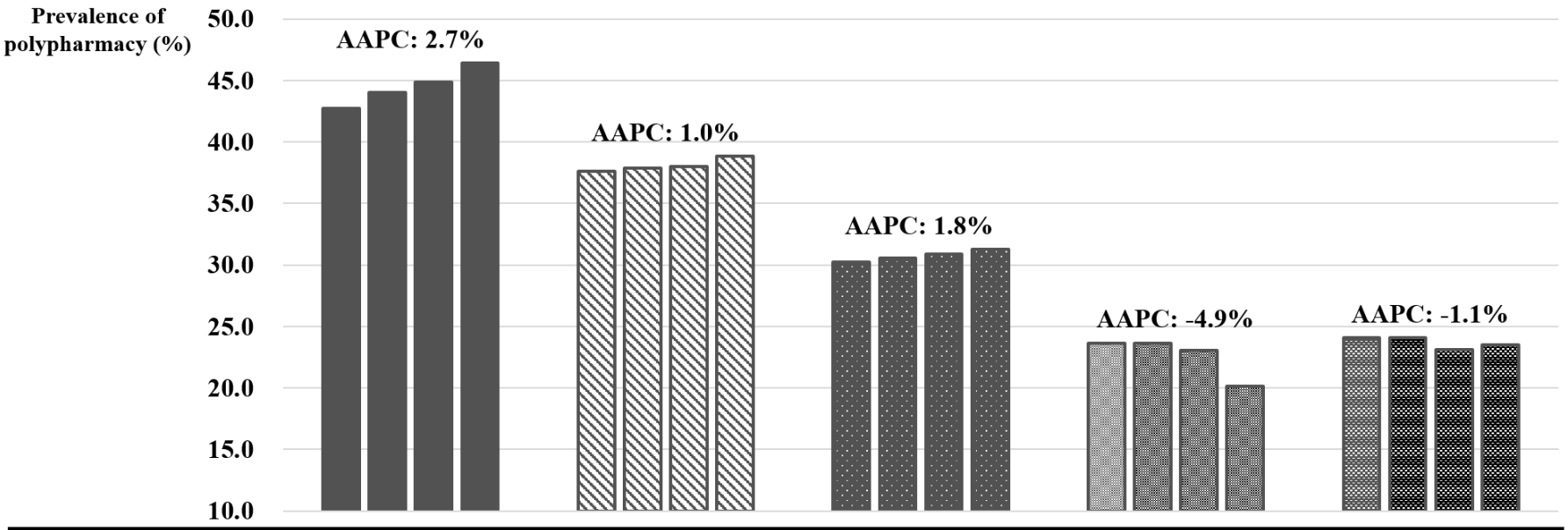
36. Zhang H, Wong ELY, Wong SYS, Chau PYK, Yip BHK, Chung RYN, et al. Comparison of adaptive versions of the Hong Kong-specific criteria and 2015 Beers criteria for assessing potentially inappropriate medication use in Hong Kong older patients. BMC Geriatr. 2021 Jun 21;21(1):379.

37. National Health Insurance Service. Symposium of Project for controlling polypharmacy under collaboration model among healthcare service providers. Medical News; 2022 [15 March 2022]; Available from: http://www.bosa.co.kr/news/articleView.html?idxno=2169413.

Table 1. Description of database and demographic characteristics in 2015

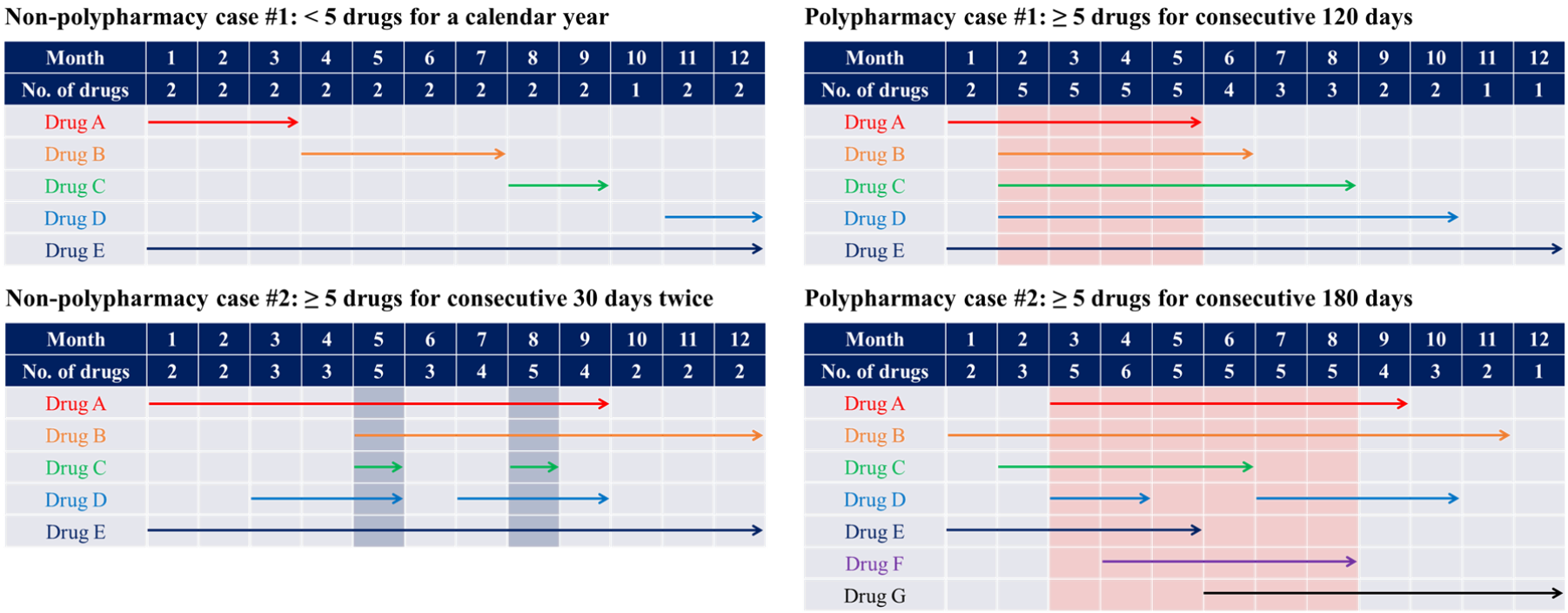
	Asia region				
	Hong Kong	**Taiwan**	**South Korea**	**Australia**	**United Kingdom**
Database	Hospital Authority Data Collaboration Lab	National Health Insurance Database	National Health Insurance Service-National Sample Cohort	Pharmaceutical Benefits Scheme	The IQVIA Medical Research Database
Covered population	0.1 million (1.4%)	2 million (5%)	1 million (2.2%)	2.5 million (10.0%)	18 million (6%)
Healthcare system	Universal	Universal	Universal	Universal	Universal
Enrolled individuals in 2016					
Total (n, %)	52,760 (100.0)	253,627 (100.0)	138,838 (100.0)	353,106 (100.0)	819,476 (100.0)
Age group (n, %)					
65-69	15,742 (29.8)	89,436 (35.3)	42,868 (32.1)	113,266 (32.1)	214,284 (26.1)
70-74	10,103 (19.1)	52,860 (20.8)	34,178 (24.7)	87,163 (24.7)	183,187 (22.4)
75-79	9,094 (17.2)	46,646 (18.4)	28,702 (17.9)	63,083 (17.9)	138,723 (16.9)
80-84	8,388 (15.9)	31,913 (12.6)	18,684 (12.6)	44,568 (12.6)	110,948 (13.5)
85+	9,433 (17.9)	32,772 (12.9)	14,406 (12.8)	45,026 (12.8)	172,334 (21.0)
Sex (n, %)					
Female	28,975 (54.9)	137,344 (54.2)	81,326 (58.6)	187,349 (53.1)	461,261 (56.3)
Male	23,785 (45.1)	116,283 (45.8)	57,512 (41.4)	165,757 (46.9)	358,215 (43.7)

As our databases were collected under the universal healthcare coverage, our results are representative of the entire population in each region or country.



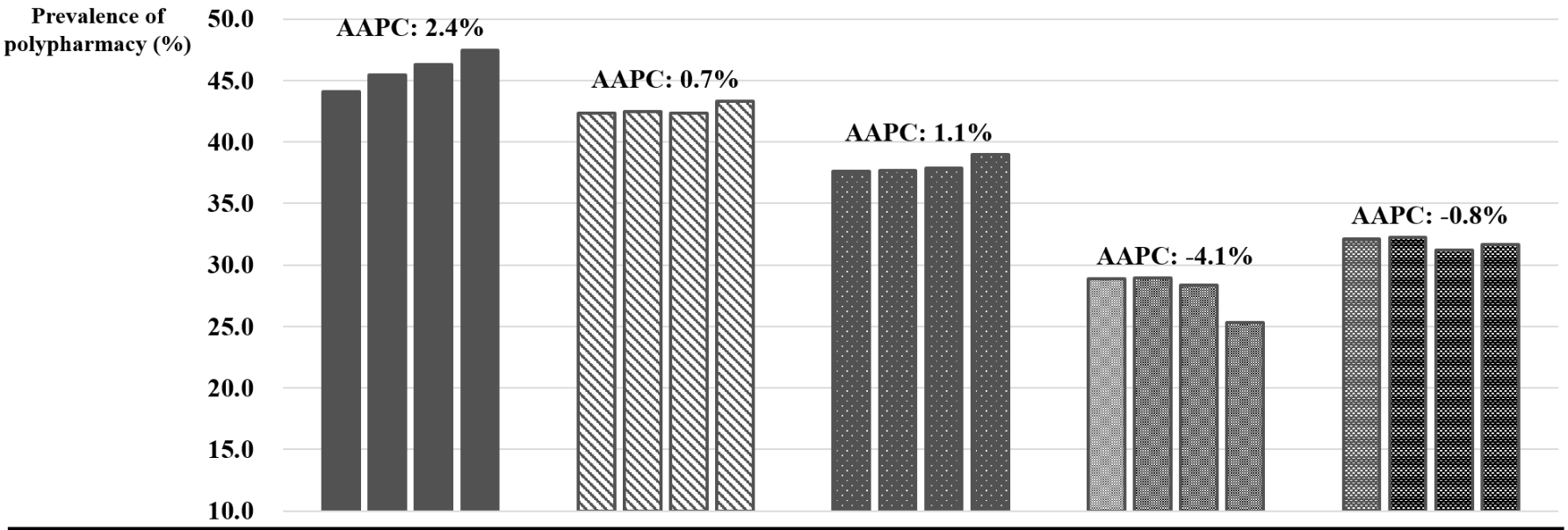
Year	Asia region			Australia	United Kingdom
	Hong Kong	Taiwan	South Korea		
2013	42.7	37.6	30.3	23.6	24.1
2014	44.0	37.9	30.6	23.7	24.1
2015	44.9	38.0	30.9	23.1	23.1
2016	46.4	38.8	32.0	20.1	23.5
Difference	**3.7**	**1.2**	**1.7**	**-3.5**	**-0.6**
AAPC (95% CI)	**2.7 (2.1 to 3.3)**	**1.0 (0.7 to 1.3)**	**1.8 (1.4 to 2.3)**	**-4.9 (-5.2 to -4.6)**	**-1.1 (-1.3 to -0.9)**

Figure 1. Trend in the age- and sex-standardized prevalence of polypharmacy in participating sites from 2003 to 2015
Abbreviations: AAPC, average annual percentage change.
* Difference was calculated by subtracting the prevalence of the first year from that of the last year.
† The change in trend was evaluated by average annual percentage change with a generalized linear model.



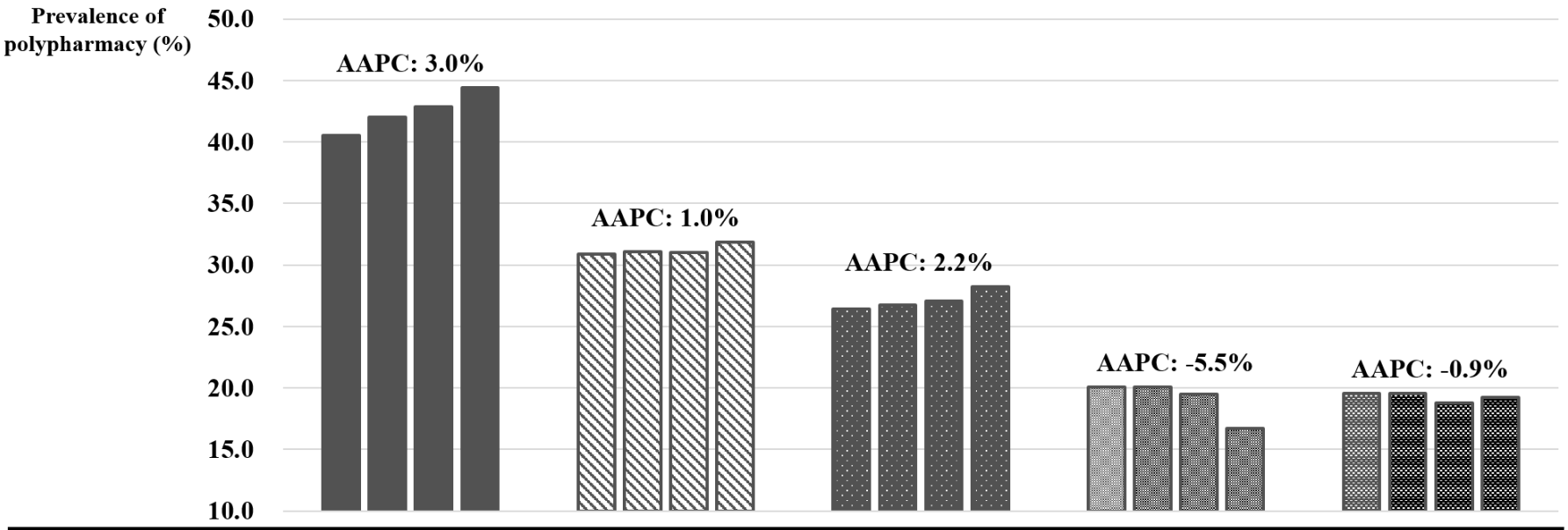
Supplementary figure 1. Illustration of polypharmacy definition

We classified the type of medication according to the fifth level of the WHO Anatomical Therapeutic Chemical (WHO-ATC) Classification System codes. The number of distinct medications used concomitantly on a daily basis was ascertained by examining outpatient medication records of all individuals for each year.



Year	Asia region			Australia	United Kingdom
	Hong Kong	Taiwan	South Korea		
2013	44.1	42.3	37.6	28.9	32.1
2014	45.4	42.5	37.7	28.9	32.3
2015	46.3	42.4	37.9	28.4	31.2
2016	47.5	43.3	39.0	25.3	31.6
Difference	**3.4**	**1.0**	**1.3**	**-3.6**	**-0.5**
AAPC (95% CI)	**2.4 (1.8 to 3.0)**	**0.7 (0.4 to 1.0)**	**1.1 (0.7 to 1.5)**	**-4.1 (-4.3 to -3.8)**	**-0.8 (-0.9 to -0.6)**

Supplementary figure 2. Sensitivity analysis of trend in the prevalence of polypharmacy with ≥ 5 medications and consecutive ≥ 30 days
Abbreviations: AAPC, average annual percentage change.
* Difference was calculated by subtracting the prevalence of the first year from that of the last year.
† The change in trend was evaluated by average annual percentage change with a generalized linear model.



Year	Asia region			Australia	United Kingdom
	Hong Kong	Taiwan	South Korea		
2013	40.5	30.9	26.4	20.1	19.6
2014	42.0	31.1	26.7	20.1	19.6
2015	42.9	31.0	27.1	19.5	18.8
2016	44.4	31.9	28.3	16.7	19.2
Difference	**3.9**	**1.0**	**1.8**	**-3.3**	**-0.3**
AAPC (95% CI)	**3.0 (2.4 to 3.6)**	**1.0 (0.6 to 1.3)**	**2.2 (1.7 to 2.6)**	**-5.5 (-5.9 to -5.2)**	**-0.9 (-1.1 to -0.7)**

Supplementary figure 3. Sensitivity analysis of trend in the prevalence of polypharmacy with ≥ 5 medications and consecutive ≥ 60 days
Abbreviations: AAPC, average annual percentage change.
* Difference was calculated by subtracting the prevalence of the first year from that of the last year.
† The change in trend was evaluated by average annual percentage change with a generalized linear model.