The risk of fall and fracture with the initiation of a prostate-selective α antagonist: a population based cohort study

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ABSTRACT

STUDY QUESTION

Do men starting treatment with prostate-specific α antagonists have increased risk of fall and fracture?

METHODS

Administrative datasets from the province of Ontario, Canada, that contain patient level data were used to generate a cohort of 147 084 men aged ≥ 66 years who filled their first outpatient prescription for prostate-specific α antagonists tamsulosin, alfuzosin, or silodosin between June 2003 and December 2013 (exposed men) plus an equal sized cohort matched 1:1 (using a propensity score model) who did not initiate α antagonist therapy. The primary outcome was a hospital emergency room visit or inpatient admission for a fall or fracture in the 90 days after exposure.

STUDY ANSWER AND LIMITATIONS

The men exposed to prostate-specific α antagonist had significantly increased risks of falling (odds ratio 1.14 (95% CI 1.07 to 1.21), absolute risk increase 0.17% (0.08 to 0.25%)) and of sustaining a fracture (odds ratio 1.16 (1.04 to 1.29), absolute risk increase 0.06% (0.02 to 0.11%)) compared with the unexposed cohort. This increased risk was not observed in the period before α antagonist use. Secondary outcomes of hypotension and head trauma were also significantly increased in the exposed cohort (odds ratios 1.80 (1.59 to 2.03) and 1.15 (1.04 to 1.27) respectively). The two cohorts were similar across 98 different covariates including demographics, comorbid conditions, medication use, healthcare use, and prior medical investigation. Potential unmeasured confounders, such as physical deconditioning, mobility impairment, and situational risk factors, may exist. The data used to

identify the primary outcomes had limited sensitivity, so the absolute risks of the outcomes are probably underestimates. The study only included men ≥ 66 years old, and 84% of exposed men were prescribed tamsulosin, so results may not be generalizable to younger men, and there may not be statistical power to show small differences in outcomes between the drugs.

WHAT THIS STUDY ADDS

Prostate-specific α antagonists are associated with a small but significant increased risk of fall, fracture, and head trauma, probably as a result of induced hypotension.

FUNDING, COMPETING INTERESTS, DATA SHARING

This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) Western Site through the Kidney, Dialysis, and Transplantation (KDT) research program. BW has received a research grant from Astellas, and L-AF does consultancy for Amgen.

Introduction

As men age, many will develop bothersome lower urinary tract symptoms such as urinary frequency, urgency, nocturia, and a weak urinary stream. These symptoms are often attributed to benign prostatic hyperplasia and are treated because of their negative impact on quality of life.¹ The introduction of several α antagonist medications in the 1990s fundamentally changed the treatment of benign prostatic hyperplasia and lower urinary tract symptoms.^{2,3} These medications relax the prostatic smooth muscle and improve urinary flow rates and symptoms.^{1,2}

Non-specific (first generation) α antagonists, such as doxazosin and terazosin, act on all α_1 receptor subtypes (α_{1A} , α_{1B} , α_{1D}) and are used for the treatment of both benign prostatic hyperplasia and hypertension. This non-selective α_1 receptor activity requires dose titration over 1-2 weeks to avoid symptomatic hypotension from α_{1B} antagonism. These non-specific α antagonists have generally fallen into disfavor as antihypertensives since the ALLHAT trial.⁴ In this randomized, double blind trial traditional antihypertensive medicines (including non-specific α antagonists) were compared with newer classes of antihypertensives; the doxazosin arm was stopped early because of a higher rate of cardiac dysfunction.

Similarly, among men with benign prostatic hyperplasia symptoms, these non-specific α antagonists have largely been replaced by prostate-specific (second generation) α antagonists.⁵ These newer drugs do not need dose titration and are solely indicated for male urinary symptoms from benign prostatic hyperplasia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prostate-specific α antagonists are commonly used to treat urinary symptoms in older men

One of the most serious side effects from these medications is hypotension, which may lead to a serious falls, fracture, or head injury

Previous observational studies have not focused solely on prostate-specific α antagonists (the predominant α antagonists used for male urinary symptoms) and have had conflicting conclusions regarding the risk of fall or fracture with the initiation of treatment

WHAT THIS STUDY ADDS

Initiation of treatment with prostate-specific α antagonists leads to a significant increase in the risk of presenting to a hospital emergency room or being admitted to hospital because of a fall, fracture, or head injury

The absolute magnitude of this risk increase is small, but, given the potential seriousness of these events in elderly people, men should be counseled on ways to decrease this risk

They include alfuzosin (which exhibits clinical uroselectivity), and tamsulosin and silodosin (which exhibit true α_{1A} receptor selectivity, which is the primary α receptor in the prostate).⁶⁻⁹ Their selectivity for the prostate hypothetically reduces the risk of hypotension due to reduced α_{1B} antagonism.

However, as a class, all α antagonists have been associated with side effects such as hypotension and dizziness.^{6 10 11} For this reason, α antagonists in general have been identified as a class of medication to discontinue in a patient who falls.¹² However, this recommendation is primarily based on perceptions of the hypotension risk associated with non-specific α antagonists, and the potentially lower risk, prostate-specific drugs have not been widely studied. In addition, previous research has failed to demonstrate a consistent conclusion regarding the risk of falls and fractures with α antagonists used for benign prostatic hyperplasia symptoms. Studies have both demonstrated^{11 13 14} and failed to demonstrate^{15 16} this risk.

The effect of benign prostatic hyperplasia treatment on falls and fractures has been identified as an important research question¹⁴ because of the direct morbidity associated with falls in the elderly (such as fracture and head injury), the common need for nursing home admission after a fall, and the substantial direct medical costs.¹² The objective of this study was to use administrative data to assess the 90 day risk of fall or fracture among men initiating a prostate-specific α antagonist.

Methods

Design and setting

We conducted a retrospective, matched cohort study using datasets from the province of Ontario (Canada) that were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. Ontario has a population of over 13 million people with universal access to a single public healthcare system, and universal drug coverage for those over 65 years of age.

This study was approved (2015 0906 137 000) by the research ethics board at Sunnybrook Hospital (Toronto, Ontario), and individual patient consent was not required. Study reporting follows the STROBE guidelines (eTable 1 in the supplement).

Data sources

The following administrative data sources have previously demonstrated validity and reliability and were used for this study: (1) Registered Persons Database (containing vital statistics),¹⁷ (2) Ontario drug benefit database (containing all prescription drug use for senior patients),¹⁸ (3) Canadian Institute for Health Information Discharge Abstract Database (identifying all inpatient admissions and procedures),¹⁹ (4) National Ambulatory Care Reporting System (identifying all emergency room encounters),²⁰ and (5) Ontario Health Insurance Plan (containing all physician billing codes for patient assessment or treatment).²¹ These databases contain patient level data in linkable files without any

direct patient identifiers and are >99.5% complete for all study variables.

Patient population

We established a cohort of men aged 66 years or older who filled their first outpatient prescription for tamsulosin, alfuzosin, or silodosin between 1 June 2003 and 31 December 2013 (exposed men). The date the prescription was filled served as the index date for the patient, and the beginning of the 90 day observation window for our outcome.

All remaining men in the province of Ontario (unexposed men) were assigned a random index date based on the distribution of index dates for men with α antagonist use. We excluded men who had used a non-specific or prostate-specific α antagonist in the three months before the index date, and those who were in hospital or had an emergency room visit in the two days before the index date (eFigure 1 in the data supplement). Men from the exposed cohort were then matched to men from the unexposed cohort based on age (within 2 years), residential status (community dwelling versus long term care residents), prior fracture status, use of 5- α reductase inhibitor, and the logit of a propensity score.

We assessed 98 different covariates representing comorbid medical conditions, medication use, and healthcare use to assure the similarity of our exposed and unexposed cohorts (coding definitions are included in eTable 2a-c in the data supplement). A five year “look back” window from the index date was used for all specific medical comorbidities, and a one year look back window was used for prior falls and fractures. Prior medications were assessed based on any prescription within the six months before the index date, and prior hospital or physician use and medical investigations and procedures were assessed based on the previous year. Of the 98 covariates, 42 were selected for inclusion in the propensity score (listed in eTable 3 in the supplement) based on a standard difference of >7%²² or a potentially important relationship with our study outcomes.

Study outcomes

We pre-specified falls and fractures as our primary outcomes. Our secondary outcomes included major osteoporotic fractures, hip fractures, hypotension, and head trauma. The data sources and validated diagnostic codes that were used, as well as their measurement characteristics, are outlined in eTable 4 in the data supplement.

We observed patients for our study outcomes for 90 days after the index date. This time period was chosen because adverse events are highest in the first few weeks after starting an α antagonist,^{6 7} long term patient adherence to α blocker therapy is modest,²³ and this time period minimizes crossover between the groups.

Statistical analysis

Baseline characteristics were compared using standardized differences, which is better at identifying

meaningful differences between very large groups than traditional hypothesis tests; a standardized difference >10% was considered an important difference.²² To create our two cohorts, we used greedy matching (1:1) with a caliper of ± 0.2 standard deviations of the logit of the propensity score.²⁴

Our primary analysis was carried out using PROC LOGISTIC (SAS 9.4, SAS Institute, Cary, NC, USA). Conditional logistic regression was used to account for matching. Conditional odds ratios and 95% confidence intervals are reported, as well as absolute risk. Secondary outcomes were assessed using similar methodology. Subgroup analysis was carried out among men stratified by age (younger or older than 75 years), type of α antagonist, residential status, and use of 5- α reductase; the significance of these subgroups was assessed using tests for interactions. We considered two tailed P values <0.05 to be statistically significant.

Men with lower urinary tract symptoms from benign prostatic hyperplasia have an increased risk of falls due to their urinary symptoms.²⁵ Therefore, to further assess the temporal relationship between α antagonist initiation and our outcomes, we wished to demonstrate that men in our exposed cohort did not have an increased risk before the index date (which, if observed, would suggest that persistence of baseline lower urinary tract symptoms among our exposed cohort may account for an observed increase in our primary outcomes). We reapplied the exclusion criteria to our cohorts on the index date minus 180 days, and eligible matched pairs were retained and used to re-calculate the 90 day primary outcomes based on this earlier index date.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Results

Cohort selection is presented in eFigure 1 of the data supplement. We retained a total of 147 084 matched pairs between our exposed and unexposed cohorts. Complete baseline characteristics of the unmatched

and matched cohorts are presented in eTable 5 in the data supplement. The median age was 75 (interquartile range 70–80) years, and groups were well balanced with no standardized difference >6% among our 98 measured covariates. These covariates covered demographics (such as region of residence and socioeconomic status), comorbid conditions (such as ocular disease, diabetes, Parkinson's disease, stroke, and seizure), John Hopkins ACG comorbidity adjustment, medication use (including antihypertensives, antipsychotics, antidepressants, and anticonvulsants), healthcare use, and prior medical investigation. The most commonly used prostate-specific α antagonist in our study was tamsulosin (n=123 537, 84%), followed by alfuzosin (n=20 827, 14%) and silodosin (n=2720, 2%). Dosage and prescription details are listed in eTable 6 in the data supplement. These medications were prescribed predominantly by a primary care physician (54%) or a urologist (27%).

The primary outcomes of 90 day hospital visit for fall or fracture, as determined from hospital and emergency room admissions, are listed in table 1. Men initiating a prostate-specific α antagonist had a significantly increased risk of presenting to hospital after a fall (odds ratio 1.14 (95% confidence interval 1.07 to 1.21) and of sustaining a new fracture (1.16 (1.04 to 1.29)). These two outcomes seem to be inter-related, as 80% of men who sustained a fracture were also identified as having a fall. Our secondary outcomes included specific fracture types. In general, there were few major osteoporotic fractures or hip fractures during our 90 day time frame, and there was no significantly increased risk for these specific fractures among men starting prostate-specific α antagonists. Other secondary outcomes included hospital admission or emergency room visit for hypotension or head trauma, both of which were significantly increased among men exposed to α antagonists (odds ratios 1.80 (1.59 to 2.03) and 1.15 (1.04 to 1.27) respectively).

We used the most common primary outcome, hospital or emergency room visit for a fall, to examine several subgroups within our study population (table 2). Men older than 75 years of age, those in long term care, and those with prior fractures all had a higher baseline level

Table 1 | 90 day risk for hospitalization or emergency room assessment for fall or fracture among men starting prostate-specific α antagonist therapy. Secondary outcomes included specific fracture subgroups (major osteoporotic, hip) and hospitalization or emergency room assessment for hypotension or head trauma

	No (%) of events			
	Exposed cohort (n=147 084)*	Unexposed cohort (n=147 084)	Odds ratio (95% CI)	Change (95% CI) in absolute risk (%)
Primary outcomes:				
Fall	2129 (1.45)	1881 (1.28)	1.14 (1.07 to 1.21)	0.17 (0.08 to 0.25)
Fracture	699 (0.48)	605 (0.41)	1.16 (1.04 to 1.29)	0.06 (0.02 to 0.11)
Secondary outcomes:				
Major osteoporotic fracture†	312 (0.21)	298 (0.20)	1.05 (0.89 to 1.23)	0.01 (−0.02 to 0.04)
Hip fracture	159 (0.11)	163 (0.11)	0.98 (0.78 to 1.21)	0.00 (−0.02 to 0.03)
Hypotension	706 (0.48)	394 (0.27)	1.80 (1.59 to 2.03)	0.21 (0.17 to 0.26)
Head trauma	888 (0.60)	773 (0.53)	1.15 (1.04 to 1.27)	0.08 (0.02 to 0.13)

* α antagonist users.

†Defined as hip, forearm, humerus, or pelvic fracture.

Table 2 | Subgroup analysis of 90 day risk for hospitalization or emergency room assessment for fall among men starting prostate-specific α antagonist therapy

	No (%) of events			Odds ratio (95% CI)	Interaction P value	Change (95% CI) in absolute risk (%)
	No at risk	Exposed cohort*	Unexposed cohort			
Age (years):						
66-74.9	72 106	603 (0.84)	515 (0.71)	1.17 (1.04 to 1.31)	0.52	0.12 (0.03 to 0.21)
≥75	74 978	1526 (2.04)	1366 (1.82)	1.12 (1.04 to 1.21)		0.21 (0.07 to 0.35)
α antagonist:						
Tamsulosin	123 537	1810 (1.47)	1625 (1.32)	1.12 (1.04 to 1.19)	0.44	0.15 (0.06 to 0.24)
Alfuzosin	20 827	279 (1.34)	226 (1.09)	1.24 (1.04 to 1.48)		0.25 (0.04 to 0.46)
Silodosin	2720	40 (1.47)	30 (1.10)	1.35 (0.83 to 2.18)		0.37 (−0.23 to 0.96)
Residential status:						
Community dwelling	143 016	1969 (1.38)	1757 (1.23)	1.12 (1.05 to 1.20)	0.25	0.15 (0.07 to 0.23)
Long term care	4068	160 (3.93)	124 (3.05)	1.30 (1.03 to 1.65)		0.88 (0.09 to 1.69)
Prior fracture in past year:						
Yes	1294	57 (4.40)	59 (4.56)	0.96 (0.66 to 1.40)	0.39	−0.15 (−1.77 to 1.46)
No	145 790	2072 (1.42)	1822 (1.25)	1.14 (1.07 to 1.22)		0.17 (0.09 to 0.25)
5- α reductase use in past 180 days:						
Yes	10 826	147 (1.36)	167 (1.54)	0.88 (0.70 to 1.10)	0.02	−0.18 (−0.51 to 0.13)
No	136 258	1982 (1.45)	1714 (1.26)	1.16 (1.09 to 1.24)		0.20 (0.11 to 0.28)
Tamsulosin dose (mg):						
0.4 (standard dose)	113 989	1622 (1.42)	1488 (1.31)	1.09 (1.02 to 1.17)	0.49	0.12 (0.02 to 0.21)
0.8 (off label dose)	6775	105 (1.55)	87 (1.28)	1.21 (0.91 to 1.62)		0.27 (−0.13 to 0.67)

* α antagonist users.

of falls, but these factors did not significantly modify the effect of α antagonists on falls ($P=0.52$, $P=0.25$, and $P=0.39$ respectively for interaction). We found that prescribing tamsulosin 0.4 mg (the most commonly prescribed prostate-specific α antagonist in our cohort) at a higher (off label) dose of 0.8 mg did not significantly modify the risk of a fall ($P=0.49$). The only other class of medications that are indicated specifically for the treatment of benign prostatic hyperplasia are 5- α reductase inhibitors, and, similar to α antagonists, they are efficacious at managing lower urinary tract symptoms.¹ The presence of a prescription for one of these medications in the 180 days before starting a prostate-specific α antagonist suggests an existing diagnosis of benign prostatic hyperplasia. There was a significant interaction ($P=0.02$) among men with prior 5- α reductase inhibitor treatment and new α antagonist use, with those who had evidence of 5- α reductase inhibitor use having a non-significant trend towards a lower risk of falls (odds ratio 0.88 (0.70 to 1.10)).

To assess the temporal relationship between α antagonist initiation and our primary outcomes, we repeated our analysis among eligible matched men 180 days before their first initiation of α antagonists. We showed that men who were to be exposed to a prostate-specific α antagonists in the future did not have a significantly higher risk of fall or fracture (odds ratios 0.92 (0.86 to 0.99) and 0.86 (0.76 to 0.97) respectively) at this earlier time point than men in the unexposed cohort (eTable 7 in the data supplement).

Discussion

Principal findings

We observed a small, but significant increase in the risk of falls and fractures among older men initiating prostate-specific α antagonist drugs. These men were also at

an increased risk of hospital admission or emergency room assessment for a traumatic head injury, another potential serious sequela of a fall. Most of those who sustained a fracture or head injury had a concomitant fall, suggesting that the mechanism for these potentially serious injuries among men initiating α antagonist therapy is probably related to syncope or postural hypotension, known side effects of the α antagonist class of drugs.⁹ This conclusion is further strengthened by our observation that men starting prostate-specific α antagonists were significantly more likely to require hospital admission or emergency room assessment for hypotension. These outcomes are relevant in an elderly population which has an estimated 50% mortality during the first year after a fall requiring hospitalization,²⁶ and an increased mortality risk after fractures.²⁷ In elderly people, falls are the most common cause of traumatic brain injury, and these older patients have greater cognitive decline and increased mortality compared with younger patients.²⁸ Finally, although the magnitude of the risk of fall and fracture was low, the potential for life threatening events or death from adverse events due to these medications has been reported to drug regulatory agencies.²⁹

Some specific results within our study deserve comment. A history of 5- α reductase use in the six months before starting α antagonist treatment was a significant effect modifier in our study ($P=0.02$) and trended towards a decreased risk of falls (odds ratio 0.88 (0.70 to 1.10)). This may be due to successful treatment of specific urinary tract symptoms (such as nocturia and incontinence) known to cause falls²⁵ or due to manipulation of testosterone levels.³⁰ In our analysis of falls and fractures in the six months before α antagonist initiation, men who were eventually started on this medication had a significantly lower risk of falls and

fractures than the matched cohort who did use α antagonists. This may be due to physicians selectively using α antagonists only among men judged to have a low risk of fall or fracture. Nevertheless, the fact that the initiation of a prostate-specific α antagonist was temporally related to a reversal in the direction of this risk further supports our conclusions.

Strengths and limitations of our study

To our knowledge this is the first cohort study of prostate-specific α antagonists that measures both the adverse event of falls and the potentially serious sequelae such as fracture and head injury. Using an extensive library of almost 100 administrative data covariates and matching and propensity score techniques, we were able to create a large cohort of men with similar health characteristics. Compared with randomized trials, large observational studies are ideally suited for the assessment of rare but serious adverse drug reactions and include patients generally excluded from randomized trials (thus better assessing real world risk).

Weaknesses of our research include the potential for unmeasured confounders related to increased falls in the elderly, such as physical deconditioning, mobility impairment, and situational risk factors.¹² However, it is unlikely such variables would change significantly over the six months period we used to confirm a temporal increase in fall and fracture risk with initiation of α antagonist treatment. The administrative data coding elements we used to identify our primary outcomes had limited sensitivity. Therefore, although our odds ratios are accurate (as there should not be differential misclassification of our outcomes between our exposed and unexposed men), we have probably underestimated the absolute risk of some of our outcomes. Furthermore, only an estimated 5% of falls lead to a hospital visit, so it is likely that we underestimated the number of less serious falls in this population.²⁶

Our primary exposure was defined as a patient filling a prescription, but we do not have any measure of drug compliance and found only about half of men refilled their α antagonist medication after the first month. This should, however, bias the odds ratio towards the null. Finally, our study only included men 66 years of age or older, and predominately included tamsulosin. The relatively small number of alfuzosin and silodosin users, and lack of younger men limits the generalizability of our results to these groups, and we may not have had enough statistical power to demonstrate small but meaningful differences in our outcomes between these medications.

Comparisons with other studies

Some previous studies in this area have shown similar results. A population based cohort study demonstrated an increased risk of hypotension requiring hospital admission among men treated initially with tamsulosin compared with 5- α reductase inhibitors, particularly in the first four weeks of treatment.¹⁰ Similarly, a post-marketing observational study of tamsulosin identified a

0.7% risk of hypotension, with both dizziness and hypotension commonly reported as reasons for discontinuing therapy.³¹ A case-control study examining the effect of 5- α reductase inhibitors demonstrated the odds of a hip fracture were two times higher with a recent α antagonist prescription.¹⁴ Two smaller studies also support our conclusions, but they included a mix of non-specific and prostate-specific α antagonists, which limits their generalizability.^{11 13}

Studies that have failed to show an effect of α antagonists on falls or fractures include a small case-control study of patients using modified release doxazosin,¹⁵ and a case-control study which defined α antagonist exposure based on the presence of any prior prescription (not current use).¹⁶ Although placebo controlled, randomized trials of tamsulosin have suggested there are no clinically relevant changes to blood pressure, dizziness as an adverse event was generally higher among tamsulosin patients than placebo patients.^{32 33}

Practice implications

Product monographs for most α antagonists have warnings about severe hypotension and syncope, but research has suggested that prostate-specific α antagonists have a lower risk of hypotension related events than non-selective α antagonists.⁹ Our study supports the continued need to counsel men about the risk of hypotension even with prostate-specific α antagonists such as tamsulosin, which have several-fold higher affinity for α_{1A} receptors in the prostate than for α_{1B} receptors in the vascular system.⁷ Measures to reduce the risk of hypotension related events include taking α antagonists in the evening, with food, and avoiding driving or potentially hazardous activities during the initiation of therapy.

Future directions

The impact of 5- α reductase inhibitors on fractures, and their potential role in modulating the risk of falls among men using dual therapy (with an α antagonist) deserves further analysis. Future studies with larger samples of men using the newest prostate-specific antagonists (such as silodosin) should be undertaken to see if increased prostate selectivity mitigates the risk of fall and fracture.

Conclusions

Prostate-specific α antagonists, which are commonly used to treat lower urinary tract symptoms among older men, are associated with a small but significant increase in the risk of hospitalization or emergency room assessment for a fall, and an increase in the risk of fracture by 16% (95% confidence interval 4% to 29%) and of head trauma by 15% (4% to 27%) during the first 90 days of use. Although the absolute magnitude of the risk increase is small, it is accentuated in patient populations with a higher baseline risk of falls, and continued caution should be exercised while initiating these medications.

Contributors: BW initiated the collaborative project, co-designed and edited the data collection protocol, wrote the statistical analysis plan,

and drafted and revised the paper. He is the guarantor. YJH co-designed the data collection plan, contributed to the analysis of the results, and revised the paper. L-AF, SD, and MO edited the data collection protocol, contributed to the data analysis, and edited the manuscript. EMCA edited the data collection protocol, performed the data programming and statistical analysis, and revised the manuscript. JH edited the data collection protocol, assisted with the data programming and analysis, and revised the manuscript.

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Competing interests: We have read and understood BMJ policy on declaration of interests. All authors have completed the ICMJE uniform disclosure form and declare: no additional support from any organization for the submitted work; BW has received research grants from Astellas, and L-AF does consultancy for Amgen; there are no other relationships or activities that could appear to have influenced the submitted work.

The opinions, results, and conclusions are those of the authors, and no endorsement by the Institute for Clinical Evaluative Sciences, Ontario Ministry of Health and Long-Term Care, or Academic Medical Organization of Southwestern Ontario is intended or should be inferred.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available because of governmental privacy regulations.

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Supplementary eTables 1–7 and eFig

1