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Clinical Research Article

Geographic Variation in Osteoporosis Treatment in Postmenopausal Women: A 15-Year Longitudinal Analysis

Alicia R. Jones,[1,2] Joanne E. Enticott,[1] Peter R. Ebeling,[2,3] Gita D. Mishra,[4] Helena J. Teede,[1,2] and Amanda J. Vincent[1,2]

[1]Monash Centre for Health Research and Implementation, Monash University, Melbourne, Australia, 3168
[2]Department of Endocrinology, Monash Health, Melbourne, Australia, 3168
[3]Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia, 3168
[4]Australian Women and Girls' Health Research Centre, School of Public Health, University of Queensland, Brisbane, Australia, 4006

Correspondence: Alicia R. Jones, PhD, MBBS, BMedSci, Monash Centre for Health Research and Implementation, Locked Bag 29, Clayon, VIC, Australia 3168, Email: Alicia.jones@monash.edu.

Abstract

Context: Osteoporosis affects more than half of older women, but many are not treated. Whether treatment differs between rural and urban areas is unknown.

Objective: To examine differences in osteoporosis treatment among postmenopausal women living in urban and rural areas of Australia.

Methods: Women participating in the Australian Longitudinal Study on Women's Health, a prospective longitudinal cohort study, born between 1946-1951, and with osteoporosis or fractures, were included. Surveys from 2004 to 2019 were linked to the Pharmaceutical Benefits Scheme (government-subsidized medications) to assess osteoporosis treatment and adherence, comparing geographical areas.

Results: Of the 4259 women included (mean age, 55.6 years), 1703 lived in major cities, 1629 inner regional, 794 outer regional, and 133 remote areas. Over the 15-year follow-up, 1401 (32.9%) women received treatment, including 47.4% of women with osteoporosis and 29.9% with fractures. Women in outer regional and remote areas were less likely to use antiosteoporosis treatment than those in major cities on univariable analysis (outer regional odds ratio, 0.83; 95% CI, 0.72-0.95; remote, 0.65; 0.49-0.86), but this did not remain significant on multivariable analysis. Median duration of use was 10 to 36 months, adherence varied by treatment type (34%-100%) but was not related to incident fractures, and of the women who stopped denosumab, 85% did not receive another consolidating treatment.

Conclusion(s): One-third of women with osteoporosis/fractures received treatment, and adherence was low. There was no difference in treatment use between urban and rural areas after adjusting for risk factors, although the specific treatment used, and adherence, differed.

Key Words: osteoporosis, fracture, anti-resorptive, longitudinal, postmenopausal women

Abbreviations: ALSWH, Australian Longitudinal Study on Women's Health; BMD, bone mineral density; BMI, body mass index; IRSD, Index of Relative Socioeconomic Disadvantage; MHT, menopause hormone therapy; PBS, Pharmaceutical Benefits Scheme.

Each year an estimated 41 million fractures occur globally in adults older than age 55 years [1, 2]. A significant proportion of these are attributable to osteoporosis or low bone density, which affects approximately two thirds of postmenopausal women [3, 4]. The consequences of osteoporosis are significant; in the 12 months following an osteoporotic fracture, >10% will suffer another fracture and almost 20% will die [5]. Despite growing awareness of osteoporosis, widely available treatments, and public health campaigns, fracture incidence continues to increase, and, combined with an aging population, the morbidity and costs associated with osteoporosis and fractures are projected to rise [6-8].

Effective antiosteoporosis treatments exist to prevent first and subsequent fractures [9]. Despite this, the majority of people at high risk of fracture are not on treatment [8]. Less than half of people sustaining a first fracture are informed that they have osteoporosis, and less than one third are commenced on preventive treatment [8, 10, 11]. People living in rural areas have even lower use of antiosteoporosis treatments than those living in urban settings [12-14]. Differences in treatment rates may relate to different populations characteristics, availability of services, access to medical practitioners, and fracture liaison services. With approximately 30% of the population of Australia living outside major cities, assessing and optimizing osteoporosis care in these regions is essential.

For those who do commence osteoporosis treatment, adherence can be poor, ranging from 12% to 95%, with adherence declining over time [15, 16]. The majority of studies of adherence are based on oral bisphosphonates, which have been the predominant treatment for osteoporosis over the past 20 years. However, in Australia, there has been a decline in bisphosphonate use over the past decade, and a steady rise in denosumab use, now the most prescribed treatment for osteoporosis [17, 18]. Studies suggest improved adherence to denosumab compared with other treatments [19]. Little is known about differences in adherence between people living in urban and rural areas.

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The aim of this study is to examine real-world antiosteoporosis drug treatment rates and adherence among Australian postmenopausal females with osteoporosis, comparing those living in rural to urban areas.

Methods

Participants

This study uses data from The Australian Longitudinal Study on Women's Health (ALSWH), an ongoing prospective study examining the health of Australian women. Full details of the study are described elsewhere; all women provided written informed consent to participate [20]. Women were randomly invited from the Australian government health insurance database (Medicare), which includes all Australian citizens and permanent residents, with oversampling of people living outside major cities. Participants complete written/online surveys every 2 to 3 years from 1996. The data have been linked to administrative health record collections, including the Pharmaceutical Benefits Scheme (PBS, Australian government-subsidized medications), and hospital separation data. Linked PBS data are available from 2002 onwards and hospital separation are state-based, with availability differing by state, and all states included from 2007.

The current study uses data from the cohort born between 1946 and 1951 who remained in the study in 2004 to allow analysis of linked PBS data. Women with a diagnosis of osteoporosis or fracture from study inception to end were included. Women were excluded if they did not provide a geographic location of residence at baseline, in 2004. Women were followed up from 2004 to 2019, completing 6 surveys. Osteoporosis was self-reported at each survey, and prior studies have found moderate to good validity of self-reported osteoporosis in this cohort [21]. Osteoporosis diagnosis was also collected from hospital separation data, using International Classification of Diseases codes in which a primary or secondary diagnosis of osteoporosis was included (Supplementary Table S1) [22]. Fractures were self-reported for the previous 12 months in all surveys excluding survey 3 (2001), although the location and number of fractures was not asked. Fractures were also collected from hospital separation data using International Classification of Diseases codes (Supplementary Table S1) [22], and fractures of the skull, hands, and feet were excluded from hospital separation data.

The surveys included demographic details, anthropometry, age of menopause (first response included, with exclusion of those who had a hysterectomy before menopause), and self-reported comorbidities. Comorbidities related to osteoporosis were included in this study (hyperthyroidism, hyperparathyroidism, rheumatoid arthritis, malabsorption, inflammatory bowel disease, chronic liver disease, chronic kidney disease, diabetes, connective tissue disorders, and any transplant). The Index of Relative Socioeconomic Disadvantage (IRSD) was included as a marker of socioeconomic status, with lower IRSD indicating greater disadvantage. The Australian Statistical Geography Standard Remoteness Structure Accessibility and Remoteness Index of Australia was used to classify participant's geographical area of residence at each survey into major city, inner regional, outer regional, remote, and very remote area [23]. Because of low numbers of participants living in remote/very remote areas, these categories were grouped.

Ethical approval was obtained from The University of Newcastle HREC (EC00144), The University of Queensland HREC (EC00456/7), the Australian Institute of Health and Welfare HREC (EC00103), the NSW Population and Health Services Research Ethics Committee (EC00410, this included submission and review of a Victorian specific module to address Victorian legislative requirements), the ACT Health HREC (EC00100), the Department of Health Western Australia HREC (EC00422), and Tasmanian Health and Medical HREC (EC00337).

Outcomes

The primary outcome was comparing antiosteoporosis treatment use between geographical areas and predictors of treatment. Secondary outcomes were adherence to treatment and menopause hormone therapy (MHT) use.

Anti-osteoporosis treatment included all PBS-listed antiosteoporosis therapy (alendronate, risedronate, etidronate [delisted 2012], zoledronic acid, denosumab [available from 2013], raloxifene, strontium [delisted 2016], teriparatide, and calcitriol). Alendronate, risedronate, and etidronate were grouped together as oral bisphosphonates. Romosozumab was not reimbursed in Australia at the time of the study. Treatment is reported as past or current use at any time point and current use per survey period. The number of prescriptions was used to determine the duration of use and adherence. Adherence was defined as ≥80% medication possession ratio, with the exception of denosumab and zoledronic acid [24]. Denosumab is known to have a rapid loss of efficacy if a dose is missed or delayed; therefore, adherence was defined as subsequent dose within 7 months of the previous dose [25]. Zoledronic acid is known to have prolonged efficacy after each dose, and so adherence was defined as subsequent dose within 18 months [26].

Menopause hormone therapy information was collected from PBS data and included transdermal or oral estradiol, conjugated equine estrogen ± medroxyprogesterone acetate, transdermal or oral estradiol/norethisterone, estrone, estradiol/cyproterone, estradiol hemihydrate, estradiol/dydrogesterone, and the combined oral contraceptive pill. Vaginal estrogen prescriptions were excluded. As for osteoporosis-specific treatment, the number of prescriptions was used to determine duration of use and adherence. MHT was also self-reported in surveys, but self-reported data did not specify type or duration of use. MHT treatment is reported as past or current use (including before study commencement), and current use of MHT per survey period.

Statistics

Continuous variables were expressed as mean ± SD when normally distributed, and median (Quartile 1, Quartile 3) when nonnormally distributed. Categorical variables were expressed as number and percentage. Chi-square tests, or Fisher exact test when numbers were small, were used to compare the frequency of osteoporosis treatment, adherence, and MHT between geographical areas for each survey period.

Generalized estimating equations for panel data were used to determine longitudinal predictors of antiosteoporosis treatment, adherence to oral bisphosphonates and denosumab, and MHT use. Women were only included in the longitudinal analysis from the point of reporting osteoporosis or a fracture onwards, for the outcome of antiosteoporosis treatment, and while using a specific treatment, for adherence. Independent variables included factors known to modify risk of osteoporosis and influence adherence. Univariable regression was

performed, and variables retained at a significance level of $P < .2$ to form the multivariable model. Interaction testing between independent variables found significant interaction between IRSD and geographical area for the outcome of anti-osteoporosis treatment, and so IRSD was excluded from that multivariable analysis. Bootstrapping was performed with 100 repetitions at 95% sampling of the original dataset to ensure robustness. All P values were calculated from 2-tailed tests of statistical significance with a type 1 error rate of 5%. Analyses were conducted using Stata, version 15 (StataCorp, Texas, USA).

Results

Of the 13,714 women originally enrolled in the study in 1996, 10,905 remained in the study in 2004. Of these, 4260 (39.1%) were diagnosed with osteoporosis or a fracture during follow-up and 4259 provided information on geographic area of residence, forming the current study cohort. Characteristics of included women at baseline (2004) are displayed in Table 1. The mean (SD) age at inclusion in 2004 was 55.6 (1.5) years, and the age at last follow up was 68.9 (4.3) years.

Anti-osteoporosis Treatment

Of the 4259 women with osteoporosis (n = 2580) or fracture (n = 2686), 1401 (32.9%) received antiosteoporosis treatment at some point (47.4% with osteoporosis and 29.9% with fracture). Of the 101 women with hip fractures, 63 (62.4%) received treatment. Excluding any woman who had ever used MHT, the proportion of women who received osteoporosis treatment remained similar (30.2%). The proportion of women who currently or previously used antiosteoporosis treatment increased over time, as seen in Fig. 1.

There was a significant difference in the number of women who used antiosteoporosis treatment between geographic areas in 2004, but in subsequent surveys, no difference was seen (Fig. 2A and 2B). Women living outside major cities were less likely to have ever used treatment than those in major cities on univariable analysis (outer regional OR, 0.83; 95% CI, 0.72-0.95; remote, 0.65; 0.49-0.86); however, this did not remain significant on multivariable analysis (Table 2). Increasing age, lower body mass index (BMI), and earlier age of menopause were associated with higher likelihood of ever receiving treatment, whereas current smoking was associated with a lower likelihood of receiving treatment (Table 2). The same predictive factors were significant when analyzing current treatment (Supplementary Table S2) [22]. Bootstrapping confirmed these results.

Types of Antiosteoporosis Treatments

The types of antiosteoporosis treatment, duration, and adherence are in Table 3. Most used either oral bisphosphonates (n = 840, 60.0%) or denosumab (n = 802, 57.2%), and the frequency of oral bisphosphonate use, but not denosumab, differed between geographic areas at different time points (Fig. 3A and 3B). Some women used more than 1 treatment during the study (344 used both oral bisphosphonates and denosumab, 89 used oral bisphosphonates and strontium, 63 used oral bisphosphonate and zoledronic acid, 52 used denosumab and zoledronic acid, 87 used denosumab and strontium). Of the 802 users of denosumab, 695 (86.7%) persisted and 107 stopped denosumab. Of those who stopped denosumab, 16 (15.0%) changed to another treatment and 91 (85.0%) stopped without another treatment.

Adherence to Antiosteoporosis Treatments

Adherence ranged from 34% to 100%, with greater adherence for parenteral therapy (denosumab, zoledronic acid, teriparatide) than oral therapies (Table 3). In longitudinal analysis, when incident fractures (per survey period) were examined in regard to current adherence, there was no increased risk of incident fracture among those currently nonadherent to either oral bisphosphonates (OR, 0.94; 95% CI, 0.74-1.20), denosumab (OR, 0.72; 95% CI, 0.51-1.02), or antiresorptive treatment combined (OR, 0.97; 95% CI, 0.81-1.16).

Adherence to oral bisphosphonates did not differ by geographical area, but younger age predicted greater adherence, whereas current smokers were less likely to be adherent (Table 4). Women living in inner regional areas were more likely than those living in major cities to be adherent to denosumab (OR, 1.59; 95% CI, 1.04-2.44; Table 5). Older age and fewer comorbidities were also associated with greater denosumab adherence (Table 5). Bootstrapping did not alter results.

Menopause Hormone Therapy

At inclusion in 2004, 2475 (58.1%) women reported past or current MHT use. PBS-derived MHT use was available for 864 women, with types of MHT shown in Supplementary Table S3 [22]. The median (Q1, Q3) duration of MHT use from PBS data (any type combined) was 17 (5, 51) months, and 26.5% of women were adherent with treatment.

Combining self-reported and PBS-derived current or past MHT, MHT was used by 2629 (61.7%) women, including 1650 (64.0%) of women with osteoporosis and 1632 (60.8%) with a fracture. A total of 909 women used both MHT and antiosteoporosis treatment, and including both osteoporosis treatment and MHT together, 3121 (73%) of women received 1 or the other treatment at some point. There was no difference between geographical areas in the number of women who had ever used MHT (Fig. 4A) or currently using MHT (Fig. 4B) at any survey. On longitudinal generalized estimating equation analysis, there was no difference in cumulative past or current MHT use between geographical areas; however, those living in remote areas were less likely to currently use MHT (OR, 0.65; 95% CI, 0.43-0.98; Supplementary Tables S4 and 5 [22]). Lower age of menopause was associated with greater likelihood of currently or having ever used MHT, increasing age was associated with having ever used MHT whereas lower age was associated with current use, and increasing BMI was associated with lower likelihood of current use (Supplementary Tables S4 and S5 [22]).

Discussion

In this longitudinal study over 15 years, only one-third of women with osteoporosis or a fracture received antiosteoporosis treatment. Women living in outer regional and remote areas had lower use of antiosteoporosis treatment on univariable, but not multivariable analysis. Of those treated, the average duration was short, less than 3 years, and adherence with treatment varied, being greater with parenteral therapies. Another 40% of women used MHT, potentially providing

Table 1. Characteristics of included women in 2004, by geographical area

		Major city (1703)	Inner regional area (1629)	Outer regional area (794)	Remote (133)	All (4259)	*P* value
Age (mean, SD)		55.62 (1.5)	55.48 (1.4)	55.58 (1.5)	55.59 (1.5)	55.56 (1.5)	.889
BMI (mean, SD)		26.64 (5.6)	27.08 (5.7)	27.26 (5.6)	27.67 (5.4)	26.96 (5.6)	.850
Education, n (%)	<High school	718 (42.6)	802 (49.6)	417 (52.8)	74 (57.4)	2011 (47.6)	<.001
	High school certificate	277 (16.4)	239 (14.8)	133 (16.8)	19 (14.7)	668 (15.8)	
	Trade/apprentice/ certificate/diploma	370 (22.0)	336 (20.8)	148 (18.7)	24 (18.6)	878 (20.8)	
	University/higher degree	321 (19.0)	240 (14.8)	92 (11.7)	12 (9.3)	665 (15.8)	
Marital status, n (%)	Partnered	1256 (74.7)	1278 (79.4)	654 (84.0)	111 (83.5)	3299 (78.5)	<.001
	No partner	425 (25.3)	332 (20.6)	125 (16.1)	22 (16.5)	904 (21.5)	
Country of birth, n (%)	Australia	1168 (69.4)	1330 (82.7)	638 (81.5)	99 (75.6)	3235 (76.9)	<.001
	Outside Australia	516 (30.6)	279 (17.3)	145 (18.5)	32 (24.4)	972 (23.1)	
Smoking, n (%)	Never	964 (56.8)	926 (57.1)	476 (60.3)	71 (53.8)	2437 (57.5)	.238
	Former	498 (29.4)	67 (28.8)	193 (24.4)	39 (29.6)	1197 (28.2)	
	Current	235 (13.9)	228 (14.1)	121 (15.3)	22 (16.7)	606 (14.3)	
Alcohol intake, n (%)	No	233 (13.9)	257 (16.0)	149 (19.1)	22 (16.8)	661 (15.7)	.010
	Yes	1448 (86.1)	1353 (84.0)	631 (80.9)	109 (83.2)	3541 (84.3)	
Comorbidities present,[a] *n* (%)		194 (11.4)	165 (10.1)	96 (12.1)	21 (15.8)	476 (11.2)	.145
IRSD (mean, SD)		1030.36 (86.7)	983.89 (76.0)	957.84 (70.8)	970.47 (74.7)	997.39 (84.5)	<.001
Age of menopause		50.09 (5.1)	50.10 (5.4)	49.55 (5.5)	50.16 (4.6)	50.00 (5.2)	.049
Current exogenous estrogen[b]		528 (31.0)	462 (28.4)	236 (29.7)	33 (24.8)	1259 (29.6)	.233

Abbreviations: BMI, body mass index; IRSD, Index of Relative Socio-economic Disadvantage.
[a]Comorbidities include hyperthyroidism, hyperparathyroidism, rheumatoid arthritis, malabsorption, inflammatory bowel disease, chronic liver disease, chronic kidney disease, diabetes, connective tissue disorders, and any transplant; the maximum number of comorbidities at baseline was 1.
[b]Exogenous estrogen includes current use of menopause hormone therapy (oral, transdermal, nasal) or the combined oral contraceptive pill.

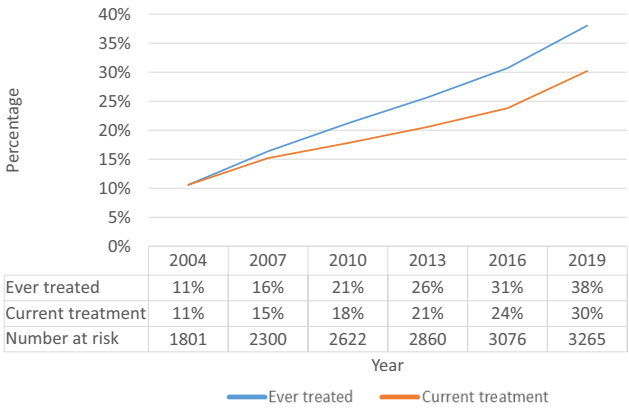

Figure 1. Current or previous antiosteoporosis treatment in women with osteoporosis or fractures. Number at risk refers to number of women with prevalent osteoporosis/fracture at that survey.

some bone protection, although adherence to MHT was low and the duration short.

The rates of osteoporosis treatment observed here reflects a worldwide treatment gap in osteoporosis, in which the majority of people at high risk for fracture are not receiving preventive treatment [8]. A 2004 cross-sectional survey of 88 000 postmenopausal females in Australia found that only 28% of those with a previous minimal trauma fracture received treatment, including MHT [10]. In the United States, <20% of postmenopausal women receive osteoporosis treatment following a minimal trauma fracture [27, 28]. Even among hip fracture patients, arguably the most serious complication of osteoporosis, treatment rates remain <50% globally [29-31]. A systematic review of treatment following minimal trauma fractures found that 3% to 65% received treatment, including MHT [11]. Given the included studies were published >15 years ago, and significant importance has been placed on improving secondary fracture prevention since then, it would be hoped that treatment rates would now be higher. However, studies have shown that the treatment gap has actually increased over time [8]. Although we observed an increase in treatment use over time, this was only 33% by study end in 2019.

Univariable analysis suggested people living in outer regional and remote areas were 17% and 35% less likely to receive antiosteoporosis treatment than those living in major cities, but this did not remain significant on multivariable analysis. However, the univariable findings are still clinically important. Women with osteoporosis/fractures living in these areas had lower use of treatment, and although this may be related to differences in age, BMI, smoking status, and their age of menopause, the fact remains that treatment use is lower. At a broad level, it may not be possible to modify the predictive factors for a whole region, so the gap in treatment is an important finding and highlights a need for policy makers.

A previous Australian study examining bisphosphonate use among people living in Western Australia demonstrated those living in rural areas were 46% less likely to use bisphosphonates before sustaining a hip fracture, although treatment rates 12 months following the fracture did not differ, and all

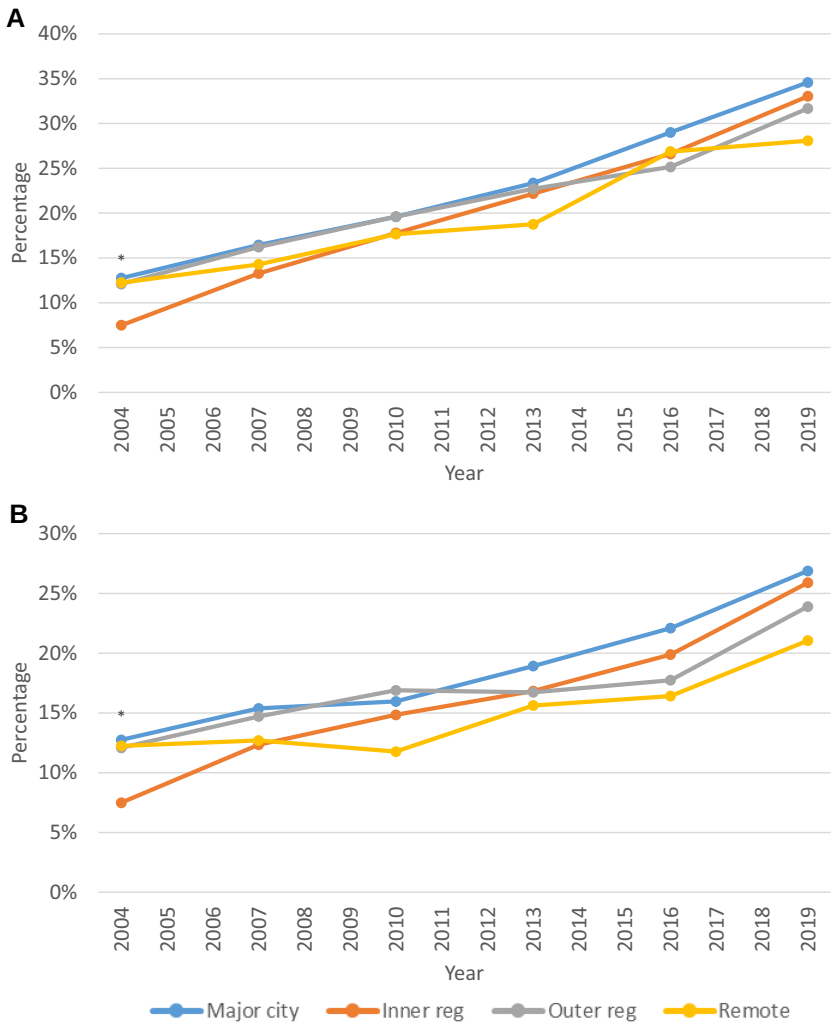

Figure 2. (A) Frequency of current or previous use antiosteoporosis treatment in women with osteoporosis/fractures by geographic area. (B) Frequency of current use of antiosteoporosis treatment in women with osteoporosis/fractures by geographic area. Frequency at each survey is compared by chi-square test/Fisher exact test. $*P < .01$.

patients were treated at the same metropolitan hospital [13]. Globally, a study of postmenopausal women in Canada found lower use of antiosteoporosis therapy in women living in rural compared with urban areas, and a study in the United Kingdom found significant geographical variation in treatment rates across different regions [12, 14]. However, many studies do not adjust for other clinical factors that may predict treatment use. A large study in the United States found no difference in treatment rates between rural and urban areas, after adjusting for other risk factors, similar to our findings [30].

Factors associated with a greater likelihood of antiosteoporosis treatment included increasing age, lower BMI, and earlier age of menopause, whereas current smoking was associated with lower likelihood of treatment. Increasing age, earlier age of menopause, and lower BMI are established risk factors for fracture, and so would be expected to increase treatment probability. Most studies confirm greater use of antiosteoporosis treatment as people age [11, 32]. Interestingly, and in contrast to previous studies, the total number of osteoporosis-related comorbidities did not increase the likelihood of treatment, and current smoking, a significant risk factor for fracture, was associated with lower likelihood of treatment and lower adherence to oral bisphosphonate [30]. The reason for this gap in care is unclear. If FRAX® or other clinical risk calculators are used for treatment decisions, these risk factors would increase prescribing. Potential reasons for the discrepancy may include access to care, frequency of medical attendance, risk perception, or patient preference. People with mental health disorders in Australia are also more likely to smoke, and this may also influence adherence, and could be explored in future studies [33].

Previous studies have found overall adherence to osteoporosis therapies is between 13% and 95%; our study showed slightly higher adherence of 34% to 100%, but with a more lenient definition of zoledronic acid adherence [15]. Nonadherence to osteoporosis medications has been associated with a 30% increased risk for fracture, albeit in shorter-term studies, where dichotomous adherence and fracture numbers are analyzed over the entire study period [34]. In contrast, we did not find increased incident fractures in those currently nonadherent to medications over a 15-year time period. The reason for this is unclear, but may be due to inadequate sample size, given that only 800 women over the 15 years received treatment and had fractures, and many of these fractures predated treatment commencing. In addition, the total number of women on treatment increased over the study, so that the follow-up time for women commencing treatment in the final surveys was only 3 to 6 years, which may be insufficient duration to detect

Table 2. Predictors of current or past antiosteoporosis treatment in women with osteoporosis/fracture, longitudinal analysis

		Univariable model				Multivariable model			
		OR	95% CI		*P* value	OR	95% CI		*P* value
Age		1.09	1.08	1.10	<.001	1.09	1.08	1.10	<.001
Geographical area	Major city	Ref							
	Inner regional	0.96	0.86	1.08	.482	0.92	0.80	1.06	.233
	Outer regional	0.83	0.72	0.95	.008	0.91	0.76	1.08	.277
	Remote	0.65	0.49	0.86	.002	0.83	0.57	1.21	.324
BMI		0.97	0.96	0.98	<.001	0.95	0.94	0.97	<.001
Country of birth	Australia	Ref							
	Outside Australia	1.04	0.91	1.20	.541	NA			
Smoking	Never	Ref							
	Former	0.93	0.85	1.02	.139	0.98	0.87	1.12	.795
	Current	0.62	0.52	0.74	<.001	0.79	0.62	0.99	.046
Alcohol	No	Ref							
	Yes	0.83	0.75	0.91	<.001	1.06	0.93	1.22	.398
Age of menopause		0.98	0.96	0.99	<.001	0.97	0.96	0.99	<.001
IRSD		1.00	1.00	1.00	<.001	NA			
Number of comorbidities		1.36	1.26	1.47	<.001	1.03	0.92	1.16	.566

Abbreviations: BMI, body mass index; IRSD, index of Relative Socio-economic Disadvantage; NA, not available.

Table 3. Types of osteoporosis treatments used in women with osteoporosis or fracture

	Number	% of patients on treatment (n = 1401)[a]	Duration (median, Q1, Q3)	Adherent (≥80% medication possession index, n, %)
PO BP	840	60.0	33 (8, 64.5)	457 (54.4)
Denosumab	802	57.2	24 (12, 42)	627 (78.2)
Zoledronic acid	118	8.4	36 (24, 60)	118 (100)
Teriparatide	10	0.07	23.5 (20, 25)	9 (90.0)
Raloxifene	65	4.6	32 (9, 62)	39 (60.0)
Strontium	153	10.9	10 (3, 30)	52 (34.0)
Calcitriol	58	4.1	16.8 (6.4, 62.4)	22 (37.9)

Abbreviation: PO BP: oral bisphosphonates, includes alendronate, risedronate, and etidronate.
[a]Percentage >100% because some people used > 1 treatment.

changes in fracture risk. A large study of women in the United States following minimal trauma fractures found 37% of women were adherent to oral bisphosphonates at 12 months, and a systematic review found 23% to 48% were adherent by 3 years [35, 36]. Studies of denosumab generally show improved adherence, with 12-month adherence >70% [19]. However, this figure does not necessarily include appropriately timed subsequent doses of denosumab or consolidation following denosumab cessation. An Australian study found that 80% of those who stop denosumab do not have another osteoporosis treatment as consolidation [18]. Similarly, in the current study, adherence to denosumab, defined as appropriate dosing within 7 months of the previous dose, was 78%, and of the 107 who stopped denosumab, 85% did not have another treatment as consolidation. This is a significant concern, considering that stopping or delaying doses of denosumab is associated with rapid loss of bone mineral density (BMD) and multiple vertebral fractures, and denosumab is the most commonly prescribed antiresorptive in Australia. Adherence to antiosteoporosis medications is clearly a significant issue, and methods targeting both consumers and providers are needed to improve this.

The most common determinants of adherence in the literature include age, medication type, and frequency of dosing [36]. Given this, we analyzed predictors of adherence separately for oral bisphosphonates and denosumab. Interestingly, younger age predicted adherence to oral bisphosphonates, whereas older age predicted adherence to denosumab. Previous studies have found similarly conflicting results for the effects of age on adherence [15]. One study suggested there may be a bimodal relationship between age and adherence, with lower adherence both in younger (40-59 years) and older (≥80 years) adults, compared with those aged 60 to 69 years [37]. People living in inner regional areas were more likely to be adherent to denosumab than those living in major cities, and reasons for this, such as access to a regular general practitioner or practice nurse, should be investigated. There is minimal previous data on adherence differences based on geographical area. A study of male and female hip fracture patients in Western Australia found no difference in 12-month adherence to oral bisphosphonates between rural and urban areas [13]. As denosumab use continues to be high in Australia, determining factors that influence and promote adherence to it are crucial.

At the start of the current study, more than half of women self-reported previous use of MHT; however, the type, dose, and duration were not collected. By study end, 62% had used MHT. MHT has been shown to improve BMD and reduce fracture risk in women, but the evidence for benefit in higher risk women, with established osteoporosis, is less clear, and BMD declines rapidly after MHT is stopped [38-40]. Although previously recommended, MHT is no longer considered first-line treatment of osteoporosis or secondary fracture prevention [39, 41, 42]. In addition, the indication for MHT in this cohort was unknown. For these reasons, we analyzed MHT separately from antiosteoporosis treatments. The frequency of MHT use in the current study use was broadly in

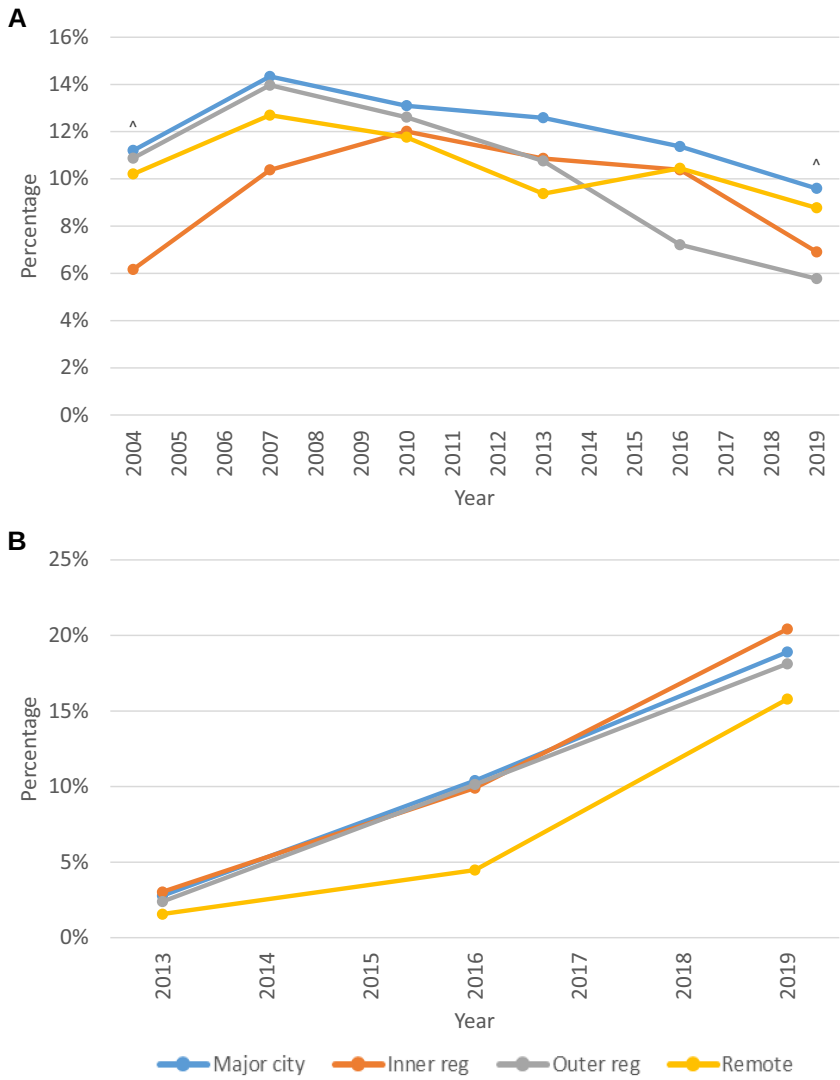

Figure 3. (A) Current use of oral bisphosphonates in women with osteoporosis or fractures by geographic area. (B) Current use of denosumab in women with osteoporosis or fractures by geographic area. Frequency at each survey is compared by chi-square test/Fisher exact test. Note that denosumab was only available on PBS in Australia from 2013. ^$P < .05$.

Table 4. Predictors of adherence to oral bisphosphonates

		Univariable model				Multivariable model			
		OR	**95% CI**		***P* value**	**OR**	**95% CI**		***P* value**
Age		0.98	0.96	1.00	.027	0.97	0.95	1.00	.025
Geographical area	Major city	Ref				NA			
	Inner regional	1.03	0.79	1.35	.813				
	Outer regional	0.82	0.59	1.16	.261				
	Remote	0.93	0.46	1.91	.847				
BMI		0.99	0.96	1.01	.211	NA			
Country of birth	Australia	Ref				NA			
	Outside Australia	1.11	0.85	1.45	.437				
Smoking	Never	Ref							
	Former	0.90	0.69	1.18	.455	1.01	0.73	1.39	.957
	Current	0.42	0.27	0.66	<.001	0.37	0.21	0.65	<.001
Alcohol	No	Ref				NA			
	Yes	1.01	0.76	1.34	.960				
Age of menopause		1.02	0.99	1.04	.143	1.02	0.99	1.05	.124
IRSD		1.00	1.00	1.00	.258	NA			
Number of comorbidities		0.93	0.74	1.16	.523	NA			

Abbreviations: BMI, body mass index; IRSD, Index of Relative Socio-economic Disadvantage; NA, not available.

Table 5. Predictors of adherence to denosumab

		Univariable model				Multivariable model			
		OR	**95% CI**		***P* value**	**OR**	**95% CI**		***P* value**
Age		1.08	1.01	1.15	.027	1.08	1.01	1.16	.029
Geographical area	Major city	Ref							
	Inner regional	1.48	1.00	2.20	.053	1.59	1.04	2.44	.034
	Outer regional	1.07	0.64	1.77	.806	1.16	0.69	1.96	.574
	Remote	2.42	0.30	19.5	.408	2.29	0.27	19.77	.450
BMI		0.97	0.93	1.01	.132	0.98	0.94	1.02	.273
Country of birth	Australia	Ref				NA			
	Outside Australia	1.05	0.74	1.48	.771				
Smoking	Never	Ref				NA			
	Former	1.04	0.72	1.52	.820				
	Current	1.37	0.54	3.50	.505				
Alcohol	No	Ref							
	Yes	1.39	0.91	2.11	.130	1.45	0.91	2.29	.116
Age of menopause		1.00	0.96	1.04	.973				
IRSD		1.00	1.00	1.00	.842	NA			
Number of comorbidities		0.67	0.52	0.87	.003	0.74	0.57	0.97	.028

Abbreviations: BMI, body mass index; IRSDI, Index of Relative Socio-economic Disadvantage; NA, not available.

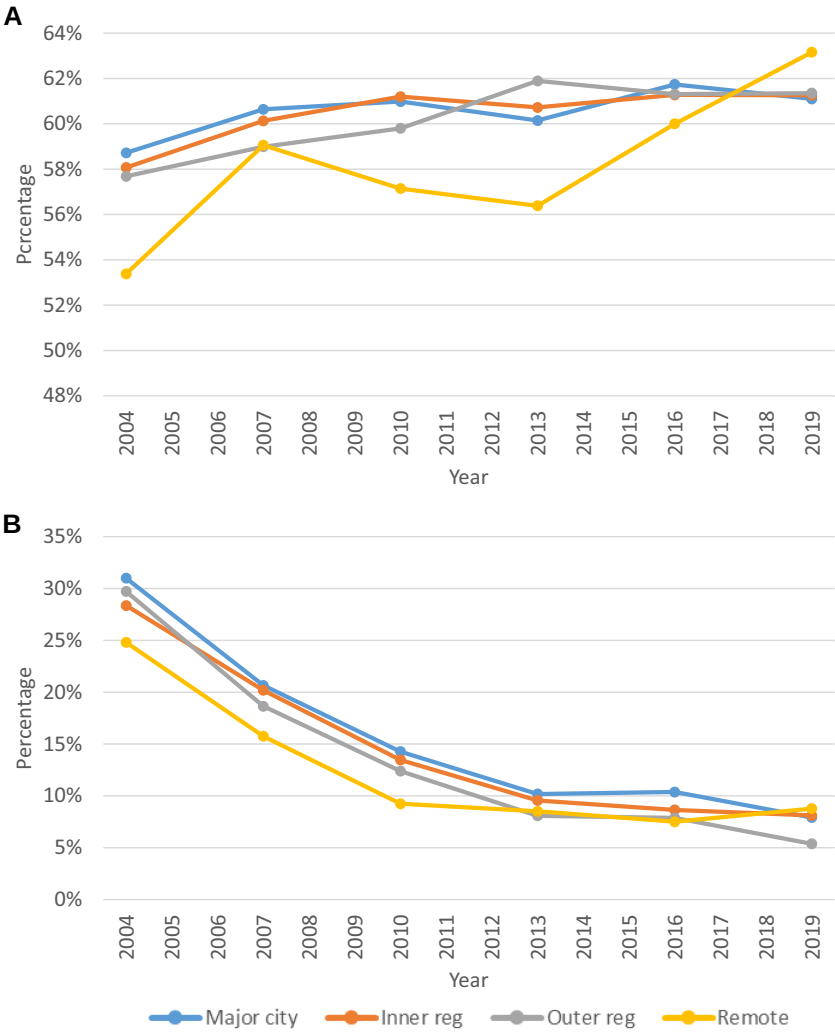

Figure 4. (A) Cumulative frequency of current or previous use of menopause hormone therapy by geographic area. (B) Current use of menopause hormone therapy by geographic area. Frequency at each survey is compared by chi-square tests.

line with existing research. A 2013 cross-sectional analysis of Australian women found 13% of women aged 50 to 69 years currently used MHT, and of those aged 65 to 69 years, 57% had ever used MHT [43]. As with the current study, women in rural and urban areas had similar cumulative use of MHT, although in our study women in remote areas were less likely to currently use MHT [44]. Consistent with current recommendations, earlier age of menopause predicted ever or current MHT use [38, 39]. In addition, increasing age predicted having ever used MHT, whereas lower age predicted current use, which is in line with practice guidelines, indicating a favorable risk/benefit profile of MHT in women younger than age 60 years or within 10 years of menopause [45].

This is a large study performed over 15 years and includes broad representation of women from across Australia. Linked data were used to accurately obtain information on the type, duration, and adherence to antiosteoporosis treatments. However, there are several limitations. We used current or past treatment with any antiosteoporosis treatment as the primary outcome, and some women only used treatment for a short time, which may not have equivalent efficacy, although the same factors predicted current use. We were unable to assess use of antiosteoporosis treatment before 2002, and there is evidence that bisphosphonates, in particular, provide long-term protection after cessation [46]. That said, before 2002, zoledronic acid, denosumab, and teriparatide were not reimbursed in Australia. Private, nonreimbursed medications were not included. Duration and adherence calculations assumed women took all medications they were dispensed, as instructed, and that parenteral therapies were administered soon after dispensing. The majority of women using MHT did so before 2004, and details on the type and duration were not collected. We analyzed MHT use separately to osteoporosis medications, and some may argue MHT should be considered an osteoporosis medication, although when women exposed to MHT were excluded, a significant treatment gap remained. Last, we were unable to include data on BMD and associations with fracture risk or treatment and adherence because BMD details were not collected through surveys or administrative databases. Comparison of the initial study cohort in 1996 to the 1996 National census data showed that included women had higher educational attainment and were more likely to be Australian-born, than the general Australian population [47].

In conclusion, this study highlights a continuing significant gap in osteoporosis treatment, with only one third of women with osteoporosis or fractures receiving treatment, suboptimal adherence, and no association between adherence and fracture risk. Women living in outer regional and remote areas had even lower use of treatment on univariable analysis, and the types of treatments and adherence to specific treatments, differed between geographic areas. Overall, this paper enforces the need for urgent action to improve treatment for osteoporosis across all regions, to prevent fractures.

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- SA NT Datalink, SA Health and Northern Territory Department of Health for the SA Public Hospital Separations and NT Public Hospital Inpatient Activity Data Collections.
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Data Availability

ALSWH survey data are owned by the Australian Government Department of Health and Aged Care and due to the personal nature of the data collected, release by ALSWH is subject to strict contractual and ethical restrictions. Ethical review of ALSWH is by the Human Research Ethics Committees at The University of Queensland and The University of Newcastle. Deidentified data are available to collaborating researchers when a formal request to make use of the material has been approved by the ALSWH Data Access Committee. The committee is receptive of requests for datasets required to replicate results. Information on applying for ALSWH data is available from https://alswh.org.au/for-data-users/applying-for-data/.

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