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Identifying temporal patterns of adherence to antidepressants, bisphosphonates and statins, and associated patient factors

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ABSTRACT

Background: Group-based trajectory modelling (GBTM) has recently been explored internationally as an improved approach to measuring medication adherence (MA) by differentiating between alternative temporal patterns of nonadherence. To build on this international research, we use the method to identify temporal patterns of medication adherence to antidepressants, bisphosphonates or statins, and their associations with patient characteristics.

Objectives: The objectives include identification of MA types using GBTM, exploration of features and associated patient characteristics of each MA type, and identification of the advantages of GBTM compared to the traditional proportion of days covered (PDC) measure.

Data and methods: We used 45 and Up Study survey data which contains information about demographics, family, health, diet, work and lifestyle of 267,153 participants aged at least 45 years across New South Wales, Australia. This data was linked to participant records of medication use, outpatient and inpatient care, and death. Our study participants initiated use of antidepressants (9287 participants), bisphosphonates (1660 participants) or statins (10,242 participants) during 2012–2016. MA types were identified from 180-day patterns of medication use for antidepressants and 360-day patterns for bisphosphonates and statins. Multinomial and binomial logistic regressions were performed to estimate participant characteristics associated with GBTM MA and PDC MA, respectively.

Results: Three GBTM MA types were identified for antidepressants and six for bisphosphonates and statins. For all three medications, MA types included: almost fully adherent; decreasing adherence and early discontinuation. The additional nonadherent types for bisphosphonates and statins were improved adherence, low adherence and later discontinuation. Participant characteristics impacting GBTM MA and PDC MA were consistent. However, several associations were uniquely found for GBTM MA as compared to PDC MA.

Conclusion: GBTM permits clinicians, policy-makers and researchers to differentiate between alternative nonadherence patterns, allowing them to better identify patients at risk of poor adherence and tailor interventions accordingly.

1. Introduction

Medication adherence (MA) refers to the extent to which a person's behaviour of taking medication corresponds with recommendations from a healthcare provider (Sabaté, 2003).

Medication nonadherence for chronic conditions requiring long-term care is widespread, estimated to be of the order of 50% (Briesacher et al., 2008; Sabaté, 2003; Yeaw et al., 2009). Multiple factors are associated with poor MA including socioeconomic factors, therapy-related factors, patient-related factors, condition-related factors, and health system or healthcare team-related factors (Brown & Bussell, 2011; Sabaté, 2003).

The cost of nonadherence to the US healthcare system has been estimated at $100 billion to $289 billion annually (New England Healthcare Institute, 2009; Osterberg & Blaschke, 2005; Peterson et al., 2003). For instance, the reported consequences of nonadherence to antidepressants include relapse and symptom recurrence, chronicity, poor psychosocial outcomes, and increased suicide rates (M. S. Lee et al., 2010); nonadherence to bisphosphonates include risk of osteoporotic fracture (Byun et al., 2017); and nonadherence to statins include recurring major cardiovascular events (Armitage et al., 2019).

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Overestimated MA can lead to treatment efficacy underestimation, leading to potentially dangerous intensification of therapy or unnecessarily expensive clinical procedures (W. Y. Lam & Fresco, 2015). Alternatively, treatment efficacy in clinical trials where MA is better controlled may overestimate treatment effectiveness. Accurate estimates of MA are also required for identifying risk factors, health outcomes, healthcare resource utilisation and other outcomes of nonadherence, and for developing effective interventions to improve MA.

Various measures have been employed to capture medication taking behaviour of patients (Forbes et al., 2018; W. Y.; Lam & Fresco, 2015), both direct (e.g., biochemical monitoring, direct observation of patient's behaviour), and indirect (e.g., pharmacy records, pill count, questionnaires). Indirect measures based on pharmacy records of prescription filling are commonly used (e.g. Hoogendoorn et al., 2019; Ihle et al., 2019; Simon et al., 2018), providing inexpensive but valid and objective adherence information (Nieuwlaat et al., 2014) with good predictive validity (e.g. Choo et al., 1999; Steiner & Prochazka, 1997) and close correlation with measures based on electric monitoring and pill count (Choo et al., 1999).

Traditionally, MA has been summarised as a single percentage value representing the amount of medicine taken relative to the total amount prescribed during a specified period, such as the medication possession ratio (MPR) (Peterson et al., 2007) or proportion of days covered (PDC) (Ho et al., 2009). Patients are considered adherent if the percentage value is greater than a threshold value, often set at 80% for chronic conditions (Nau, 2012). However, a single percentage MA measure does not account for the temporal pattern of taking medications, which may significantly impact outcomes (Alhazami et al., 2020; Franklin et al., 2013).

Group-based trajectory modelling (GBTM) has been explored as an improved approach to describe MA (Alhazami et al., 2020). This application of finite mixture models (Nagin, 2014), categorises individuals based on types of longitudinal medication use (Modi et al., 2011). It considers the amount of medication taken as measured by PDC or MPR, and timing of discontinuation as measured by medication persistence.

GBTM MA types can also be expressed via intuitive plots, can be meaningfully related to patient factors, health outcomes and healthcare resource utilisation (Guo et al., 2017; Modi et al., 2011; Walsh et al., 2021) and are more homogeneous than those identified using PDC (Franklin et al., 2013). Improved predictive accuracies were found when using GBTM adherence trajectories compared to PDC measures for predicting future cardiovascular events from statin adherence (Franklin et al., 2015) and for predicting diabetes-related hospitalisation and ED visits from adherence to oral hypoglycemics (Lo-Ciganic et al., 2016).

Further research on measuring MA using GBTM is needed for different populations and medication types and a wider range of risk factors. For instance, GBTM adherence trajectories have not been identified for bisphosphonates or antidepressants, which is a medication class that has typical poor adherence. Several studies have analysed patient factors associated with GBTM adherence trajectories (Li et al., 2014; Paranjpe et al., 2020; Vadhariya et al., 2019), but factors such as access to healthcare and family and living arrangements have not been considered. Little is known of whether GBTM permits better identification of risk factors associated with MA than conventional MA measures. Only one such study, Aarnio et al. (2016), found that GBTM, compared to PDC, allows more differentiative identification of relationships between MA to statins and socioeconomic status.

We had two objectives. First, it aimed to identify GBTM MA types using temporal patterns of medication use, explore characteristics of each type, and determine if the categorisation provide MA information potentially advantageous compared to PDC. Second, it examined patient factors associated with the GBTM MA types and compared these with factors associated with PDC MA to determine if GBTM identifies different or additional factors.

Our study explored the use of antidepressants, bisphosphonates and statins. These were chosen because the prevalence of each associated chronic condition (depression, osteoporosis and cardiovascular disease, respectively) is relatively high and imposes a large burden on society (Hoy, 2016). Widespread low MA for these medications leads to poorer health outcomes and greater use of healthcare resources (Cutler et al., 2018). These three medication groups are also used in different ways for different populations, allowing our study to test the applicability of GBTM across different contexts.

2. Data

2.1. Data sources

Data were linked from five sources: the Sax Institute's 45 and Up Study (45 and Up Study Collaborators, 2008), the Medicare Benefit Schedule (MBS) data (Sax Institute, 2020), the Pharmaceutical Benefit Scheme (PBS) data (Sax Institute, 2020), the Cause of Death Unit Record File (CODURF) (NSW Ministry of Health, 2020a) and the Admitted Patient Data Collection (APDC) (NSW Ministry of Health, 2020b). The MBS and PBS data were linked to the 45 and Up Study by the Sax Institute using a deterministic method based on a unique identifier (Sax Institute, 2020). The CODURF and APDC data were further linked by the Centre for Health Record Linkage (http://www.cherel.org.au) using a probabilistic method based on multiple non-unique linkage variables (Centre for Health Record Linkage, n.d.). The linkages provide deidentified personal health records for the 45 and Up Study participants. Data were securely accessed by the Secured Unified Research Environment (SURE). Consent for long term follow-up including linkage to personal health records was provided by participants.

The 45 and Up Study is a large-scale study based on repeated surveys with recruitment of 267,153 participants (for the baseline survey) aged 45 years or above across NSW, approximately 10% of such population. Eligible individuals were randomly sampled from the Services Australia (formerly Australian Government Department of Human Services) Medicare enrolment database, and the response rate was 18%. The questionnaires distributed via post contained questions about demographic information, family, health, diet, work, and lifestyle, and were self-administered by the participants. Responses from the follow-up survey conducted during 2012–2015 were used for our research.

MBS and PBS data sets are automated data collections held by Services Australia which record information about subsidised healthcare services (e.g., general practice visits, specialist visit outside of hospital) and subsidised medications, respectively. Individuals in the Services Australia Medicare enrolment database (from which the 45 and Up Study participants are sampled) are eligible for these subsidies. The periods covered are 2001–2017 and 2004 to 2017 for MBS and PBS data sets, respectively. Service date and type, medication type and pack, and amount of medication filled were used for this research.

CODURF is a data collection at the Australian Coordinating Registry which records information on deaths in Australia. The period covered is 2004–2017. Date of death was used for this research.

APDC is a data collection held by the NSW Ministry of Health containing records of admitted patient services in NSW. Variables showing episode start date and diagnosis codes during 2004–2017 were used for this research.

2.2. Sample selection

Selected participants for our study are 45 and Up Study participants who initiated using any type of antidepressants, bisphosphonates or statins, as specified by the Anatomical Therapeutic Chemical (ATC) (WHO Collaborating Centre for Drug Statistics Methodology, 2020) code of N06A, M05BA or M05BB, and C10AA, respectively, after conducting the follow-up survey during 2012–2016. Consistent with previous research (Kettunen et al., 2019; Kjellberg et al., 2016; Zhao et al., 2014), initiation was defined as filling a medication for the first time if

medication of the same type (e.g., any antidepressant) had not been filled in the year prior. Participants were further required to be alive to the end of MA measuring period. Three non-exclusive cohorts were constructed for the three types of medications for separate analyses.

An additional exclusion criterion was given only for the bisphosphonate cohort. That is, participants who show any historical APDC record of malignant neoplasms or Paget's bone disease, as specified by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 2004) codes of C00–97 and M88, respectively, were excluded to address non-general use of bisphosphonates, an approach also taken in other bisphosphonate studies (Kjellberg et al., 2016; LaFleur et al., 2015; Sunyecz et al., 2008).

2.3. Covariates

Covariates were selected from the 45 and Up Study, PBS and MBS for analyses to identify participant characteristics or use of medications and healthcare services that are associated with MA, or to act as control variables. MA is influenced by multiple factors related to socioeconomics, patients, diseases, regimens and healthcare systems (Brown & Bussell, 2011; Sabaté, 2003). Covariates were selected from the data available based on potential risk factors identified in the literature. Covariates from the 45 and Up Study include demographic, health, lifestyle, family, living, work, income and insurance factors. Covariates from the MBS and PBS data sets include other types of medications used during the MA measuring period to control for implied but unobservable health conditions, number of different types of medications used during the MA measuring period, whether a participant later used a type of studied medication different to the index medication type during the MA measuring period and the extent to which the participant saw the same general practitioner (continuity of care, COC) calculated using Bice-Boxerman COC (Bice & Boxerman, 1977) during the one-year period before initiating the medication (Chen & Cheng, 2016).

Missing values from unanswered 45 and Up survey questions were treated by imputing the most reasonable value by considering other factors in the data set using RandomForest analysis (Liaw & Wiener, 2002), a method found to produce unbiased regression parameter estimates and to be more efficient than the alternative, parametric multivariate imputation by chained equations (Shah et al., 2014). The entire set of covariates is listed in the electronic supplementary Appendix A, along with the proportion of missing values where these exist for the covariate. The total proportion of missing values across the entire dataset is 2.5%.

3. Methods

3.1. Adherence types using GBTM

GBTM (L Jones & Nagin, 2012; Nagin, 2014; Nagin & Land, 1993; Nagin & Odgers, 2010) was used to identify types of MA based on temporal patterns of medication use. GBTM is also known as latent class growth analysis, and represents an application of finite mixture modelling to identify a chosen number of distinctive trajectories, or groups, that are most likely to exist within data of individual patterns. Estimation is via maximum likelihood on simultaneously estimated multiple regression models.

Individuals are assigned to a GBTM group based on posterior probabilities (i.e., estimated probabilities that each individual pattern belongs to the identified groups) to form meaningful groups of statistically similar trajectories. In this study, such assignments created a categorical response variable, GBTM MA.

In medication and clinical research that aim to identify different trajectories for certain developments or patterns (e.g., change of weight, MA) that may exist within a population, GBTM has often been chosen over other methods that also examine variability of individual trajectories including growth curve modelling (GCM) and growth mixture modelling (GMM) (Chien et al., 2019; B.; Feldman et al., 2020; Nagin & Odgers, 2010). While GCM only explains individual-specific variations with random effects around the same average trend, GMM and GBTM assume the existence of multiple subpopulations and identify multiple trends. GMM assumes that individuals in each subpopulation follow varied trajectories according to GCM. GBTM assumes that individuals in a subpopulation follow a homogeneous trajectory (Nagin & Odgers, 2010). The relative simplicity and modelling approach focussing on identification of distinguishable trajectories (Frankfurt et al., 2016) permits GBTM to better identify homogenous set of trajectories from the population (B. J. Feldman et al., 2009; Shearer et al., 2016).

GBTM is widely used and has been found in several studies to perform better than other methods to group longitudinal patterns; for example, GBTM achieved higher sensitivity than k-means clustering and Bayesian regression for predicting patient outcome after cardiac arrest (Elmer et al., 2020); and GBTM outperformed K-means clustering, a two-step approach with mixed modelling and K-means clustering, latent class analysis and GMM in identifying underlying trajectories (Twisk & Hoekstra, 2012).

Our study applied GBTM to individual MA patterns identified from PBS data as the 80% adherence in each 30-day block of time (e.g., "1" if greater than 24 of 30 days were covered and "0" otherwise) during a 180-day MA measuring period since initiation for antidepressants and a 360-day period for bisphosphonates and statins. The 180-day time frame was chosen according to the minimum time of adherence to antidepressant therapy recommended by the American Psychiatric Association guidelines (Gelenberg et al., 2010). For bisphosphonates and statins, 360-day adherence was evaluated to reflect longer term adherence as these medications are generally recommended to be used continually. The chosen time frames are consistent with those used in other MA studies, allowing comparability (Ereshefsky et al., 2010; Kjellberg et al., 2016; Mehta et al., 2019; Sharman Moser et al., 2016; Vega et al., 2017; Zhao et al., 2014). A 30-day block was chosen to provide reasonably smooth (compared to shorter length) and more informative (compared to longer length) longitudinal patterns to GBTM. For each 30-day block, medication coverage was assessed daily considering previous medication fills.[1]

The number of days covered by each medication fill was estimated using the modal gap between consecutive fills across the entire PBS dataset for each medication pack. An estimate was required because the PBS dataset does not include dosage information. Other studies have used a similar approach applied to the PBS dataset (Lu & Roughead, 2012; Roughead et al., 2009). The mode was considered the most appropriate measure because the collected data contained outliers, large gaps in the case of discontinuation followed by later re-initiation. We found general consistencies between our estimates – mostly 28 days – and those based on the defined daily dose (DDD) provided by WHO Collaborating Centre for Drug Statistics Methodology (2020).

GBTM analyses were undertaken using the LCMM package (Proust-Lima et al., 2015) under R version 4.0, using a probit model for binary longitudinal data. Mean trajectories were specified using quadratic functions of time. The number of groups between two and six was chosen by minimising BIC with the condition that no group comprised less than 5% of the entire sample, to ensure that every group is practically meaningful and likely to be statistically useful for subsequent regression analyses (Dillon et al., 2018; Nagin, 2014).

The results of GBTM were assessed by three diagnostic criteria suggested by Nagin (2005). First, the average maximum posterior probability (AMPP) for each group (i.e., the average, within individuals

[1] For example, if a participant newly filled 10 days' medications when it is seven days to the end of adherence measuring period and medications for 5 days' use are still remaining, only 2 days' dose from the new fill is counted for MA measurement.

assigned to a certain group, for the posterior probabilities that they belong to that group) was calculated with the suggested cut-off of at least 70% in all groups (Nagin, 2005). Second, odds of correct classification relative to a random classification (OCC) were calculated as follows:

$$\frac{\frac{AMPP_j}{1-AMPP_j}}{\frac{EGP_j}{1-EGP_j}}$$

where estimated group probability (EGP_j) is the size of the group j as a proportion of the entire sample as estimated by GBTM, with a suggested cut-off of at least 5.0 for all groups (Nagin, 2005). Third, EGP for each group was compared to the proportion of the sample actually assigned to each group; similar values for the two proportions in all groups suggest a good model fit.

3.2. Adherence using PDC

Defining adherence for participants who achieved at least 80% of PDC was done to provide a conventional MA measure. The PDC was calculated by dividing the total number of days covered with medication by the total number of days in the MA measuring period. The PDC was then dichotomised according to whether PDC is at least 80% (adherence) or not (nonadherence) to form a binary variable, PDC MA.

3.3. Analysis of factors associated with adherence

Descriptive statistics were computed to show comparisons between GBTM MA and PDC MA, and distribution of GBTM MA types across sex and age groups.

Unordered multinomial logistic regressions (MNL) were used to estimate participant and healthcare characteristics (covariates) that significantly impact GBTM MA (response). MNL is a regression method for a categorical response variable with no natural ordering (Luce, 1959; McFadden, 1974), as is the case for GBTM MA. For the modelling of MNL, the reference category was chosen to be the category demonstrating the highest adherence based on PDC. Binomial logistic regressions (BNL), a special case of MNL otherwise known as logistic regression, were used to estimate participant and healthcare characteristics that significantly impact the binary response variable PDC MA. Coefficients were estimated using maximum likelihood estimation and the Newton-Raphson procedure (Wooldridge, 2002, pp. 372–374). From the estimated coefficients, relative risk ratios (RRR) and average marginal effects (AME) (Long & Freese, 2006) were calculated and reported. RRR estimates the impact of a covariate of interest on the relative probability of belonging to a certain category within the response variable compared to the reference category, and AME estimates the average impact on the absolute probability. STATA MP 16 (StataCorp LP, College Station, TX, USA) was used for all regression analyses. The Huber-White sandwich estimator of variance (Freedman, 2006) was

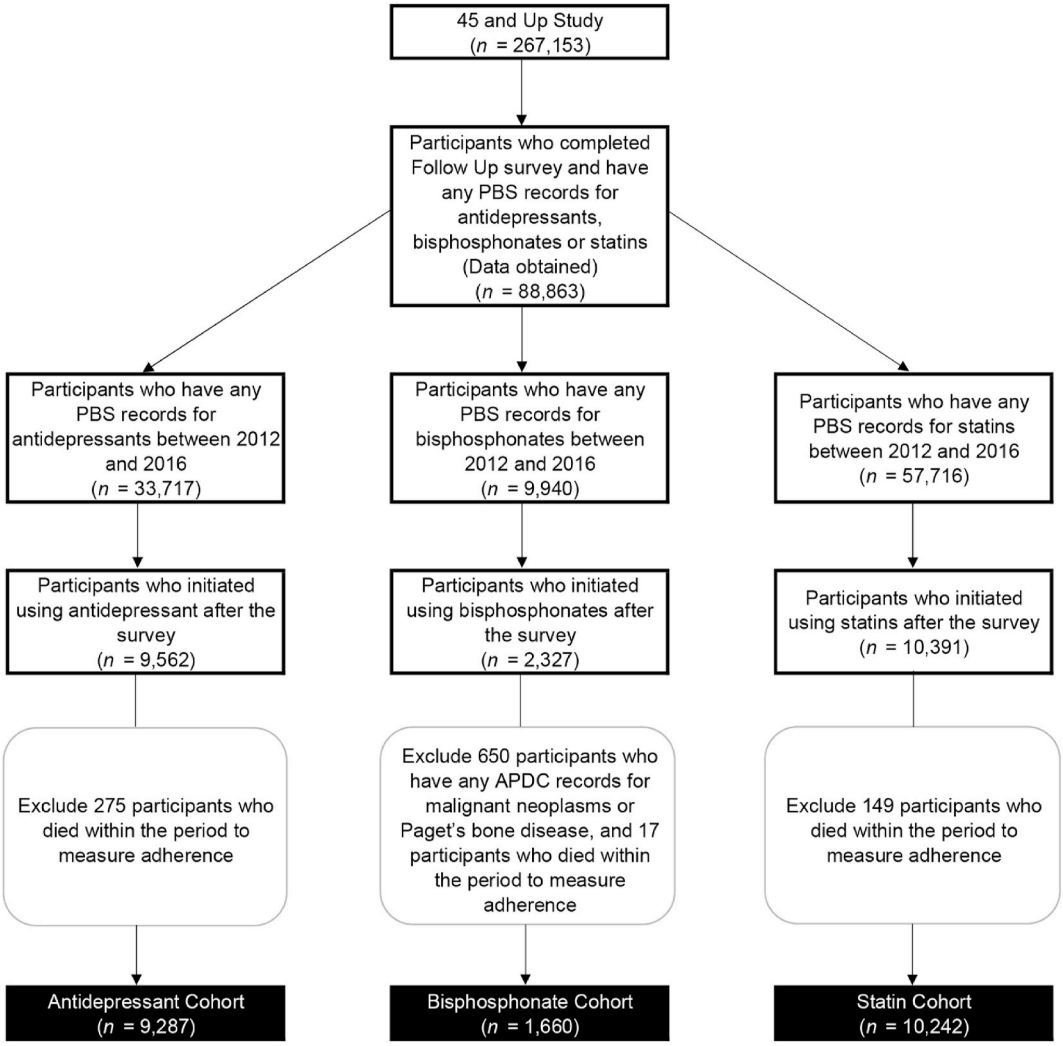

Fig. 1. Participant flow diagram.

used to account for heteroskedasticity in residual distribution to ensure robustness of the results. Considerations of assumptions for the regression models are present in Appendix C.

4. Results

4.1. Cohort characteristics

The numbers of participants chosen were 9,287, 1660 and 10,242 for antidepressants, bisphosphonates, and statins cohorts, respectively. Fig. 1 is a participant flow diagram showing how the three cohorts were formed using the inclusion and exclusion criteria. Several characteristics of the cohorts are presented in Table 1.

4.2. GBTM adherence types

The GBTM identified three GBTM MA types for antidepressants and six types for bisphosphonates and statins, as shown in Fig. 2. Justifications for the number of MA types identified based on BIC and whether each group size is greater than 5% are shown in Table 2. The identification of GBTM MA types for all three medications sufficiently met all evaluation criteria specified by Nagin (2005): AMPP ≥70%, OCC ≥5 and differences between EGP and GP at most 3%, as shown in Table 3.

There is a broad consistency in the GBTM MA types between the three medication types, which have been labelled as follows:

- *Adherent* (all medication types): Adherence throughout.
- *Improved* (bisphosphonates and statins): Moderate adherence followed by higher adherence.
- *Decreasing* (all medication types): Gradually declining adherence over time.
- *Low* (bisphosphonates and statins): Low but continued use of medications. Participants showing simply irregular medication fills belong to this group.
- *Discontinued mid* (bisphosphonates and statins): Discontinuation after seven to eight months.
- *Discontinued early* (all medication types): Early discontinuation, usually when a participant filled a medication once only.

In the antidepressants cohort, the proportion of participants assigned to *Discontinued early* (44%) was larger than those in the other cohorts (19% for bisphosphonates, 18% for statins) while other participants were fairly evenly distributed into the two other groups, Adherent (27%) and Decreasing (29%) over the 180-day period. Although not reported, similar patterns were identified when a 360-day period was used.

For the bisphosphonates and statins cohorts, the same numbers of groups with similar trajectories over the 360-day period were identified with somewhat elevated adherences for bisphosphonates in the *Adherent*, *Improved* and *Decreasing* groups. For the two cohorts, similar percentages were assigned to four groups, *Adherent* (36% and 35% for bisphosphonates and statins, respectively), *Improved* (16% and 19%), *Decreasing* (7% and 6%), and *Discontinued early* (19% and 18%). The proportion of participants in *Low* was higher for statins (16% compared to 10%) while that in *Discontinued mid* was higher for bisphosphonates (13% compared to 7%).

Comparisons between GBTM and PDC, and distributions of GBTM MA types across PDC MA, sex and age groups (see Table 4) found that those adherent by GBTM MA were mostly also adherent by PDC MA and those adherent by PDC MA were mostly those categorised as *Adherent* or *Improved* by GBTM MA. Average PDC was lower for antidepressants (49%) compared to bisphosphonates (67%) and statins (63%). Distributions of GBTM MA types are similar across sex, and younger antidepressant users seem more adherent while the opposite is observed in statin users.

Table 1
Description of cohorts by medication cohort.

	Antidepressants	Bisphosphonates	Statins
Total number, *n*	9287	1660	10,242
Mean age [a]	69 (10)	72 (9)	68 (9)
% Female	63%	78%	53%
Income>$150,000 (%)	7%	3%	9%
Income<$30,000 (%)	28%	32%	23%
Education - University or higher (%)	24%	23%	28%
Education - No school (%)	10%	10%	9%
% Full-time worker	17%	8%	19%
% Part-time worker	13%	11%	13%
% Retired	49%	60%	45%
% Private insurance holder	78%	76%	82%
% Smoking	12%	11%	12%
Self-rated health [b]	2.7	2.6	2.5
% Non-English language spoken at home	6%	7%	7%
Average time between survey completion and initiation of corresponding medication (days)	534	498	541

[a] Standard deviation is reported in parenthesis.
[b] 1 = excellent; 2 = very good; 3 = good; 4 = fair; and 5 = poor.

4.3. Participant factors associated with adherence

Results from MNL (for GBTM MA) and BNL (for PDC MA) regressions for antidepressants are shown in Table 5, for bisphosphonates in Table 6 and for statins in Table 7. These tables present the results for covariates showing significant association with at least one type of nonadherence. The full results are available in the electronic supplementary Appendix B.

4.3.1. Covariates associated with both PDC and GBTM nonadherence

For all three medication cohorts, covariates highly significantly associated ($p < 0.01$) with PDC nonadherence were generally also significantly associated with at least one type of GBTM nonadherence; across the entire set of analyses there were only two exceptions to this, one each for bisphosphonates and statins. For example, within the antidepressant cohort, an additional year of age was associated with 2% increased likelihoods (i.e., RRR minus 1) of becoming *Nonadherent* (PDC) and *Discontinued early* (GBTM) ($p \leq 0.001$) and 1% increased likelihood of *Decreasing* (GBTM)($p \leq 0.05$), relative to *Adherent*. AME shows that an additional year of age on average increases probability of being *Nonadherent* (PDC) and *Discontinued early* (GBTM) by 0.27% ($p < 0.001$) and 0.36% ($p < 0.001$), respectively.

The covariates found to be highly significantly ($p < 0.01$) associated with increased likelihood or probability of PDC nonadherence and also significantly ($p < 0.05$) associated with at least one type of GBTM nonadherence for antidepressants were increased age, living in a remote region (with mixed direction of effects in different GBTM groups), non-English language, separated rather than married, living in a house rather than nursing home or hostel, reduced weight, index medication type not being Selective Serotonin Reuptake Inhibitors (SSRI), not switching medication type (with mixed direction of effects), and non-use of antipsychotic or antidementia medications. For bisphosphonates, the relevant covariates were living in a remote region, not having private insurance without extra cover, index medication not being ibandronic or zoledronic versus risedronic acid, and not switching medication type (with mixed direction of effects). For statins, the relevant covariates were higher Depression Score, Non-English language, lesser time living in Australia, not holding a healthcare card, index medication being simvastatin versus rosuvastatin, having a liver test (with mixed direction of effects), switching medication type (with mixed direction of effects), lesser use of blood forming medication, and greater use of systemic hormonal medication. It can be seen that covariates common to at least two medication types are living in a remote region, non-English

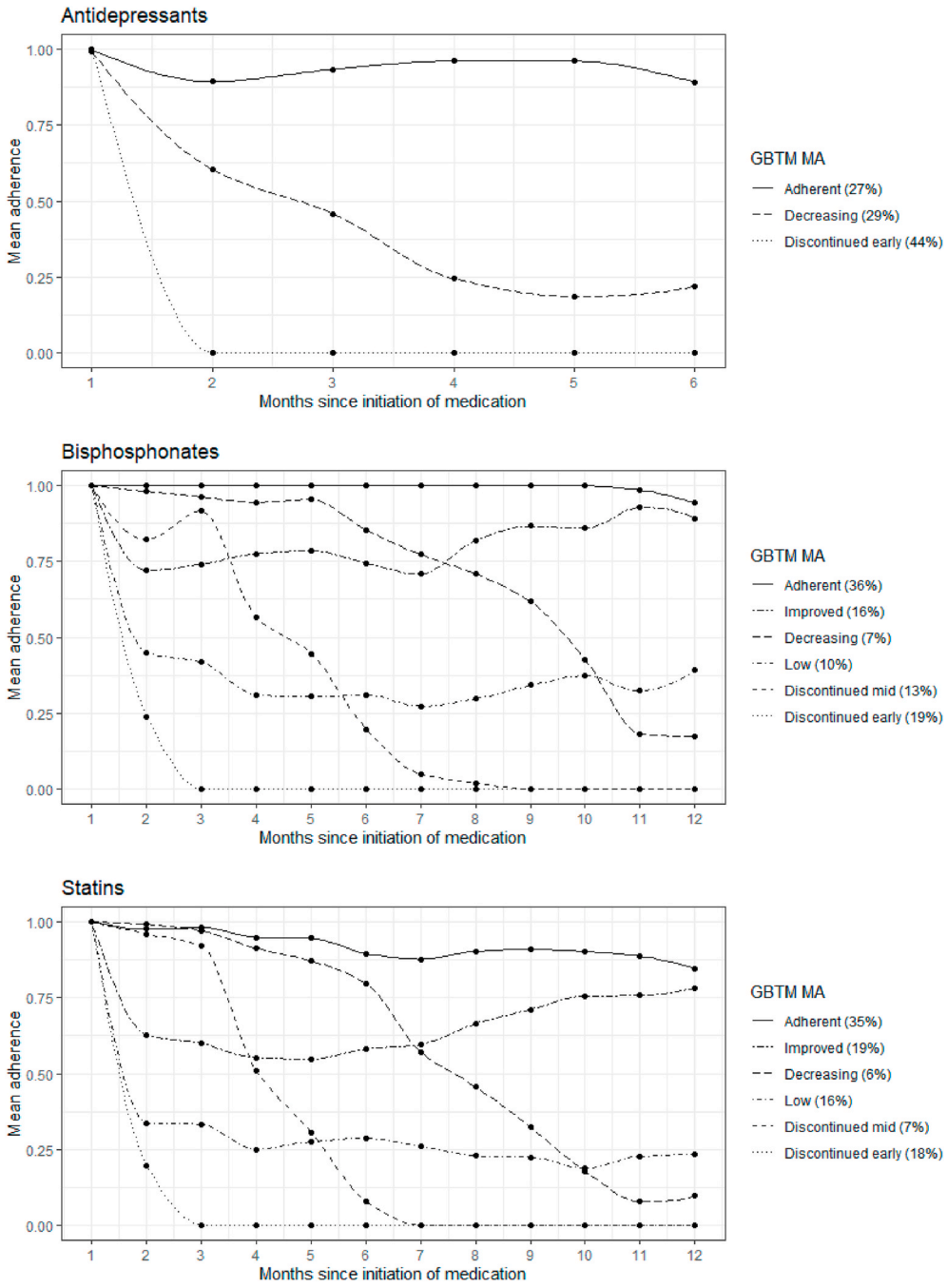

Fig. 2. GBTM types by medication cohort.

language, and switching medication type.

4.3.2. Cases where GBTM provides additional nuance and insight over PDC

There are several cases where covariates highly significantly associated ($p < 0.01$) with PDC MA were highly significantly associated ($p < 0.01$) only with some GBTM MA types, and therefore where the GBTM has provided additional nuance and insight over PDC MA. For example, within the bisphosphonate cohort, those living in a remote area were 5.9, 10.2 and 10.1 times more likely to become *Nonadherent* (PDC), *Low* (GBTM) and *Discontinued mid* (GBTM) relative to *Adherent*, all at $p < 0.001$, but were not more or less likely to become *Improved*, *Decreasing* or *Discontinued early*. The covariates found to be highly significantly associated with PDC nonadherence but only some types of GBTM nonadherence for antidepressants were increased age, non-English language, living in a house rather than nursing home, reduced weight, index medication being other antidepressants versus SSRI, and reduced use of antidementia medication (all associated only with *Discontinued early*). For bisphosphonates, these were living in a remote region (*Low* and *Discontinued mid*) and not switching medication type (*Discontinued mid* and *Discontinued early*, and opposite effect for *Improved* and *Low*). For statins, they are higher Depression Score (all types except *Improved*), Non-English language (*Low*, *Discontinued mid* and *Discontinued early*), less time living in Australia (*Low*), not having a healthcare card (*Discontinued early*), use of simvastatin rather than rosuvastatin (*Low* and *Discontinued early*), later time to have a liver test (*Low*, *Discontinued mid* and *Discontinued early*, and opposite effect for *Decreasing*), switching medication (*Improved*, *Decreasing* and *Low,* and opposite effect for *Discontinued early*), non-use of blood forming medication (*Improved*, *Low*,

Table 2
Size of the smallest group and BIC of GBTM analysis by specified number of groups.

	Two groups	Three groups	Four groups	Five groups	Six groups
Antidepressants					
Size of the smallest group	32.4%	29.0%	0.0% [a]	0.0% [a]	3.5%
BIC	46055.7	42191.9	42228.5	42202.1	41625.8
Bisphosphonates					
Size of the smallest group	41.0%	23.4%	18.0%	9.2%	6.6%
BIC	15667.3	14406.5	13966.9	13804.9	13674.2
Statins					
Size of the smallest group	42.6%	17.8%	17.8%	4.5%	5.6%
BIC	120933.0	115014.4	113483.8	112815.9	112419.7

GBTM = group-based trajectory modelling; BIC = Bayesian Information Criterion.
[a] 0% is achieved when no individual is given the highest posterior probability for a certain group and hence assigned to that group.

Table 3
Evaluation of GBTM categorisations by medication cohort.

Medication	GBTM MA types	AMPP	OCC	EGP	GP
Antidepressants	Adherent	93%	39	26%	27%
	Decreasing	93%	29	31%	29%
	Discontinued early	95%	23	43%	44%
Bisphosphonates	Adherent	93%	25	33%	36%
	Improved	90%	42	18%	16%
	Decreasing	83%	60	7%	7%
	Low	87%	56	10%	10%
	Discontinued mid	87%	50	12%	13%
	Discontinued early	97%	121	19%	19%
Statins	Adherent	87%	14	33%	35%
	Improved	77%	13	20%	19%
	Decreasing	76%	47	6%	6%
	Low	84%	25	17%	16%
	Discontinued mid	77%	44	7%	7%
	Discontinued early	93%	70	17%	18%

GBTM = group-based trajectory modelling; MA = medication adherence AMPP = average maximum posterior probability; OCC = odds of correct classification; EGP = estimated group probability; and GP = proportion of sample actually assigned to each group.

Discontinued mid and *discontinued early*).

4.3.3. Covariates associated with GBTM nonadherence only

In addition, there were cases where a highly significant result ($p < 0.01$) was identified only with GBTM and not (at $p < 0.01$) with PDC. In most cases the association was with only some GBTM MA types. The covariates where a highly significant association with nonadherence was identified only using GBTM for antidepressants were poorer self-rated memory, main job not being looking after home or family, not having private health insurance with extra cover, reduced use of analgesics (all associated only with *Discontinued early*), more alcohol drinks, single rather than married, not working full time, non-use of respiratory medication (*Decreasing*) and use of anxiolytics (*Discontinued early* and opposite effect for *Decreasing*). For bisphosphonates, the covariates were greater number of medications used, not being an informal carer, English as primary language, less time living in Australia, married rather than widowed, non-use of respiratory medication (*Discontinued mid*), less alcohol drinks (*Discontinued early*), main job being looking after home or family, index medication being risedronic acid rather than other types with supplemental calcium and colecalciferol (*Improved)*, employed, work type not being other, not participating in volunteering activities (*Decreasing*), living in a house rather than a nursing home (*Decreasing* and *Discontinued mid*) or hostel (*Decreasing*, *Low*), retired due to reached age (*Discontinued mid* and opposite effect for *Discontinued early*), and use of antiparasitic medication (*Improved* and opposite effect for *Decreasing, Low* and *Discontinued mid*). For statins, the covariates were being male, separated versus married, self-employed (*Low*), living in house rather than nursing home (*Decreasing* and *Low*) or hostel (*Low*), being female, index medication being simvastatin rather than fluvastatin (*Decreasing*) or atorvastatin (*Discontinued early* and *Low*), higher self-rated quality of life (*Discontinued early*), and heavier weight (*Improved* and opposite effect for *Low*).

5. Discussion

Our study has identified distinctive trajectories of MA using GBTM and analysed whether such categorisation provides information different or additional to the conventional MA measure, PDC, within the three medication groups, antidepressants, bisphosphonates and statins. Compared to PDC, which measures amount of medication use only, GBTM has the potential to provide a more nuanced understanding of nonadherence.

For all three medication groups, GBTM identified adherence types for almost full adherence, decreasing adherence and early discontinuation; for the bisphosphonate and statin cohorts, there are additional nonadherence types for improved following moderate adherence, low adherence throughout and later discontinuation. Participants classified as adherent based on GBTM were mostly also adherent based on PDC for all medication groups, meaning that GBTM provides more nuanced classification of individuals with absolute medication coverage less than 80%. This is especially true for the bisphosphonate and statin groups where five types of nonadherence were identified, compared with only two for antidepressants.

The proportion of GBTM adherent users was comparable between bisphosphonates (36%) and statins (35%) and lower for antidepressants (27%). These figures are within the ranges of nonadherence rate estimated in previous research for bisphosphonates (18%–75%) (Fatoye et al., 2019) and statins (18%–92%) (Deshpande et al., 2017) but marginally lower for antidepressants (35%–55%) (Ta et al., 2021). More participants discontinued early for antidepressants (44%) compared to bisphosphonates (19%) and statins (18%).

The identified GBTM MA types are broadly consistent with those found by previous studies including for medication types not explored in this research. For instance, Lo-Ciganic et al. (2016) identified similar six trajectories for oral hypoglycemics. Aarnio et al. (2016) and Franklin et al. (2015) identified five statin trajectories similar to ours other than the type, *Low*. Librero et al. (2016) identified three MA types for statins for a 12-month measuring period showing adherent throughout, decreasing adherence and discontinuation in around five months. Their study did not include a group with discontinuation soon after initiation possibly because it examined patients admitted through the Emergency Department and discharged with a main diagnosis of coronary heart disease implying greater need of statins. Mårdby et al. (2016) identified five antidepressant MA types for a two-year period including perfect adherence, moderate decline, rapid decline followed by increase, rapid decline and very rapid decline. Finding an increasing adherence type for antidepressants could be due to the longer follow-up period, not identified in this research and other shorter studies.

This research identified a number of factors associated with nonadherence consistent with previous studies including: older age (Gallagher et al., 2018; Pietrzykowski et al., 2020), female (Altıparmak & Altıparmak, 2012; V. W.; Lee et al., 2013), living in a remote region (Holt et al., 2014; Turner et al., 2009), psychological distress (Gentil et al., 2012; Krousel-Wood et al., 2010; Warren et al., 2013), number of alcoholic drinks per week (Cooper et al., 2005), non-English language (Bird et al., 2011; Hsu et al., 2010; Warren et al., 2013), living in a house rather than nursing home or hostel (Altiparmak & Altiparmak, 2012),

Table 4
Distributions across GBTM MA by PDC MA, sex and age group.

Medication	GBTM MA types	Count	Average PDC	PDC MA		Sex		Age					
				Adherent	Nonadherent	Male	Female	45–54	55–64	65–74	75–84	85–94	95–104
Antidepressants	Adherent	2492	94%	94%	2%	28%	26%	35%	29%	25%	24%	26%	32%
	Decreasing	2693	53%	6%	38%	30%	28%	29%	29%	28%	29%	30%	40%
	Discontinued early	4102	19%	0%	60%	42%	46%	36%	42%	47%	47%	44%	28%
	N	9287	49% [a]	2471	6816	3468	5819	693	3028	2974	1832	735	25
Bisphosphonates	Adherent	594	99%	68%	0%	38%	35%	28%	36%	35%	37%	36%	0%
	Improved	271	88%	27%	5%	16%	16%	22%	12%	18%	18%	12%	50%
	Decreasing	110	79%	5%	8%	5%	7%	11%	5%	8%	6%	6%	0%
	Low	158	52%	1%	20%	9%	10%	6%	14%	8%	8%	10%	50%
	Discontinued mid	208	38%	0%	27%	13%	12%	14%	14%	11%	12%	15%	0%
	Discontinued early	319	11%	0%	41%	19%	19%	19%	18%	20%	19%	21%	0%
	N	1660	67% [a]	878	782	366	1294	36	377	623	449	173	2
Statins	Adherent	3567	93%	76%	1%	36%	34%	23%	30%	38%	41%	39%	55%
	Improved	1922	78%	21%	17%	20%	18%	18%	21%	18%	16%	14%	0%
	Decreasing	570	68%	2%	8%	5%	6%	6%	5%	6%	5%	6%	0%
	Low	1685	46%	0%	30%	17%	16%	24%	19%	15%	13%	12%	9%
	Discontinued mid	671	36%	0%	12%	6%	7%	6%	6%	6%	7%	6%	18%
	Discontinued early	1827	12%	0%	32%	16%	19%	22%	18%	17%	17%	23%	18%
	N	10,242	63% [a]	4592	5650	4828	5414	566	3873	3684	1599	509	11

Note: Figures (except for count) represent the percentage of column total.
GBTM = group-based trajectory modelling; PDC = proportion of days covered; MA = medication adherence.
[a] Average PDC of the entire cohorts is provided instead of the total number of participants.

Table 5
Factors associated with MA to antidepressants.

	GBTM - Decreasing				GBTM - Discontinued early				PDC - Nonadherence			
	RRR		AME		RRR		AME		RRR		AME	
Age	1.01	*	−0.0007		1.02	***	0.0036	***	1.02	***	0.0027	***
Remote	1.17		−0.0566	**	2.00	***	0.1285	***	1.50	***	0.0622	***
Self-rated memory	0.99		0.0103		0.91	**	−0.0194	***	0.95		−0.0086	
Depression Score	1.00		0.0022	*	0.99		−0.0027	*	1.00		−0.0008	
Use of health supplementary products	0.90		−0.0051		0.88	*	−0.0139		0.89	*	−0.0186	*
No. of alcohol drinks per week	1.01		0.0015	**	1.00		−0.0011		1.00		0.0002	
Non-English language	1.39	*	−0.0012		1.68	***	0.0680	**	1.55	***	0.0675	***
Single vs Married	1.26		0.0564	**	0.94		−0.0428	*	1.10		0.0152	
Separated vs Married	1.62	**	0.0664	*	1.30		−0.0086		1.52	*	0.0641	**
Nursing home vs House	0.39		−0.0431		0.26	**	−0.1692	*	0.25	**	−0.2548	**
Hostel for aged vs House	0.30	**	−0.0817		0.24	**	−0.1616	*	0.29	***	−0.2243	**
Work-Full-time	0.63	**	−0.0590	*	0.77		−0.0008		0.82		−0.0325	
Work-Self-employed	0.72	*	−0.0480	*	0.87		0.0106		0.89		−0.0195	
Work-Home	0.98		0.0311		0.75	*	−0.0576	**	0.89		−0.0199	
Work-Retired	0.86		0.0006		0.77	*	−0.0350		0.88		−0.0203	
School vs University or higher	0.95		−0.0263		1.14		0.0337	*	1.11		0.0173	
Private insurance with extra cover	0.92		0.0134		0.79	**	−0.0407	**	0.82	*	−0.0324	*
Private insurance without extra cover	1.01		0.0250		0.83		−0.0401	*	0.90		−0.0182	
Volunteer	0.48	*	−0.0826		0.63		−0.0196		0.64		−0.0771	
Weight	1.004[a]	*	0.0000		0.99	***	−0.0010	**	0.99	**	−0.0009	**
NSMRI vs SSRI	6.87	***	0.0498	***	11.54	***	0.2717	***	9.34	***	0.3206	***
Other antidepressants vs SSRI	1.13		−0.0103		1.32	***	0.0432	**	1.18	**	0.0272	**
Start month - Apr vs Jan	1.23		0.0486	*	0.94		−0.0381		1.00		0.0006	
Start month - Jun vs Jan	1.27		0.0539	*	0.95		−0.0403		0.90		−0.0166	
Start month - Jul vs Jan	1.21		0.0505	*	0.90		−0.0454		0.94		−0.0105	
If medication type was switched	0.91		0.1863	***	0.14	***	−0.3308	***	0.49	***	−0.1259	***
Med-Cardiovascular	0.88		−0.0035		0.84	*	−0.0206		0.87	*	−0.0228	*
Med-Antiinfectives	1.00		−0.0149		1.14	*	0.0268	*	1.05		0.0082	
Med-Respiratory	0.79	**	−0.0269	*	0.86		−0.0043		0.85	*	−0.0274	*
Med-Anxiolytics	0.83		−0.0588	***	1.22		0.0639	**	0.98		−0.0025	
Med-Antipsychotics	0.56	**	0.0052		0.33	***	−0.1572	***	0.44	***	−0.1464	***
Med-Antidementia	0.58	*	0.0286		0.27	***	−0.1921	***	0.48	**	−0.1322	**
Med-Analgesics	0.86	*	−0.0047		0.82	**	−0.0247	*	0.85	*	−0.0264	*
Number of participants	2693				4102				6816			

Note: The results for covariates showing significant association with at least one type of nonadherence are presented. The full results are available in the electronic supplementary Appendix B (Table B1).
GBTM = group-based trajectory modelling; PDC = proportion of days covered; RRR = Relative risk ratio; AME = Average marginal effect.
*p < 0.05; **p < 0.01, ***p < 0.001.
[a] The figure is exceptionally rounded to 3 d.p. to provide a meaningful result.

Table 6
Factors associated with MA to bisphosphonates.

Covariate	GBTM - Improved		GBTM - Decreasing		GBTM - Low		GBTM - Discontinued Mid		GBTM - Discontinued early		PDC - Nonadherence	
	RRR	AME	RRR	AME	RRR	AME	RRR	AME	RRR	AME	RRR	AME
Female	1.03	−0.0051	1.88	0.0300 *	1.04	−0.0020	1.04	−0.0023	1.01	−0.0099	1.12	0.0213
Remote	2.69	−0.0546	2.15	−0.0318	10.17 ***	0.1337 *	10.12 ***	0.1459 **	3.59	−0.0242	5.91 ***	0.2761 ***
Number of medications used	1.02	0.0005	1.03	0.0005	0.93	−0.0078 *	1.11 **	0.0093 **	1.03	0.0008	1.04	0.0074
Care Sick	1.06	0.0251	1.04	0.0091	0.94	0.0029	0.46 *	−0.0619 **	0.93	0.0065	0.75	−0.0547
Help disability	0.52 *	−0.0601 *	0.55	−0.0221	0.57	−0.0289	1.50	0.0770 *	0.84	−0.0006	1.14	0.0243
Self-rated quality of life	1.03	−0.0042	1.35 *	0.0147 *	1.04	−0.0014	0.98	−0.0087	1.11	0.0088	0.97	−0.0062
Depression Score	0.99	−0.0030	0.99	−0.0015	1.01	0.0000	1.04	0.0031	1.04	0.0038	1.04 **	0.0073 **
No. of alcohol drinks per week	0.99	0.0007	0.96 *	−0.0014	0.99	0.0001	0.99	0.0010	0.97 **	−0.0033 *	0.99	−0.0027
Non-English language	0.63	−0.0220	0.67	−0.0046	1.02	0.0324	0.31 **	−0.0705 **	0.74	0.0049	0.90	−0.0202
Length of time in Australia	0.99 *	−0.0005	0.98 *	−0.0003	1.00	0.0008	0.98 **	−0.0013 *	0.99 *	−0.0005	0.99	−0.0012
Partnered vs Married	2.11	0.0538	2.96 *	0.0529	2.55	0.0574	0.90	−0.0472	1.07	−0.0524	1.06	0.0102
Widowed vs Married	1.29	0.0163	1.33	0.0096	1.98 *	0.0566	0.61	−0.0586 **	1.14	0.0012	0.99	−0.0013
Separated vs Married	0.57	−0.0349	1.16	0.0330	0.27	−0.0594 *	0.49	−0.0393	0.91	0.0393	0.64	−0.0835
Nursing home vs House	0.98	0.0158	0.00 ***	−0.0664 ***	0.93	0.0033	0.00 ***	−0.1257 ***	1.69	0.1545	0.78	−0.0473
Hostel for aged vs House	0.57	0.0064	0.00 ***	−0.0666 ***	0.00 ***	−0.0956 ***	0.50	−0.0093	0.64	0.0298	0.51	−0.1269
Unpaid work hours per week	0.99	−0.0019	1.00	−0.0004	1.02	0.0019 *	1.00	−0.0007	1.01	0.0016	1.01	0.0019
Work-Home	1.78 *	0.0946 **	0.53	−0.0327	0.99	−0.0054	0.80	−0.0262	0.90	−0.0223	0.67	−0.0741
Work-Unemployed	1.40	0.0405	0.00 ***	−0.0683 ***	1.05	−0.0037	1.67	0.0556	1.04	−0.0076	0.89	−0.0226
Work-Unpaid	0.85	−0.0074	0.38	−0.0382 *	0.81	−0.0094	1.21	0.0370	0.90	−0.0009	0.95	−0.0090
Work-Other	1.43	0.0185	0.29	−0.0514 **	1.42	0.0101	1.09	−0.0175	1.87	0.0807	1.11	0.0201
Retire-Reached Age	1.69 *	0.0395	1.24	−0.0040	1.22	−0.0068	2.43 ***	0.0780 **	0.92	−0.0601 **	0.93	−0.0131
Higher school vs University or higher	1.49	0.0671	0.44	−0.0376 *	0.80	−0.0195	1.24	0.0260	0.82	−0.0340	0.84	−0.0327
$0-$29,999 vs $30,000-$69,999	1.09	−0.0211	2.19 *	0.0329	1.11	−0.0110	1.03	−0.0238	1.82 *	0.0632 *	1.25	0.0415
Private insurance without extra cover	0.79	0.0156	0.68	−0.0018	0.61	−0.0138	0.57	−0.0218	0.54 *	−0.0448	0.58 **	−0.1018 **
Volunteer	0.79	−0.0468	0.00 ***	−0.0667 ***	2.39	0.0946	2.12	0.0926	0.82	−0.0497	1.27	0.0447
Clodronic Acid vs Risedronic Acid	0.00 ***	−0.1642 ***	0.00 ***	−0.0664 ***	2.90	0.2308	1.65	0.1332	0.00 ***	−0.1924 ***	3.14	0.1911
Alendronic Acid vs Risedronic Acid	0.97	−0.0123	0.95	−0.0071	1.00	−0.0051	0.79	−0.0311	1.49	0.0663 *	1.16	0.0277

(*continued on next page*)

Table 6 (*continued*)

Covariate	GBTM - Improved				GBTM - Decreasing				GBTM - Low				GBTM - Discontinued Mid				GBTM - Discontinued early				PDC - Nonadherence			
	RRR		AME		RRR		AME		RRR		AME		RRR		AME		RRR		AME		RRR		AME	
Ibandronic Acid vs Risedronic Acid	0.00	***	−0.1634	***	0.00	***	−0.0666	***	0.00	***	−0.0952	***	0.00	***	−0.1253	***	0.00	***	−0.1922	***	0.00	***	−0.4715	***
Zoledronic Acid vs Risedronic Acid	0.00	***	−0.1954	***	0.00	***	−0.0811	***	0.03	***	−0.0922	***	0.01	***	−0.1467	***	0.01	***	−0.2211	***	0.02	***	−0.5337	***
Risedronic Acid and Calcium, Sequential vs Risedronic Acid	0.42	*	−0.0493		0.55		−0.0054		0.40	*	−0.0322		0.51		−0.0189		0.61		0.0006		0.79		−0.0451	
Risedronic Acid, Calcium and Colecalciferol, Sequential vs Risedronic Acid	0.41	*	−0.0962	***	0.70		−0.0191		0.76		−0.0198		1.35		0.0368		1.57		0.0948	*	1.64	*	0.0901	*
Alendronic Acid, Calcium and Colecalciferol, Sequential vs Risedronic Acid	0.53		−0.0748	**	1.54		0.0319		1.04		0.0059		1.40		0.0436		0.94		−0.0100		1.42		0.0646	
Start month - Jun vs Jan	1.14		−0.0194		0.61		−0.0497		1.74		0.0230		1.76		0.0338		1.82		0.0612		1.92	*	0.1207	*
If medication type was switched	2.53	**	0.1624	***	0.64		−0.0280		2.47	*	0.0931	**	0.46		−0.0720	**	0.36	*	−0.1320	***	0.57	**	−0.1064	**
Med-Cardiovascular	1.10		0.0175		0.94		−0.0016		1.40		0.0307		0.65		−0.0454	*	0.92		−0.0061		0.82		−0.0377	
Med-Genito-urinary	1.13		0.0141		0.84		−0.0112		1.83	*	0.0607	*	0.85		−0.0189		0.80		−0.0389		0.88		−0.0234	
Med-Antineoplastic	2.40		0.0478		3.47	*	0.0513		2.35		0.0289		1.59		−0.0119		1.46		−0.0325		1.40		0.0618	
Med-Antiparasitic	17.14	**	0.2762		0.00	***	−0.0665	***	0.00	***	−0.0955	***	0.00	***	−0.1261	***	11.30	*	0.1790		2.55		0.1609	
Med-Respiratory	0.75		−0.0022		0.57		−0.0144		1.25		0.0501	*	0.44	**	−0.0509	**	0.60	*	−0.0346		0.72	*	−0.0612	*
Number of participants	271				110				158				208				319				782			

Note: The results for covariates showing significant association with at least one type of nonadherence are presented. The full results are available in the electronic supplementary Appendix B (Table B2).
GBTM = group-based trajectory modelling; PDC = proportion of days covered; RRR: Relative risk ratio, AME: Average marginal effect.
*p < 0.05; **p < 0.01, ***p < 0.001.

not married (Cooper et al., 2005), greater cost burden shown by not holding a healthcare card or not holding private health insurance (Holt et al., 2014; Warren et al., 2013; Zivin et al., 2010), use of non-SSRI antidepressants versus SSRI (Ben-Ami Shor et al., 2017; Keyloun et al., 2017), use of simvastatin versus atorvastatin (Morotti et al., 2019), and low continuity of care (Warren et al., 2015).

In particular, our findings were consistent with Warren et al. (2013) that also conducted research using the 45 and Up Study participants and found positive associations between nonadherence to statins and several factors including not holding private health insurance, non-English language and psychological distress. Compared to their study, we distinguished these associations for different types of nonadherence; for example, that private health insurance is associated with the types, *Discontinued mid* and *Discontinued early*, and psychological distress with all types of nonadherence except *Improved*.

There was broad consistency in the participant factors found to be associated with adherence for GBTM and PDC, clearer on the factors highly associated with PDC MA. For RRR results across all medication types, all factors associated with the PDC MA at $p < 0.001$ were also associated in the same direction with at least one GBTM MA type at $p < 0.001$. This is unsurprising because similar sets of nonadherent participants were identified by GBTM and PDC.

However, GBTM has extracted more information from temporal patterns on differences across nonadherent types. For instance, bisphosphonate users living in a remote area were more likely to be nonadherent but only for the types *Low* and *Discontinued mid*, possibly suggesting delayed medication filling due to limited access to healthcare in remote areas (Holt et al., 2014; Turner et al., 2009). Statin users who use non-English language at home were more likely to show nonadherence especially the types *Low* and *Discontinued mid*, suggesting that cultural differences or literacy may influence persistence following initial adherence as suggested in several studies (Bird et al., 2011; Hsu et al., 2010). Using a larger number of medications was positively associated with later discontinuation but negatively with low adherence for a bisphosphonate user. This may suggest that concurrent use of many medications is a barrier to becoming persistent (P. W. Lam et al., 2007; Tsai et al., 2012), but can assist with maintaining medication dosage over the longer term. Psychological distress was generally associated with nonadherence in all medications as suggested by previous studies (Gentil et al., 2012; Krousel-Wood et al., 2010). However, it reduced the likelihood of early discontinuation in antidepressants, suggesting that a greater need of antidepressants increases persistence at initiation, consistent with the findings of Falcaro et al. (2019). Non-SSRI antidepressants were highly significantly associated with increased likelihood of early discontinuation, potentially due to greater side effects (Bet et al., 2013).

Several different associations were found among different medication types. Age was positively associated with all types of nonadherence in antidepressants, but not significantly associated with those in other medications. While age can influence MA negatively (Alfian et al., 2018; Rossom et al., 2016) through forgetfulness that is a major contributor to nonadherence to chronic medications (Choudhry et al., 2017), the influence can be weakened by increased awareness of health status at older ages (Kim et al., 2019, p. 98). Indeed, previous studies variously reported positive (Alfian et al., 2018; Rossom et al., 2016), negative (Gallagher et al., 2018; Pietrzykowski et al., 2020) and nonlinear (Janssen et al., 2019; Umeda et al., 2019) associations. Here, forgetfulness may account for the nonadherence found for older antidepressant users, while bisphosphonate and statin adherence might have been also impacted by increasing awareness of health status by age.

Females were more likely to be *Decreasing* in bisphosphonates and *Discontinued mid* in statins, but less likely to be *Low* in statins. Some similarities were found in previous trajectory studies including greater likelihoods of discontinuation (Lo-Ciganic et al., 2016), declining adherence and gap in adherence (Vadhariya et al., 2019) in females, and consistently low adherence in males (Chen & Cheng, 2016).

Living in a remote area was highly significantly associated with nonadherence for both antidepressants and bisphosphonates, but with different types by RRR, early discontinuation for antidepressants (potentially related to side effects and worsening depressive symptoms in early weeks of treatment) and low adherence and later discontinuation for bisphosphonates. The earlier impact to antidepressants may be due to ineffective treatment with limited mental health support in remote areas (e.g., difficulty to have a combined therapy, psychotherapy with pharmacotherapy) as shown by significantly smaller numbers of psychiatrists, mental health nurses and psychologists than non-remote areas (Australian Institute of Health and Welfare, 2021). Future studies are needed for better understanding of why limited access to healthcare impacts earlier for antidepressants.

Different results related to switching medication type were found. For antidepressants and bisphosphonates, switching was associated with decreased overall likelihood of nonadherence primarily due to reduced discontinuation, suggesting that switching was part of a successful follow-up to improve therapy. In contrast, for statins, switchers were more likely to show nonadherence except early discontinuation, suggesting that follow-up to improve clinical efficacy or to respond to side effects is less common or less effective for this medication. Our data didn't permit an analysis of adherence behaviour before and after switching and future research incorporating this analysis would be helpful in clarifying the dynamics and impact of medication switching.

Our study provides further evidence that GBTM can be usefully applied to identify typical MA trajectories for patients initiating antidepressants, bisphosphonates or statins. It is the first application of the GBTM on adherence to bisphosphonates and the first application to Australians using antidepressants.

Identification of relationships between various patient factors and GBTM MA types can help tailor targeted MA interventions by revealing complex processes of nonadherence not explained by conventional MA measures. While several intervention methods are effective in reducing nonadherence, including simplification of dose regimen, reminders, patient education, motivation and support (Schroeder et al., 2004), the most suitable method and timing of intervention will depend on MA trajectories and reasons for or processes of nonadherence. For example, an earlier intervention (e.g., follow-up call) should be given to those at risk of early discontinuation compared to other types. A patient at risk of having low but not discontinued use of medication, possibly a 'forgetful' patient, will be aided by simplification of dose regimen or reminders as intervention. In a trial of reminder devices, the failure to tailor intervention to potentially forgetful patients was found to be a reason for the absence of improvements in adherence (Choudhry et al., 2017). Hence the type of nonadherence and associated patient factors can be jointly used to tailor interventions for maximum effectiveness.

Our study has several limitations. First, while the 45 and Up Study cohort is broadly representative of the Australian population in that age group, the response rate was not high at 18% and the participants are likely to be healthier and have lower hospitalisation rates than the general population (Mealing et al., 2010). However, research has shown that even in the absence of representativeness, internal comparisons are valid (Rothman et al., 2013). In addition, the general healthiness of the cohort has been allowed for by including several covariates of health-related behaviours such as smoking and health-supplementary medicine consumption. Second, sample size seems to have been a barrier in finding MA associated factors, as shown by the many fewer factors identified for the relatively small bisphosphonate cohort. A future bisphosphonate study with larger cohort size will be useful in finding more factors.

Third, several limitations of using the PBS data include: having to assume that all medications were consumed in the most commonly used way, unavailability of prescription information, inability to know if medication was actually taken, and existence of patients hoarding medications by filling them more frequently than usual typically in the several months before January (Australian Institute of Health and

Table 7
Factors associated with MA to statins.

Covariate	GBTM – Improved				GBTM – Decreasing				GBTM - Low				GBTM - Discontinued mid				GBTM - Discontinued early				PDC - Nonadherence			
	RRR		AME		RRR		AME		RRR		AME		RRR		AME		RRR		AME		RRR		AME	
Female	0.98		−0.0066		1.08		0.0032		0.87		−0.0263	**	1.35	**	0.0181	**	1.14		0.0191		1.06		0.0146	
Remote	1.05		−0.0001		1.55	*	0.0255	*	0.93		−0.0188		1.13		0.0049		1.08		0.0050		1.02		0.0037	
Number of medications used	0.98		−0.0018		1.01		0.0013		0.97	*	−0.0042	*	1.01		0.0015		0.99		0.0006		1.00		−0.0006	
Continuity of care	1.02		0.0171		0.70	*	−0.0160	*	0.90		−0.0050		0.88		−0.0031		0.84		−0.0167		0.86	*	−0.0340	*
Number of people in house	0.99		−0.0025		1.03		0.0012		1.03	*	0.0037	*	0.99		−0.0010		1.02		0.0013		1.01		0.0019	
Care Sick	0.94		−0.0211		1.02		−0.0020		1.19		0.0194		1.17		0.0065		1.16		0.0155		1.14	*	0.0313	*
Self-rated memory	1.05		0.0071		1.00		−0.0004		1.04		0.0057		1.02		0.0010		0.94		−0.0113	*	0.98		−0.0052	
Self-rated quality of life	0.94		−0.0112		0.90		−0.0054		1.00		0.0006		0.97		−0.0015		1.09	*	0.0152	**	1.02		0.0053	
Depression Score	1.01		−0.0003		1.04	***	0.0013	**	1.02	**	0.0014		1.03	***	0.0011	*	1.02	**	0.0009		1.02	***	0.0050	***
If regular smoker	1.04		0.0044		0.84		−0.0101	*	1.07		0.0094		0.96		−0.0034		1.03		0.0030		1.02		0.0040	
Non-English language	1.34	*	0.0056		1.13		−0.0074		1.57	***	0.0308		1.90	***	0.0286	*	1.46	**	0.0203		1.47	***	0.0888	***
Length of time in Australia	1.00		0.0000		1.00		0.0002		0.99	**	−0.0007	*	1.00		−0.0001		0.99	*	−0.0004		0.99	**	−0.0012	**
Divorced vs Married	1.30	*	0.0287		1.12		−0.0001		1.34	*	0.0304	*	0.88		−0.0143		1.06		−0.0090		1.08		0.0175	
Separated vs Married	1.04		−0.0155		1.36		0.0113		1.59	**	0.0640	*	1.12		−0.0007		0.99		−0.0222		1.27		0.0558	
Nursing home vs House	0.28		−0.0860		0.00	***	−0.0557	***	0.11		−0.1271	**	1.43		0.1113		0.16		−0.1224		0.49		−0.1672	
Hostel for aged vs House	2.00		0.0927		1.56		0.0094		0.32		−0.1245	**	1.76		0.0202		2.02		0.0889		1.06		0.0135	
Other housing vs House	0.78		−0.0495		1.06		0.0003		1.10		0.0045		1.05		−0.0009		1.47		0.0644	*	1.41	*	0.0780	*
Unpaid work hours per week	1.00		−0.0002		1.01		0.0003		1.00		−0.0008		1.00		0.0000		1.01	*	0.0013	**	1.00		0.0000	
Work-Self-employed	1.24		0.0080		1.29		0.0047		1.45	**	0.0334	*	1.25		0.0036		1.21		0.0029		1.22	*	0.0467	*
Work-Unpaid	0.75	*	−0.0287		0.92		0.0021		0.95		0.0114		0.76		−0.0098		0.81		−0.0159		0.96		−0.0098	
Work-Disabled	0.77		−0.0196		0.62		−0.0160		0.78		−0.0136		0.96		0.0071		0.81		−0.0102		0.66	**	−0.0989	**
Work-Other	0.80		0.0044		0.91		0.0087		0.57	*	−0.0427		0.46	*	−0.0274		0.64		−0.0309		0.74		−0.0705	
Work-Retired	0.87		−0.0037		0.96		0.0046		0.76	*	−0.0235		0.76		−0.0101		0.85		−0.0072		0.83	*	−0.0445	*
$70,000-$149,999 vs $30,000-$69,999	1.21	*	0.0290	*	1.19		0.0078		1.01		−0.0053		0.98		−0.0040		0.96		−0.0140		0.99		−0.0018	
Healthcare card	0.83	*	−0.0119		1.06		0.0102		0.85		−0.0056		0.88		−0.0008		0.73	***	−0.0319	**	0.83	**	−0.0451	**
Private insurance with extra cover	0.99		0.0127		0.76		−0.0112		0.96		0.0058		0.80		−0.0095		0.81	*	−0.0236		0.85	*	−0.0372	*
Private insurance without extra cover	0.92		0.0037		0.79		−0.0073		0.97		0.0116		0.68	*	−0.0164		0.77	*	−0.0259		0.82	*	−0.0477	*
Other type of insurance	0.96		−0.0036		1.04		0.0034		1.09		0.0193		1.02		0.0027		0.81		−0.0297	*	0.93		−0.0160	
Weight	1.00		0.0007	**	1.00		−0.0001		0.99	**	−0.0007	**	1.00		0.0001		1.00		−0.0004		1.00	*	−0.0007	*
Fluvastatin vs Simvastatin	0.65		−0.0665		2.19		0.0633		0.67		−0.0554		0.00	***	−0.0657	***	1.78		0.1299		1.41		0.0788	
Atrovastatin vs Simvastatin	0.78	*	−0.0136		1.21		0.0205		0.71	**	−0.0255		0.98		0.0098		0.64	***	−0.0463	**	0.84	*	−0.0413	*
Rosuvastatin vs Simvastatin	0.73	*	−0.0112		1.02		0.0143		0.62	***	−0.0349	*	0.85		0.0057		0.56	***	−0.0547	***	0.74	**	−0.0686	**
Liver test[a]	1.0006	*	−0.0001		0.9998		−0.0001	**	1.0017	***	0.0001	***	1.0010	**	0.0000		1.0023	***	0.0002	***	1.0015	***	0.0003	***
Start month - Jul vs Jan	1.08		−0.0119		1.46		0.0127		1.21		0.0073		1.28		0.0066		1.37	*	0.0312		1.20		0.0435	
If medication type was switched	2.34	***	0.0950	***	2.07	***	0.0194		2.54	***	0.1006	***	1.69	*	0.0072		0.65	*	−0.1043	***	1.93	***	0.1458	***
Med-Alimentary tract	1.03		0.0131		0.79	*	−0.0106		1.04		0.0141		0.82	*	−0.0097		0.84	*	−0.0224	*	0.91		−0.0213	
Med-Blood forming	0.80	**	−0.0016		0.83		0.0019		0.63	***	−0.0366	***	0.67	***	−0.0117		0.68	***	−0.0268	**	0.71	***	−0.0816	***
Med-Systemic-hormonal	1.15		0.0061		1.25		0.0065		1.25	*	0.0175		1.04		−0.0044		1.18	*	0.0093		1.17	**	0.0368	**
Med-Musculo-skeletal	1.19	*	0.0212	*	1.12		0.0033		1.07		0.0015		1.16		0.0058		0.98		−0.0126		1.08		0.0170	
Med-Sensory	0.96		0.0006		0.85		−0.0060		0.93		−0.0030		0.87		−0.0060		0.94		−0.0018		0.88	*	−0.0296	*
Number of participants	1922				570				1685				671				1827				5650			

Note: The results for covariates showing significant association with at least one type of nonadherence are presented. The full results are available in the electronic supplementary Appendix B (Table B3).
GBTM = group-based trajectory modelling; PDC = proportion of days covered; RRR: Relative risk ratio, AME: Average marginal effect.
*p < 0.05; **p < 0.01, ***p < 0.001.
[a] RRRs rounded to 4 d.p. are exceptionally provided to keep the results meaningful.

Welfare, 2018). Such limitations were mitigated by selecting medications widely used with standardised clinical guidelines and using month of initiating medication use as a control factor. Fourth, we broadly explored various factors associated with MA across different MA measures and across different medication types, but more specific studies with different methodology (e.g., interviews) are needed to more fully explore reasons for individual relationships. Last, we considered only a single period to measure MA (i.e., six months for antidepressants and one year for bisphosphonates and statins). Studies with variation in timing are needed to address potentially different MA patterns in longer or shorter periods and associated factors.

6. Conclusion

This study illustrated the use of GBTM in identifying distinctive and interpretable typical medication adherence trajectories and associated patient characteristics and use of healthcare services, for antidepressants, bisphosphonates and statins. It was found that GBTM successfully categorised nonadherent patients by trajectories showing discontinuation, decreasing, improving or low adherence, and that the factors associated with those trajectories were broadly consistent with but more comprehensive and nuanced than those associated with PDC. Using GBTM MA allows clinicians, policy-makers and researchers to meaningfully differentiate between alternative types of nonadherence and hence to better identify patients at risk of poor adherence based on their characteristics, and tailor interventions accordingly. Following our broad exploration, investigation of each factor associated with MA trajectories will help in designing intervention programs.

Ethics approval

The study was approved by the NSW Population & Health Services Research Ethics Committee (Project no: 2019/ETH12440) and the Macquarie University Human Research Ethics Committee (Reference no: 5201952579218). The conduct of the 45 and Up Study was approved by the University of New South Wales.

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Data and code availability

Data used in this study are not available for distribution as required by the ethics approvals. The R and STATA code used in the analysis and original statistical outputs are available from the corresponding author on reasonable request.

Authors' contributions

Kyu Hyung Park: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Project administration. **Leonie Tickle:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition. **Henry Cutler:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Ethical Statement for SSM – Population Health

Hereby, I, Kyu Hyung Park, consciously assure that for the manuscript, "Identifying temporal patterns of adherence to antidepressants, bisphosphonates and statins, and associated patient factors", the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
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I agree with the above statements and declare that this submission follows the policies of SSM – Population Health as outlined in the Guide for Authors and in the Ethical Statement.

Declaration of competing interest

Authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2021.100973.

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