Factors associated with the initiation of testosterone replacement therapy in men from the 45 and Up Study

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Background and objectives
There have been large increases in testosterone prescribing since 2000. The aim of this study was to identify factors associated with testosterone replacement therapy (TRT) initiation in men.

Methods
Data were from the 45 and Up Study, an ongoing cohort study involving 266,942 participants from New South Wales aged ≥45 years. Baseline data (2006–09) were linked to administrative data on government-subsidised prescriptions and medical services.

Results
The study included 105,429 men. In two years following baseline, 2.9 per 1000 men (95% confidence interval: 2.6, 3.2) had initiated TRT. Men with self-rated poor health, those treated for osteoporosis; anxiety, depression or high blood cholesterol, and those who lived in major cities or were aged 55–74 years had greater odds of TRT initiation. In the six months before TRT initiation, 41% of men had a hormone test record.

Discussion
The high rate of TRT initiation and low rate of recommended investigations suggest TRT may have been prescribed outside recommended indications.

TESTOSTERONE REPLACEMENT THERAPY (TRT) is clinically indicated for men with proven hypogonadism.[1,2] However, the therapeutic benefit to men who are not clinically deficient remains unclear. A systematic review found no TRT benefit for various outcomes.[3] Conversely, TRT trials sponsored by the National Institutes of Health showed benefits; however, they also showed potential harms.[4–6] Despite lack of evidence for wider use, there have been large increases in testosterone prescribing in Australia[7] and globally[8–10] since 2000.

The increasing testosterone demand has raised concerns of unwarranted off-label use.[9] The 2000 Endocrine Society of Australia (ESA) guidelines, updated in 2016, recommended that TRT should be started after two separate hormone assays measuring luteinising hormone (LH), follicle-stimulating hormone (FSH) and testosterone.[1,2] Where the diagnosis is not clear, referral to an endocrinologist is recommended.[2] In April 2015, the Pharmaceutical Benefits Scheme (PBS) TRT criteria were updated to require lower testosterone levels (6 nmol/L rather than 8 nmol/L)[11] prior to TRT initiation. Additionally, the PBS subsidises TRT for symptomatic men without evidence of pituitary or testicular disease only if the general practitioner (GP) provides evidence of androgen deficiency confirmed by two separate blood tests and a specialist (endocrinologist, urologist or Member of the Australian Chapter of Sexual Health Medicine) referral.

Understanding the TRT prescription context strengthens prescribing practice. However, few studies have examined this, and none in Australia. We aimed to investigate the sociodemographic and clinical factors associated with TRT initiation among middle-aged and older men, and assess whether hormone tests or specialist visits occurred before initiation.

Methods

Sampling and procedures

Data were obtained from the Sax Institute's 45 and Up Study, an ongoing cohort study in New South Wales (NSW), Australia. Prospective participants were randomly sampled from the Department of Human Services (formerly Medicare Australia) enrolment database, which provides near-complete coverage of the population. People aged ≥80 years and residents of rural and remote areas were oversampled. A total of 266,942 participants completed the baseline questionnaire (between January 2006 and December 2009) and gave signed consent for follow-up and linkage of their information to routine health databases including the Medicare Benefits Schedule (MBS) and PBS database. Of those invited, 18% participated and 11% of the NSW population aged ≥45 years participated.[12] The study is described elsewhere[12] and questionnaires are available at www.saxinstitute.org.au/our-work/45-up-study. The 45 and Up Study was approved by the Department of Health and Aging Departmental Ethics Committee (Approval number 1/2005) and the University of New South Wales Human Research Ethics Committee (Approval number HC15408).

PBS and MBS records from 2004–14 were included in the current analysis.

These datasets were supplied by the Department of Human Services, and the Sax Institute[12] linked them to the baseline 45 and Up Study data.

Outcomes

TRT initiation was defined by a PBS prescription filled for a testosterone-based drug (Anatomical Therapeutic Chemical code G03BA03) up to 24 months after the baseline survey for males with no prescription filled 24 months prior. Baseline surveys were completed between 2006 and 2009; therefore, the end of two-year follow-up was between 2008 and 2011. It is noted that the PBS records do not account for all testosterone prescribing, such as private scripts. Participants who self-reported holding a Department of Veterans' Affairs (DVA) card were excluded as they have access to a broader range of subsided medications under a separate government program.

We identified whether men had a hormone test (MBS item number 66695) in the six months before TRT initiation. This MBS item includes hormone assays for testosterone deficiency, but it also includes insulin assays; therefore, we excluded participants with diabetes on the basis of survey or prescription data. This may have the effect of underestimating the amount of TRT initiation in the population. A specialist visit was defined as any claim under MBS Category 1 attendances, which comprise a wide range of specialist consultations including but not specifying an endocrinologist, urologist or a Member of the Australian Chapter of Sexual Health Medicine consultation.

Explanatory variables

We examined whether various demographic and clinical characteristics were associated with TRT initiation. The demographics were age, education, area of residence, marital status, country of birth, language spoken at home and work status.

The clinical characteristics included body mass index (BMI), smoking, alcohol intake, physical activity,[13] physical impairment,[14] fruit and vegetable intake, self-rated health, need for help because of long-term illness or disability, history of enlarged prostate/prostate cancer/prostatectomy, prostate symptom score, vasectomy, fracture in the past five years and psychological distress.[15] We created dichotomous variables for history of heart disease, high blood pressure, high cholesterol, stroke and anxiety/depression on the basis of self-reported (at baseline) doctor-diagnosis of, or recent treatment in the last month for, these conditions, and dichotomous variables for inability to maintain an erection, treatment for osteoporosis and low bone density. Full details of the categorisation of variables is available in the online Appendix.

Statistical analysis

Frequency counts and percentages were calculated for participant characteristics. We calculated the percentage of participants who had TRT initiated and had a hormone test or specialist visit before TRT initiation. We tested the difference in characteristics between the TRT group and non-TRT group with chi-square tests. We used logistic regression to explore the factors associated with the initiation of TRT. All factors were included in this multivariable model, and we report adjusted odds ratios (aOR) and 95% confidence intervals (CI) for significant (P <0.05) factors. Multiple imputation was performed using the fully conditional method to account for missing data. Twenty imputation models were created, and the parameter estimates were combined using Rubin's rules.[16] Data were analysed using SAS version 9.4 (SAS Institute Inc.).

Results

Respondents' demographics and clinical characteristics

There were 123,846 male baseline participants in the 45 and Up Study, of which 105,429 were analysed. The mean age was 62.9 years. The following participants were excluded:

- 4,312 with a DVA white or gold care card
- 13,465 with a doctor-diagnosis of, or recent treatment for, diabetes
- 640 with testosterone PBS prescriptions filled 24 months before baseline.

Factors associated with TRT initiation

In the two-year follow-up period, 2.9 per 1000 men (302) had a prescription filled for TRT (95% CI: 2.6, 3.2). Univariate analyses showed that the demographics associated with TRT initiation were age, area of residence and work status (Table 1), while associated clinical characteristics were BMI, physical activity level, physical impairment, self-rated health, long-term illness or disability, prostate symptom score, erection difficulty, vasectomy, osteoporosis or low bone density, fractures in last five years, psychological distress, history of heart disease/heart attack/angina, high blood pressure, high blood cholesterol and anxiety/depression (Table 2).

In the multivariable model, men aged 55–74 years, residing in major cities, with a history of osteoporosis, recent fractures, high cholesterol, anxiety/depression or lower self-rated health had greater odds of TRT initiation (Table 3).

Among the men who initiated TRT, 255 (84%) had TRT prescribed again in the first year after the initial prescription. The numbers decreased to 163 (53.9%), 143 (47.4%) and 143 (47.4%) in the second, third and fourth years, respectively. There were 117 (38.7%) who had a TRT prescription filled in each of the four years following initiation.

Hormone tests and specialist visits before TRT initiation

Among 302 respondents who initiated TRT, 125 (41%) had a hormone test and 178 (59%) had a specialist visit in the six months before the prescription was dispensed.

Discussion

During the two-year study period, three per 1000 men initiated TRT and nearly 40% of them continued the testosterone use in the following four years. Factors associated with TRT initiation were older age and residing in a major city. Almost 60% of men who initiated TRT did not have a prior hormone test, which suggests that prescribing of TRT was inconsistent with contemporaneous clinical guidelines.

Table 1. Demographics of participants who had testosterone replacement therapy (TRT) initiation or not in the two-year follow-up (n/%)

Demographics characteristics	TRT initiation (n = 302)	TRT non-initiation (n = 105,127)	Total (n = 105,429)	*P**
Age group				
45–54 years	60 (0.2)	29,278 (99.8)	29,338 (27.8)	0.0006
55–64 years	126 (0.4)	33,993 (99.6)	34,119 (32.4)	
65–74 years	75 (0.3)	24,332 (99.7)	24,407 (23.2)	
75 and older years	41 (0.2)	17,524 (99.8)	17,565 (16.7)	
Education				
No school cert	30 (0.3)	10,618 (99.7)	10,648 (10.3)	0.7326
School cert	67 (0.3)	25,290 (99.7)	25,357 (24.5)	
Apprenticeship/diploma	125 (0.3)	40,030 (99.7)	40,155 (38.7)	
University degree or higher	78 (0.3)	27,484 (99.7)	27,562 (26.6)	
Area of residence†				
Major cities	182 (0.3)	55,420 (99.7)	55,602 (53.8)	0.0228
Inner regional	87 (0.2)	35,924 (99.8)	36,011 (34.8)	
More remote	26 (0.2)	11,723 (99.8)	11,749 (11.4)	
Marital status				
Married/de facto	247 (0.3)	85,021 (99.7)	85,268 (81.6)	0.6621
Not married/de facto	52 (0.3)	19,135 (99.7)	19,187 (18.4)	
Country of birth				
Australia	235 (0.3)	77,220 (99.7)	77,455 (74.1)	0.1148
Other	66 (0.2)	27,011 (99.8)	27,077 (25.9)	
Language spoken at home				
English	272 (0.3)	94,680 (99.7)	94,952 (90.1)	0.9991
Other	30 (0.3)	10,445 (99.7)	10,475 (9.9)	
Current work status				
Paid work	148 (0.3)	55,225 (99.7)	55,373 (52.9)	0.0054
Retired	118 (0.3)	42,490 (99.7)	42,608 (40.7)	
Other‡	33 (0.5)	6,737 (99.5)	6,770 (6.5)	

**Chi-square test was applied for comparison of category variables. The sum of each variable may not be the same because of the missing values*
†Based on the Accessibility/Remoteness Index of Australia
‡Other includes doing unpaid work/studying/looking after family/unemployed/disabled/sick

The prevalence of hypogonadism is estimated at five per 1000 men,[2] but this may be an underestimate due to underdiagnosis.[2,7] Our estimated initiation rate of three per 1000 patients per two-year period suggests more men are being treated than would be expected to be diagnosed with hypogonadism during this time frame; however, our estimate may be an underestimate as we did not capture all testosterone-prescribing, such as private scripts and scripts for patients with diabetes. Our initiation rate is higher than was seen in a study in the UK, where the yearly initiation rate was 0.5 per 1000 men in 2011, but lower than that in the US, where the yearly initiation rate was 7.6 per 1000 men in 2011.[8] TRT prevalence rates from Canada (11 per 1000 men in 2012)[10] and Sweden (six per 1000 men in 2014)[17] were also higher than expected. The decrease in observed continuation rates may indicate that men are stopping therapy because the treatment does not relieve their symptoms.[18]

The factors associated with TRT initiation were similar to those seen in other studies. Studies in the US and Canada also observed that urban men were more likely to initiate TRT.[10,19] We observed higher initiation rates among men aged 55–74 years, and a Swedish study reported highest testosterone use among men aged 65–69 years.[17] Our findings showed that TRT initiation was more likely among men with low bone density, osteoporosis, fractures, and anxiety or depression. Similarly to our findings, studies in Canada, US and UK reported men using TRT had multiple comorbidities,[8,10] and a US study found TRT was more likely among patients with depression and anxiety disorder.[20] Such treatment may be beneficial given the known link between hypogonadism and low bone density, loss of motivation, mood or concentration.[2] A previous Australian study reported that low testosterone was associated with higher cholesterol levels,[21] and in our study, participants with higher cholesterol levels were more likely to have TRT initiated. This is concerning given recent research suggesting that TRT increases the risk of a coronary plaque in men.[4]

The updated 2016 ESA position statement supports TRT prescribing in men with hypogonadism with a confirmed laboratory diagnosis.[1] The role of TRT in other settings is still not evidence-based. Low testosterone without elevated LH and FSH is due to chronic diseases as opposed to primary hypogonadism.[1] Adverse effects, particularly increased cardiovascular risk, are still a concern.[4]

A revised clinical practice guideline from Andrology Australia[22] and a recent published review[23] also suggest there is no evidence-based role for TRT in managing erection difficulty.

We found that 60% of participants had no record of a hormone test before TRT initiation, similar to other findings.[8,10] The lack of testosterone measurement was contrary to the 2000 ESA guidelines.[2] The revised PBS guidelines in 2015 require a higher diagnostic threshold as well as a consultation with a specialist; since their release, testosterone PBS prescription rates have fallen, with a striking decline after 2015 in new testosterone prescriptions among men aged 40–80 years.[24] However, GPs have suggested these restrictions may lead to more underdiagnosis because of long waiting periods for specialists and the cost of private prescriptions.[25] Hypogonadism remains significantly undertreated in Australia,[7] but concerns about testosterone overuse may be overshadowing the underdiagnosis and undertreatment of androgen deficiency.

Strengths and limitations

A strength of our study is the inclusion of all prescriptions and medical services captured by the PBS and MBS, and the participants' detailed characteristics from the 45 and Up Study. In database studies we are limited by the data available. The limitations in this study include the lack of data regarding non-PBS testosterone prescriptions, DVA-scheme prescriptions and visits to specialists where a claim is not made through the MBS. A diagnosis of testosterone deficiency is also not recorded in the PBS and MBS databases.

PBS prescriptions accounted for approximately 70% of all TRT prescriptions in 2010.[7] One limitation of the current study is that our initiation rate is likely to be an underestimate. We excluded people with diabetes from the analysis as we were unable to differentiate between hormone tests for testosterone deficiency and insulin assays, but this group of men may also be subject to inappropriate prescription of testosterone given common non-specific symptoms and comorbidities. Removing this group would have an effect of underestimating the rate of initiation in the population. Another limitation is the potential overestimation of the percentage of patients having a testosterone test before TRT initiation, as the MBS item number for a testosterone test includes other tests (eg insulin and cortisol). Similarly, the percentage of men with a relevant specialist visit may be an overestimate. Additionally, clinical characteristics recorded in the 45 and Up Study are self-reported, and we can only analyse the relevant associated factors that were collected in the study database. Finally, the participation rate of about 18% of the 45 and Up Study cohort means that great care should be taken if generalising these statistics to the general population.

Implications for general practice

Our findings suggest that testosterone prescribing occurred outside of the 2000 ESA guidelines, which were current at the time. This may be attributed to a combination of factors including prescribing practices of individual clinicians and consumer requests for therapy. The lack of hormone assays performed in men receiving TRT suggests inadequate diagnostic and monitoring activities by the prescribing clinicians. The PBS restrictions were introduced in April 2015, which may have added barriers to men requiring TRT but might also be driving GPs to prescribe privately, putting more men at a disadvantage.

To ensure appropriate TRT prescribing, evidence-based education programs for health professionals that highlight existing guidelines and how to address inappropriate patient requests for testosterone, such as those provided by Andrology Australia (www.andrologyaustralia.org), are essential. Along with evidence-based consumer campaigns, these could discredit false testosterone advertising claims and ensure underdiagnosed and undertreated cases are given due attention.

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Table 2. Clinical characteristics of participants who had testosterone replacement therapy (TRT) initiation or not in the two-year follow-up (n/%)

Clinical characteristics	TRT initiation (n = 302)	TRT non-initiation (n = 105,127)	Total (n = 105,429)	*P**
Body mass index				
Underweight (<18.5 kg/m^2)	21 (0.3)	6,435 (99.7)	6,456 (6.1)	<0.0001
Normal weight (18.5 to <25 kg/m^2)	58 (0.2)	31,436 (99.8)	31,494 (29.9)	
Overweight (25 to <30 kg/m^2)	129 (0.3)	47,260 (99.7)	47,389 (45)	
Obese (≥30 kg/m^2)	94 (0.5)	19,996 (99.5)	20,090 (19.1)	
Smoking status				
Never smoker	142 (0.3)	52,610 (99.7)	52,752 (50.3)	0.3155
Past smoker	138 (0.3)	43,724 (99.7)	43,862 (41.8)	
Current smoker	20 (0.2)	8,200 (99.8)	8,220 (7.8)	
Alcohol consumption'				
None	81 (0.4)	22,830 (99.6)	22,911 (22)	0.0949
≤14 drinks/week	146 (0.3)	55,167 (99.7)	55,313 (53.2)	
>14 drinks/week	71 (0.3)	25,746 (99.7)	25,817 (24.8)	
Physical activity level				
At risk (<150 min per week)	102 (0.4)	25,990 (99.6)	26,092 (34.4)	0.0009
Not at risk (≥150 min per week)	125 (0.3)	49,565 (99.7)	49,690 (65.6)	
Physical impairment				
No limitation(score of 100)	60 (0.2)	33,223 (99.8)	33,283 (37.5)	<0.0001
Minor limitation (90–99)	73 (0.3)	29,623 (99.7)	29,696 (33.5)	
Moderate limitation (60–89)	72 (0.4)	18,204 (99.6)	18,276 (20.6)	
Severe limitation(0–59)	44 (0.6)	7,473 (99.4)	7,517 (8.5)	
Fruit and vegetable intake				
Adequate (≥2 servings of fruit and ≥5 servings of vegetables per day)	36 (0.2)	14,688 (99.8)	14,724 (17.4)	0.2247
Inadequate (<2 servings of fruit or <5 servings of vegetables per day)	212 (0.3)	69,505 (99.7)	69,717 (82.6)	
Self-rated health				
Excellent	21 (0.1)	15,029 (99.9)	15,050 (14.7)	<0.0001
Very good	94 (0.2)	38,963 (99.8)	39,057 (38.2)	
Good	103 (0.3)	35,241 (99.7)	35,344 (34.6)	
Fair	50 (0.5)	11,012 (99.5)	11,062 (10.8)	
Poor	21 (1.2)	1,767 (98.8)	1,788 (1.8)	
Long-term illness or disability				
Yes	30 (0.7)	4,030 (99.3)	4,060 (4.0)	<0.0001
No	255 (0.3)	96,430 (99.7)	96,685 (96.0)	
History of enlarged prostate				
Yes	49 (0.3)	16,857 (99.7)	16,906 (16.0)	0.9283
No	253 (0.3)	88,270 (99.7)	88,523 (84.0)	
History of prostate removal operation				
Yes	25 (0.3)	8,575 (99.7)	8,600 (8.2)	0.9387
No	277 (0.3)	96,552 (99.7)	96,829 (91.8)	

Table 2. Clinical characteristics of participants who had testosterone replacement therapy (TRT) initiation or not in the two-year follow-up (n/%) (cont'd)

Clinical characteristics	TRT initiation (n = 302)	TRT non-initiation (n = 105,127)	Total (n = 105,429)	*P**
History of prostate cancer				
Yes	12 (0.2)	6,173 (99.8)	6,185 (5.9)	0.1609
No	290 (0.3)	98,954 (99.7)	99,244 (94.1)	
Prostate symptom score				
Less than P_{25}	48 (0.3)	19,052 (99.7)	19,100 (29.4)	0.0232
P_{25}–P_{50}	49 (0.3)	18,272 (99.7)	18,321 (28.2)	
P_{50}–P_{75}	44 (0.4)	11,726 (99.6)	11,770 (18.1)	
Above P_{75}	65 (0.4)	15,824 (99.6)	15,889 (24.4)	
Erection difficulty				
Yes	209 (0.3)	77,494 (99.7)	77,703 (83.6)	0.0194
No	58 (0.4)	15,218 (99.6)	15,276 (16.4)	
Vasectomy operation				
Yes	89 (0.3)	26,699 (99.7)	26,788 (25.4)	0.1045
No	213 (0.3)	78,428 (99.7)	78,641 (74.6)	
Treatment for osteoporosis or low bone density last month				
Yes	24 (1.2)	2,066 (98.8)	2,090 (2.0)	<0.0001
No	278 (0.3)	103,061 (99.7)	103,339 (98.0)	
Bone broken in last 5 years				
Yes	48 (0.5)	8,709 (99.5)	8,757 (8.3)	<0.0001
No	254 (0.3)	96,418 (99.7)	96,672 (91.7)	
Psychological distress (K10 scale)				
Low (<16)	165 (0.3)	63,852 (99.7)	64,017 (80.0)	0.0115
Moderate (16–21)	44 (0.4)	11,221 (99.6)	11,265 (14.1)	
High (22–29)	14 (0.4)	3,510 (99.6)	3,524 (4.4)	
Very high (30–50)	7 (0.6)	1,223 (99.4)	1,230 (1.5)	
History of heart disease/heart attack or angina				
Yes	60 (0.4)	15,675 (99.6)	15,735 (14.9)	0.0158
No	242 (0.3)	89,452 (99.7)	89,694 (85.1)	
History of high blood pressure				
Yes	126 (0.3)	37,417 (99.7)	37,543 (35.6)	0.0263
No	176 (0.3)	67,710 (99.7)	67,886 (64.4)	
History of high blood cholesterol				
Yes	75 (0.5)	15,192 (99.5)	15,267 (14.5)	<0.0001
No	227 (0.3)	89,935 (99.8)	90,162 (85.5)	
History of stroke				
Yes	14 (0.4)	3,148 (99.6)	3,162 (3.0)	0.0949
No	288 (0.3)	101,979 (99.7)	102,267 (97.0)	
History of anxiety/depression				
Yes	80 (0.6)	12,717 (99.4)	12,797 (14.1)	<0.0001
No	193 (0.3)	77,890 (99.8)	78,083 (85.9)	

**Chi-square test was applied for comparison of category variables. The sum of each variable may not be the same because of the missing values*
†The categorisation of alcohol consumption is based on NHMRC. Australian guidelines to reduce health risks from drinking alcohol. Canberra: Australian Government National Health and Medical Research Council 2009

Table 3. Factors associated with testosterone replacement therapy initiation in the two-year follow-up (n = 105,429)

Factors	Group	AOR	95% CI	*P*
Age	45–54 years (reference group)			0.0008
	55–64 years	1.82	1.31, 2.51	
	65–74 years	1.72	1.11, 2.67	
	75 and older years	1.19	0.68, 2.07	
Area of residence	Major cities (ref)			0.0044
	Inner reginal	0.68	0.52, 0.89	
	More remote	0.61	0.40, 0.93	
Treatment for osteoporosis or low bone density last month	No (ref)			<0.0001
	Yes	2.87	1.82, 4.51	
Bone broken in last 5 years	No (ref)			0.0008
	Yes	1.73	1.26, 2.39	
History of high blood cholesterol	No (ref)			0.0015
	Yes	1.57	1.19, 2.08	
History of anxiety/ depression	No (ref)			<0.0001
	Yes	2.04	1.52, 2.75	
Self-rated health	Excellent (ref)			0.0467
	Very good	1.44	0.89, 2.33	
	Good	1.43	0.86, 2.39	
	Fair	1.65	0.90, 3.04	
	Poor	3.26	1.50, 7.12	

Also adjusted by other demographics and clinical characteristics present in table 1 and 2. Covariates with P value >0.05 were not shown in the table
AOR, adjusted odds ratio; CI, confidence intervals.

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Appendix

Measures

Outcomes

The initiation of testosterone replacement therapy (TRT) was defined as a man being dispensed with a testosterone-based drug (testosterone, testosterone enanthate and testosterone undecanoate) during the 24 months following the completion of baseline survey among males who did **not** receive TRT in the 24 months prior to the baseline survey (2006–2009). Dispensed testosterone medications were identified from the Pharmaceutical Benefits Scheme (PBS) dataset as those with Anatomical Therapeutic Chemical (ATC) classification codes beginning with G03BA03. Participants who self-reported holding a Department of Veterans' Affairs card were excluded, as they have access to a broader range of subsided medications under a separate government program.

We identified whether men had a hormone test or visited a specialist in the six months before the initiation of TRT. A hormone test is derived from MBS item number 66695, which is defined as 'Quantitation in blood or urine of hormones and hormone binding proteins – ACTH, aldosterone, androstenedione, C-peptide, calcitonin, cortisol, DHEAS, 11-deoxycortisol, dihydrotestosterone, FSH, gastrin, glucagon, growth hormone, hydroxyprogesterone, insulin, LH, oestradiol, oestrone, progesterone, prolactin, PTH, renin, sex hormone binding globulin, somatomedin C(IGF-1), free or total testosterone, urine steroid fraction or fractions, vasoactive intestinal peptide, – 1 test'.[1] Although the Medicare Benefits Schedule (MBS) item 66695 covers most of the hormone tests applying to the diagnosis of testosterone deficiency, it is also used when insulin tests are ordered, hence we excluded participants with a self-reported history of diabetes, recent treatment for diabetes (in last month) or a prescription filled for a diabetes drug (ATC classification codes beginning with A10) from 2004 to 2014. The definition of a specialist visit is based on a combination of MBS groups under MBS Category 1 attendances,[2] which include other non-referred attendances, specialist attendances, consultant physician attendances and prolonged attendances. The specialist visit is not able to differentiate an endocrinologist, urologist or Member of the Australian Chapter of Sexual Health Medicine who are relevant to the diagnosis and treatment of TRT.

Explanatory variables

We examined whether the following demographic and clinical characteristics were associated with the initiation of TRT. The demographics characteristics were: age; education (no school certificate, school certificate, apprenticeship/trade/certificate/diploma or university degree or higher); area of residence based on the Accessibility/Remoteness Index of Australia (major cities, inner regional or more remote); marital status (married/de facto or not married/de facto); country of birth (Australia or other); language spoken at home (English or other); current work status (paid work, retired or other [doing unpaid work/studying/looking after family/unemployed/disabled/sick]); body mass index (BMI, categorised as underweight [<18.5kg/m^2], normal weight [18.5 to <25kg/m^2], overweight [25 to <30kg/m^2] and obese [≥30 kg/m^2] according to World Health Organization [WHO] criteria).

The clinical characteristics included: smoking status (never, past, current); alcohol consumption (drinks per week categorised as none, ≤14 drinks/week, >14 drinks/week[3]); physical activity (based on the total time one spent on moderate-to-vigorous-intensity physical activity and categorised as at-risk or not according to WHO recommendations on physical activity for health[4]); physical impairment (derived from the physical functioning scale of the SF-36 health survey[5] and categorised as no limitation (score of 100), minor limitations (90–99), moderate limitations (60–89), severe limitations (0–59);[6] fruit and vegetable (including both raw and cooked vegetables) intake was assessed as servings per day and categorised as adequate (≥2 servings of fruit and ≥5 servings of vegetables per day) or inadequate (less than these amounts) according to the National Health and Medical Research Council guidelines;[7,8] self-rated health (categorised as excellent, very good, good, fair or poor); need help due to long-term illness or disability (yes/no); history of enlarged prostate/prostate cancer/prostate removal operation (based on self-reported ever doctor-diagnosed enlarged prostate and prostate cancer, and prostate removal operation and categorised as yes/no, respectively); prostate symptom score (quartiles based on the international prostate symptom[9]); vasectomy operation (yes/no); bone broken in last five years (yes/no). Psychological distress (based on responses to the Kessler 10 scale[10] and categorised as low [score of <16], moderate [16–21], high [22–29] and very high [30–50]) according to the classification of Australian Bureau of Statistics surveys.[11] In addition, we created dichotomous variables for history of heart disease, high blood pressure, high blood cholesterol, stroke and anxiety/depression based on self-reported (at baseline) doctor-diagnosis of, or recent treatment in the last month for, these conditions. We also created a dichotomous variable for treatment for osteoporosis or low bone density based on self-reported (at baseline) treatment in the last month for this condition. We created an additional dichotomous variable for erection difficulty based on self-reported inability to maintain an erection for satisfactory sexual activity.

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