特集　認知症（AD，DLB）およびパーキンソン病における認知障害と抑うつ症状

アルツハイマー病とうつ状態

水上　勝義

アルツハイマー病（AD）は進行性の記憶障害を中心とした認知機能障害のほかに，経過中さまざまな行動・心理症状（BPSD）が認められる．うつ状態もADのBPSDの中で主要な症状の1つである．ADのうつ状態の頻度は報告によってばらつきがあるが，経過中およそ2〜3割の患者に大うつ病エピソードがみられると報告されている．病初期には自己の能力の低下に対する不安や自信の欠如に端を発したうつ状態が生じやすく，進行とともにうつ状態の頻度が増加するなどと報告されたが，最近のメタ解析の結果はうつ状態の頻度と重症度との関連に否定的である．ADのうつ状態は通常のうつ病と同様に生物・心理・社会的要因のいずれの影響も受けるが，とくに生物学的な要因の比重が大きいと考えられる．うつ状態を呈するADは，大脳皮質の神経原線維変化の発現が多いとの報告，アミロイドβ蛋白とうつ状態との関連を示唆する報告，またADの扁桃体にレビー小体が存在するとうつ状態が出現しやすいなどの報告がある．ADにうつ状態が現れると，ADLや認知機能にさらなる障害を引き起こし，介護負担の増加や施設入所を促進することが報告されている．我々は，ADにみられた大うつ病エピソードと，年齢や重症度を一致させた大うつ病の臨床的特徴を比較検討した．大うつ病エピソードを認めるADでは，大うつ病に比べて生活機能の障害がより高度であった．またうつ症状の比較では，両者ともに抑うつ気分，興味の喪失，不安が高くうつ状態の基本的な症状は一致するが，ADの大うつ病エピソードは抑制が強く，大うつ病は身体的不安や睡眠障害がより強かった．ADのうつ状態の対応に際しては，非薬物療法と薬物療法が用いられる．支持的に接しながら，能力を超えない範囲の活動を通して楽しみや達成感が得られるように支援することが基本的な対応である．このほか非薬物療法として，バリデーション，回想法，運動，介護者に対する心理社会的介入の効果が報告されている．大うつ病エピソードに対しても，SSRIやSNRIを中心とした薬物療法が行われるが，現時点では抗うつ薬の効果について評価は定まっていない．コリンエステラーゼ阻害薬もADのうつ状態に対する効果が認められているため，非薬物療法やコリンエステラーゼ阻害薬の効果を見定めてから抗うつ薬治療の検討をするのが望ましい．

＜索引用語：アルツハイマー病，うつ状態，非薬物療法，薬物療法＞

はじめに

アルツハイマー病（AD）は，記憶障害や遂行機能障害など進行性の認知機能障害を特徴とする変性認知症疾患であり，本邦で最も多い認知症の原因疾患である．ADの症状には認知機能障害のほかに行動・心理症状（behavioral psychological symptoms of dementia：BPSD）があるが，うつ状態はBPSDの1症状である．ADにうつ状態が出現すると，認知機能[8]やADL[12]のさらなる悪化をきたし，介護負担が増加する[6]．結果として施設入所を促進することになる[22]．本稿ではADのうつ状態について，その臨床的特徴や対応について概説する．

Ⅰ．ADのうつ状態の頻度

BPSDの評価尺度である，Neuropsychiatry

著者所属：筑波大学大学院人間総合科学研究科

Inventroy（NPI）を用いた検討では，高度の症例ではおよそ6割にうつ症状がみられるという[14]．大うつ病エピソードの頻度は，レビー小体型認知症（DLB）には及ばないものの，ADの20～25%に出現するといわれている[15]．老年期の大うつ病の頻度2～3%[7]と比較すると，ADはうつ状態が現れやすいといえる．

ADの経過や重症度とうつ状態との関連については，認知機能障害に対する病識が良好な早期ADに比較的軽症の反応性のうつ状態がみられる一方，大うつ病エピソードは前駆期も含め全経過にみられるなどと報告されているが，最近の24論文のメタ解析結果は，ADの重症度とうつ病あるいはうつ状態の頻度の関連性に否定的である[24]．

Ⅱ．ADのうつ状態の背景

ADのうつ状態も，認知症をもたないうつ病と同様に，生物・心理・社会的要因のいずれもが関与するが，とくに生物学的要因の影響が大きいと考えられる．高齢のうつ病患者においては，タウやアミロイドβ蛋白などのAD関連病理の出現が多いとする報告がある[10]．また神経病理学的検討から，うつ状態を呈したADは神経原線維変化病変が高度の例が多いことが示されている[20]．さらに患者脳の扁桃体にレビー小体関連の病変があると，うつの率が2倍に上昇することが報告されている[11]．

Ⅲ．ADの大うつ病エピソードと大うつ病の比較

ADに出現する大うつ病エピソードは老年期の大うつ病と臨床的特徴にどのような違いがあるのだろうか，この点を検討した研究は少ない．AD＋大うつ病エピソード（MDE）92例と年齢を一致させた大うつ病（MDD）47例のハミルトンうつ病尺度（HAM-D）得点を比較したChemerinskiら[3]の報告によれば，両者とも抑うつ気分，興味の喪失，不安が最もめだつ点で共通していた．一方AD＋MDEにより多くみられた症状は抑制であり，MDDにより多くみられた症状は，身体的不安，食欲低下，体重減少であった．我々は，MDEを認めたAD 14例と年齢とうつ病の重症度を一致させたMDD 22例の臨床的特徴を比較した[16]．その結果，年齢やうつ状態の重症度が同じでも，GAFでみた生活機能はAD＋MDEが有意に低かった（AD＋MDE 34.1±12.3，MDD 49.6±7.6，p=0.0003）．HAM-D得点は，両者ともに抑うつ気分，興味の喪失，不安の3項目が最も高かった．両者の相違点としてAD＋MDEは，抑制の得点がより高く（p=0.003），MDDでは，入眠障害（p=0.048），早朝覚醒（p<0.001），身体的不安（p=0.004）がより高値であった．すなわちChemerinskiらの報告と我々の報告の結果はよく一致しており，AD＋MDEとMDDは，ともに抑うつ気分，興味の喪失，不安が高く，抑うつ状態の基本症状は一致しているが，AD＋MDEでは抑制がよりめだち，MDDでは身体的不安や身体的症状がよりめだつといえよう．ただしChemerinskiらの研究では，自殺念慮はMDDに強かったが，本研究では，AD＋MDEに比較的強かった．これまでのところADの自殺に関しては定説はみられないが，我々の検討から，ADに大うつ病エピソードがみられた場合，希死念慮に注意が必要なことが示唆された．

Ⅳ．ADのうつ状態に対する治療

ADのうつ状態に対する治療は非薬物療法と薬物療法の2つに大別される．

1．非薬物療法

非薬物療法の基本は，患者に対する支持的な対応である．高齢者や認知症患者は，これまでできていたことができなくなる体験から自己効力感の低下や自己価値観の低下を招きやすく，それがうつ状態の引き金になる．支持的，受容的な支援による自己価値観の改善や成功体験の積み重ねによる自己効力感の向上によりうつ状態の改善を図ることが大切である．このほか，バリデーション，回想法，介護者に対する心理社会的介入などの有効性が示されている[2,17]．

またADのうつ状態に対する運動の効果につい

ては，3つの比較対照試験の結果が報告され，有酸素運動，柔軟運動，バランス運動などを3〜4ヵ月間実施することで気分の改善効果を認めている[4]．運動により海馬の神経栄養因子の増加[9]や海馬の血流増加[18]が報告されているが，これらの機序が抗うつ効果と関連する可能性が考えられる．

2．薬物療法

ADのうつ状態に対しても抗うつ薬が用いられる場合がある．5つの無作為比較対照試験のメタ解析[23]の結果から反応率も寛解率も抗うつ薬治療群が有効と報告されている（反応率 $p<0.04$，寛解率 $p<0.03$）．ただしこのメタ解析にはイミプラミンやクロミプラミンのデータが含まれている．クロミプラミンの有効性が報告[19]されているが，基本的に三環系抗うつ薬は抗コリン作用が強いためADに対しては控えるべきであろう．ADの大うつ病エピソードに対しては，SSRIやSNRIを中心に選択することになる．しかしこれらの抗うつ薬の有効性について評価は定まっていないのが現状である．かつてはセルトラリンの有効性が報告されたが[13]，最近のセルトラリンやミルタザピンについての検討では，対照群の効果と有意差を認めず，また対照群に比較して副作用の発現が高いことが報告されている[1,21]．SNRIについては我々のミルナシプランについての報告のみである．14例の大うつ病エピソードを認めたADに対して，平均投与量40.4±18.5 mgの少量で，最終評価時（10.1±4.7週），HAM-D平均得点は18.0±3.6から5.7±5.8に改善した（$p=0.0001$）[16]．しかしオープンスタディという限界がある．以上の現状をふまえ抗うつ薬の使用に関しては慎重に適否を検討するべきである．

ところで，うつと類似した状態にアパシーがある．意欲，関心，活動性が低下するが，うつと異なり自ら苦痛を訴えずむしろ自らの状態を気に留めない．アパシーに対しては抗うつ薬は効果がないばかりか，SSRIがアパシーを悪化させることがあるため，抗うつ薬を投与する前に両者の鑑別が必要である．

抗うつ薬以外の薬物療法としては，AD治療薬であるコリンエステラーゼ阻害薬の効果が報告されている．中等度から高度のADを対象としたドネペジルの臨床試験において，NPIのうつ，不安，アパシーの3項目でドネペジル群は対照群より有意に優れていた[5]．すなわちADのうつ状態に対しては，非薬物的対応やAD治療薬の効果を見極めてから抗うつ薬の投薬について検討することが望ましい．

おわりに

最近の疫学調査の結果から，認知症患者数は460万人と推計されている．さらに高齢化が進むにつれ患者数はさらに増加していくことが予想される．このことは今後ADにともなううつ状態を呈する患者数もますます増加することを示唆する．ADにうつ状態が合併するとすでに述べたように患者の施設入所を促進させることから適切な対応が重要である．さらにはADのうつ状態の予防についてもエビデンスにもとづく有効な方策が喫緊の課題といえる．

なお，本論文に関して開示すべき利益相反はない．

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Alzheimer's Disease and Depression

Katsuyoshi MIZUKAMI

Graduate School of Comprehensive Human Sciences, University of Tsukuba

In Alzheimer's disease (AD) patients, depression is not rare. The prevalence of major depressive episodes has been reported to be within the range of 20-25% in AD patients, despite there being no association between the severity of AD and prevalence of comorbid depressive symptoms or diagnosed depression. Depression in AD patients is associated with greater impairment of the quality of life and an increased caregiver burden. As well as earlier placement in a nursing home, bio-psycho-social factors are also associated with the manifestation of depression in AD patients, and biological factors, such as the brain pathology, may be the main influence. Depressive mood, loss of interest, and anxiety are among the most marked symptoms of depression in AD patients. In comparison with major depressive disorder, in depression in AD, psychomotor retardation is more prominent, while, in major depressive disorder, somatic anxiety is more marked.

In the treatment of depression in AD, non-pharmacological and pharmacological therapies are applied. Basically, support and encouragement are required. In addition, psychosocial interventions, such as validation, reminiscence, physical exercise, and interventions for caregivers of those with dementia have been reported to be useful. The results of RCT with antidepressants are inconsistent. As the efficacy of cholinesterase inhibitor for depression in AD has been reported, it is reasonable to initially provide treatment with cholinesterase inhibitors rather than antidepressant therapy.

<Author's abstract>

<Keywords: Alzheimer's disease, depression, non-pharmacological intervention, antidepressants, cholinesterase inhibitor>

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Original Study

Low Testosterone Levels, Depressive Symptoms, and Falls in Older Men: A Cross-Sectional Study

Noriaki Kurita MD, FJSIM [a], Shigeo Horie MD, PhD [b,c], Shin Yamazaki PhD [a], Kenichi Otoshi MD, PhD [d], Koji Otani MD, PhD [d], Miho Sekiguchi MD, PhD [d], Yoshihiro Onishi MPH, PhD [e], Misa Takegami RN, PhD [f], Rei Ono MPH, PhD [g], Shin-ichi Konno MD, PhD [d], Shin-ichi Kikuchi MD, PhD [d], Shunichi Fukuhara MD, DMSc [a,h,*]

[a] Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[b] Department of Urology, Juntendo University School of Medicine, Tokyo, Japan
[c] Department of Urology, Teikyo University School of Medicine, Tokyo, Japan
[d] Department of Orthopedic Surgery, Fukushima Medical University School of Medicine, Fukushima, Japan
[e] Institute for Health Outcomes and Process Evaluation Research (i-Hope International), Kyoto, Japan
[f] Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, Osaka, Japan
[g] Department of Community Health Sciences, Kobe University Graduate School of Health Sciences, Kobe, Japan
[h] Center for Innovative Research in Clinical Evaluative Science (CiRCLE), Fukushima Medical University, Fukushima, Japan

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ABSTRACT

Objectives: While several studies have cited a potential association between testosterone deficiency and risk of falls among community-dwelling older men, evidence for such an association is conflicting. Depressive symptoms, which occasionally accompany testosterone deficiency but which are often neglected as associated symptoms, may actually provoke falls independent of or jointly with testosterone deficiency. We examined the association between testosterone levels, depressive symptoms, and falls, and assessed the joint effect of testosterone levels and depressive symptoms on falls among older men.
Design, Setting, and Participants: Data for this cross-sectional study were obtained from 869 men aged over 60 years who participated in health check-ups conducted in 2010 from 2 Japanese municipalities. Salivary testosterone (sT) levels were measured using an enzyme-linked immunosorbent assay, and depressive symptoms were assessed via the short form of the Center for Epidemiologic Studies Depression Scale.
Main outcome measures: Self-reported "any fall" over the 1-month period.
Results: Among the total of 482 participants analyzed (median age, 70 years), 10.8% reported any fall. On comparison between 90th percentile sT levels and lower levels, our logistic regression model with restricted cubic splines showed that lower sT levels were associated with an increased likelihood of suffering any fall after adjustment for sociodemographic characteristics, comorbidities, and mobility function. For example, 5th percentile sT was associated with any fall [adjusted odds ratio (OR), 4.23; 95% confidence interval (CI), 1.66–10.8]. Depressive symptoms were also strongly associated with any fall [adjusted OR, 3.49 (95% CI, 1.52–8.04)]. We noted no apparent interaction of sT and depressive symptoms with falls ($P = .079$), suggesting that the joint effect of testosterone deficiency and depressive symptoms on falls was multiplicative. Indeed, compared with a combination of 90th percentile sT values and no depressive symptoms, adjusted OR for any fall in a combination involving 5th percentile sT and depressive symptoms was 14.8-fold (95% CI, 3.76–58.0).
Conclusions: Our findings indicated that both relatively low testosterone levels and presence of depressive symptoms were independently associated with falls among older men. Causality of these associations should be confirmed in future prospective studies.

Falls are a serious public health problem, with one-third of community-dwelling individuals aged over 65 years falling at least once annually[1] and with 5% to 10% of falls resulting in fracture, head injury, or other serious injuries.[2] While falls in older individuals are multifactorial, age-related decline in lower extremity strength or

N. Kurita and S. Horie contributed equally to this work.
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* Address correspondence to Shunichi Fukuhara, MD, DMSc, Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.
E-mail address: fukuhara.shunichi.6m@kyoto-u.ac.jp (S. Fukuhara).

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mobility function are recognized as important contributors.[3–5] Separately, age-related decline in testosterone levels in men is a growing concern, with approximately 30% of men aged 40–79 years showing testosterone deficiency.[6] However, while previous studies have suggested that low testosterone levels are associated with reduced extremity strength or mobility function in older men,[7,8] relatively few have examined the association between low testosterone levels and falls, with conflicting results despite the ostensibly plausible biological connections.

One concern with these previous studies examining the relationship between testosterone deficiency and falls is their lack of consideration for presence of depressive symptoms.[9–11] Testosterone-deficient individuals are likely to have concurrent depressive symptoms,[12] and depressive symptoms are also associated with falls.[4] One study found no association between testosterone levels and incident falls after adjustment for confounders including depressive symptoms,[13] suggesting the potential importance of examining the effects of testosterone deficiency on falls independent of depressive symptoms. In addition, if both testosterone deficiency and depressive symptoms are proven to be associated with falls, whether or not men with *both* testosterone deficiency and depressive symptoms are more likely to suffer falls than those with either condition alone would also be of clinical relevance, as these individuals are likely to be seen by physicians specialized in treating testosterone deficiency.[14,15]

Here, to examine whether or not testosterone deficiency and depressive symptoms are independently associated with falls in community-dwelling older men, we analyzed data from the Locomotive Syndrome and Health Outcome in Aizu Cohort Study (LOHAS). We further evaluated how the strength of the association between the composite of testosterone deficiency and depressive symptoms and falls is larger or smaller than the product of the strength of the association between testosterone deficiency and falls and that between depressive symptoms and falls.

Methods

Our cross-sectional study was approved by the Research Ethics Committee of Fukushima Medical University School of Medicine. The LOHAS is a population-based study conducted starting in 2008 involving residents aged 40–80 years who participated in annual health check-ups among 2 communities (Tadami and Minamiaizu Towns) in Fukushima Prefecture, Japan. Eligibility criteria for this study were "aged over 60 years" and "participated in the health check-up conducted in 2010." No exclusion criteria were set. All participants provided written informed consent. Details of the design of the LOHAS have been reported previously.[16]

Measurement of Salivary Testosterone

Salivary concentration of testosterone (sT) was the main exposure, measured using an enzyme-linked immunosorbent assay (ELISA) on the RE52631 system (IBL International GmbH, Hamburg, Germany) and expressed in pg/mL (to convert to picomoles per liter, multiply by 3.47). sT reflects the level of free testosterone in plasma. Saliva was collected in the morning, at least 30 minutes after breakfast. Participants rinsed their mouth gently with water and were asked to avoid brushing their teeth. All participants collected whole saliva by directly spitting into polypropylene tubes through a polypropylene straw-tube. If a participant had little saliva, he was instructed to chew gum prepared specially for saliva collection. The supernatants of saliva obtained after centrifugation (3000 × g, 10 minutes) were kept at −80°C for further analysis. sT was measured in the laboratory of Teikyo University (Tokyo, Japan). For men aged 20–40 years, median sT is 139.4 pg/mL (10th to 90th percentile, 43.8–288.0 pg/mL). The intra- and interassay coefficients of variance were 3.9%–8.8% and 6.7%–8.0%, respectively. Slight cross-reactions with other natural steroids in the human body and their profiles were as follows: dihydrotestosterone, 2.5%; androstenedione, 0.85%; and others, <0.1%.[17]

Depressive Symptoms

Depressive symptoms were considered as secondary exposures in light of their usefulness in predicting fall risk according to the literature and their potentially close association with testosterone deficiency.[4,12] Depressive symptoms were assessed using the 10-item version of the Center for Epidemiological Studies Depression Screening Index (CES-D). The cutoff score for depressive symptoms was set as a score of 10 or greater, as was recommended in the literature.[18] Although data on physician-diagnosed depression was unavailable in the LOHAS study, we assumed its use would considerably underestimate the true proportion of depression, as previous studies have shown that depression is underdiagnosed more often by Japanese physicians than those in other countries due to stigma related to psychiatric disorders within Japanese society.[19,20]

Clinical Outcomes

We examined "any fall over a 1-month period" as the clinical outcome based on participants' answers to the question, "Over the past year, have you fallen down?" to establish fall history. Participants who responded, "Yes," were then asked the follow-up question, "How many times have you fallen down over the past month?" with responses of "zero," "once," "twice," or "three or more times" allowed. Those who reported at least "once" were considered to have had "any fall" over the previous month. Regarding our decision to examine falls over the previous month instead of the previous year, we believed that reverse-causality would be more unavoidable if we were to use fall over the past year rather than the past month in investigating relationship with present sT level, and a systematic review has suggested that recalling fall experience at a 1-year interval might underestimate true fall incidence compared to recalling incidence at a 1-month interval.[21]

Measurement of Potential Confounding Variables

Potential confounding variables examined in the present study were sociodemographic characteristics including age, exercise habit, and living alone, as well as the presence of cerebrovascular disease and the presence of incontinence, all obtained via self-reported questionnaire; body mass index and blood pressure, as measured by local nurse practitioners; hypertension, defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or by individuals reporting attending a physician for treatment; diabetes, defined as having glycosylated hemoglobin values ≥6.1%, as described by the Japanese Diabetes Society [equivalent to ≥6.5% described in National Glycohemoglobin Standardization Program values[22]] or by individuals reporting attending a physician for treatment; and timed up and go (TUG) test. Individuals were considered to engage in exercise if they answered "yes" to the question concerning whether or not they had participated in moderate physical activity (making the individual breathe somewhat harder than normal and including situations such as carrying light loads, bicycling at a regular pace, or doubles tennis) in the previous 7 days. Individuals were considered to have incontinence if they answered "once a week or more" to the question of whether or not they leaked urine because they could not defer the sudden urge to urinate. The TUG test, in which individuals are timed when rising from a chair, walking 3 m, and turning to return to sit on the chair, is considered to be a reflection of function in

gait, balance, and mobility[23] with a greater score indicating more mobility problems.

Statistical Analysis

Participants with complete data were entered into primary analyses. Statistical analyses were conducted using Stata v. 11.0 (StataCorp, College Station, TX). sT, depressive symptoms, sociodemographic characteristics, comorbidities, TUG, and any fall over the previous month were described. Box plots for sT stratified by age categories were also created. Effect measures in the present study were odds ratios (OR)s of sT and depressive symptoms for likelihood of having any fall in the past month estimated using logistic regression models. To estimate adjusted ORs, the potential confounding variables described above were simultaneously forced into the models along with sT and depressive symptoms.

Given that the association of sT (as continuous variables) and falls might have been nonlinear, as such nonlinear relationships are well-established for several hormonal systems in the endocrinology literature, separate models were constructed to assess the shape of the association between sT and falls, where sT was included as (1) a linear variable, (2) a log-transformed variable, (3) a transformation using restricted cubic splines with 3 knots, and (4) 5 quintiles. To assess the fitness of these models, the Akaike information criterion, which is a likelihood-based measure that adds a penalty for model complexity, were reported.[24]

While nonlinear models were superior to the linear model in terms of the Akaike information criterion, the 5-quintile model and the restricted cubic spline model were similar to one another (Supplementary Table 1). We therefore chose the restricted cubic spline model for primary analysis, as this model provided a good fit and was the most parsimonious, and we based all further testing on it. In this model, the 90th percentile of sT was chosen as a reference, as it corresponds to the median of the highest quintile. The potential effect modification of depressive symptoms on the association between sT and any fall over the previous month was examined by likelihood ratio test, adding interaction pair (the product terms of sT with depressive symptoms) to the logistic regression models.

Sensitivity Analysis

In addition to the above, we also conducted 3 sensitivity analyses. First, the association between sT and fall was reported, with 5 quintiles of sT included, citing the top category of the quintiles as reference. Second, the association between sT and falls was examined including 280 participants with missing covariate values. In this analysis, restricted cubic splines with 3 knots were used with adjustment for covariates via the missing indicator method. Third, CES-D was used as exposure instead of depressive symptoms, and the association between CES-D score and fall was examined. *P* value of <.05 was considered statistically significant.

Results

Of the 869 men who underwent the health check exam (Figure 1), 58 and 13 participants were missing data for sT and any falls, respectively. After exclusion of 36 participants with poor-quality saliva specimens (because of inadequate amount obtained or suspected blood contamination), 762 (87.7%) remained with both sT and outcome variables. After exclusion of a further 280 participants with at least 1 confounding variable missing, the remaining 482 participants were ultimately entered into the primary analyses.

Baseline characteristics are presented in Table 1. Median age in the present study was 70 years (10th to 90th percentile, 63–78 years).

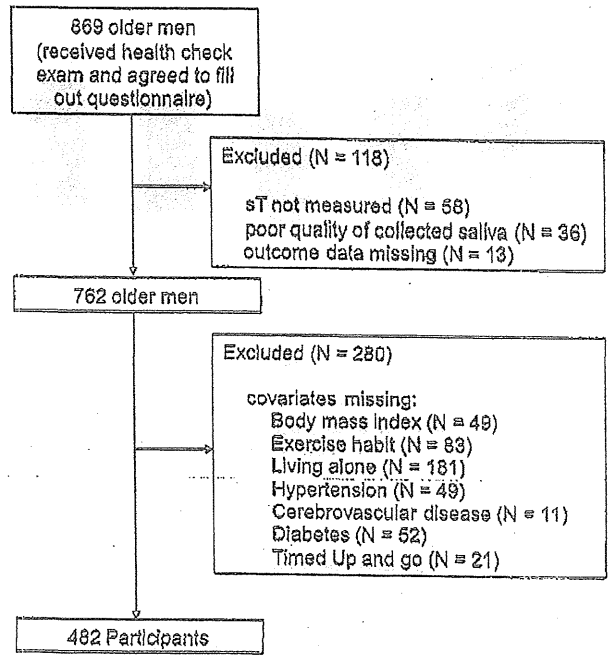

Fig. 1. Flow chart of study participants. Sum of number of participants with missing values for each covariate exceeds 280 because 90 participants had missing values for 2 or more covariates. sT, salivary testosterone.

The prevalence of hypertension and diabetes were 69.3% and 14.5%, respectively. Median sT was 58.7 pg/mL (10th to 90th percentile, 26.3–146 pg/mL). Box plots for sT showed that median sT was highest among those aged 60–64 years and lowest among those aged over 80 years (Figure 2). The prevalence of depressive symptoms was 11.6%. The prevalence of any fall over the previous month was 10.8%.

Sociodemographic characteristics were similar between participants with and without missing confounding variables (Supplementary Table 2) except for exercise habit. As a group, their sT, TUG value, proportion with depressive symptoms, and proportions of any fall over the 1-month period examined were similar. As a group, baseline characteristics among participants in the primary

Table 1
Baseline Characteristics of the Analysis Population

	Total (n = 482)	No Falls Over the Previous Month (n = 435)	Any Fall Over the Previous Month (n = 47)
Age, y			
Median	70	70	71
10th to 90th percentile	63–78	63–78	63–79
Body mass index, kg/m^2			
Median	23.8	23.8	24.4
10th to 90th percentile	20.2–27.3	20.2–27.4	21.1–26.6
Exercise habit, n (%)	264 (54.8)	235 (54.0)	29 (61.7)
Living alone, n (%)	61 (12.7)	53 (12.2)	8 (17.0)
Incontinence, n (%)	38 (7.9)	35 (8.1)	3 (6.4)
Hypertension, n (%)	334 (69.3)	302 (69.4)	32 (68.1)
Cerebrovascular disease, n (%)	28 (5.8)	21 (4.8)	7 (14.9)
Diabetes, n (%)	70 (14.5)	64 (14.5)	7 (14.9)
Timed Up and Go, s			
Median	7.1	7.1	8.0
10th to 90th percentile	5.4–9.5	5.3–9.4	5.7–10.5
Depressive symptoms, n (%)	56 (11.6)	45 (10.3)	11 (23.4)
Salivary testosterone, pg/mL			
Median	58.7	61.0	47.8
10th to 90th percentile	26.3–146	26.3–147	25.8–133

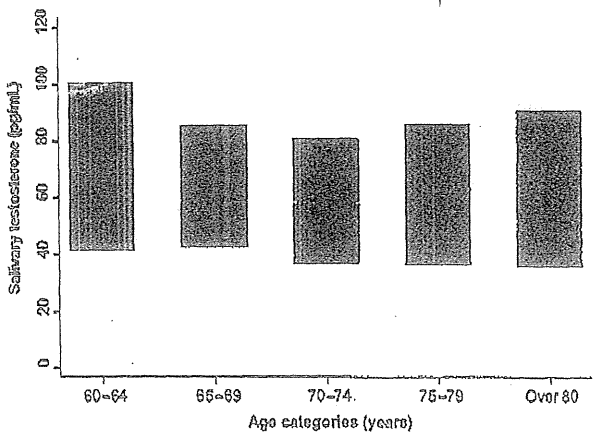

Fig. 2. Box plots for salivary testosterone levels stratified by age categories. White line in the boxes indicates median of sT in each category. Top and bottom of the boxes indicate 75th and 25th percentiles of sT in each category, respectively. sT, salivary testosterone.

analysis set were similar to those among whole older men, except for with respect to exercise habit, age (slightly younger), and TUG value (slightly lower) (Supplementary Table 3).

In the covariate-adjusted restricted cubic spline model, the splines demonstrated a nonlinear relationship between sT and falls ($P = .0021$ for nonlinearity). The estimated shape of the sT is shown in Figure 3, suggesting that the lower the sT level, the greater the likelihood of having any fall, citing 90th percentile of sT as a reference. In this model, the adjusted ORs of depressive symptoms for any fall were 3.49 [95% confidence interval (CI), 1.52–8.04]. We noted no apparent effect modification by depressive symptoms on the association between the sT and any fall ($P = .079$ for interaction).

To estimate the strength of the association of combination of sT levels and depressive symptoms, estimated ORs of combination of a given sT and depressive symptoms were shown in Table 2. Compared

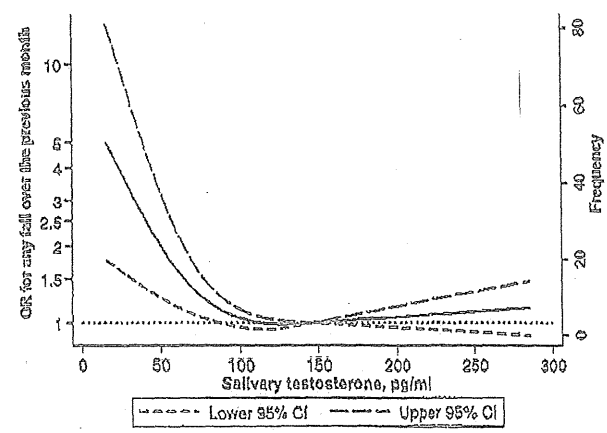

Fig. 3. Adjusted odds ratio (OR) of any fall over the previous month in men aged over 60 years.[a] CI, confidence interval.
[a]Logistic regression analysis with restricted cubic spline adjusted for covariates (age, body mass index, exercise habit, living alone, timed up and go, depressive symptoms, incontinence, hypertension, diabetes, cerebrovascular disease). Reference was set as 90th percentile of the salivary testosterone level (ie, median of the fifth quintile). The left vertical axis shows OR in log scale. Solid line indicates point estimates of OR. Dotted lines indicate CI. Gray bars indicate frequency of the salivary testosterone values. The right vertical axis shows frequency of each gray bar.

Table 2
Adjusted Odds Ratio (OR) of Any Fall Over the Previous Month in Men Aged Over 60 Years[a]

Salivary Testosterone		Adjusted OR (95% CI) for Any Fall Over the Previous Month	
Percentile	pg/mL	Participants Without Depressive Symptoms	Participants With Depressive Symptoms
5th	21.8	4.23 (1.66–10.8)	14.8 (3.76–58.0)
10th	26.3	3.74 (1.58–8.83)	13.1 (3.54–48.2)
30th	43.1	2.39 (1.34–4.26)	8.35 (2.78–25.1)
50th	58.9	1.67 (1.17–2.38)	5.83 (2.23–15.3)
70th	80.3	1.21 (1.03–1.43)	4.23 (1.77–10.1)
90th	146.5	1 [reference]	3.49 (1.52–8.04)
95th	211.4	1.07 (0.95–1.20)	3.72 (1.60–8.70)

CI, confidence interval.
[a]Logistic regression analysis with restricted cubic spline adjusted for covariates (age, body mass index, exercise habit, living alone, timed up and go, depressive symptoms, incontinence, hypertension, diabetes, cerebrovascular disease). Combination of 90th percentile of the salivary testosterone level (ie, median of the fifth quintile) and not having depressive symptoms was cited as reference.

with 90th percentile of sT, lower sT is associated with greater likelihood of having any fall. For example, OR for any fall in 5th percentile of sT is 4.23-fold (95% CI, 1.66–10.8). Compared with combination of 90th percentile of sT and no depressive symptoms, OR for any fall in combination of 5th percentile sT and depressive symptoms is 14.8-2fold (95% CI, 3.76–58.0).

In sensitivity analysis using sT quintiles citing the top quintile as reference, the lowest quintile of sT is associated with greater likelihood of having any fall (Supplementary Table 4). Similarly, depressive symptoms were associated with an increased likelihood of having any fall, although this quintile model performed only slightly worse than the spline model (Supplementary Table 1). Another sensitivity analysis using a restricted cubic spline model among 762 participants showed similar associations between sT and increased ORs for any fall (Supplementary Figure 1). When CES-D was used as exposure instead of depressive symptoms, CES-D score was associated with any fall (Supplementary Table 5).

Discussion

In this cross-sectional study of community-dwelling older men, low testosterone levels were independently associated with any falls over the previous month. We also observed an increased association between depressive symptoms with any fall. In addition, combination of low testosterone levels and depressive symptoms had stronger association with falls than either parameter alone. These findings suggest that clinicians should be aware of the increased risk of falls in older men with testosterone deficiency or depressive symptoms.

Our findings regarding the relationship between low testosterone levels and increased likelihood of falling concur with results from previous studies. A study in France among adults aged 50–85 years found that low free testosterone levels were associated with increased likelihood of suffering falls over the last year (OR of decreased level of free testosterone vs normal level, 1.54).[11] Similarly, reduced bioavailable testosterone levels were found to be associated with increased likelihood of suffering falls in the future among adults in the United States aged 65–99 years (risk ratio of the lowest quartile of bioavailable testosterone vs the highest quartile, 1.40).[10] Other studies also noted an association between low total testosterone levels and increased likelihood of suffering falls in the future among adults in the United States aged over 65 years (OR of the highest quartile of total testosterone vs the lowest quartile, 0.22).[9]

However, conflicting results have also been reported. For example, a study in The Netherlands noted no association between total

testosterone levels and incident falls among adults aged 65–88 years.[13] Such conflicting findings may be explained in part by differences between measured fractions of circulating testosterone and ones in commercial assays, as well as by inclusion of depressive symptoms and other confounding factors for adjustment. As such, increased likelihood of suffering a fall among individuals with low testosterone levels may be due to their increased likelihood of having depressive symptoms in studies where such symptoms are not assessed. Only in a study in The Netherlands, the relationship between testosterone level and falls was evaluated with statistical adjustment for presence of depressive symptoms. In addition to these previous findings, our present findings here further noted that joint effect of low testosterone levels and depressive symptoms on falls in combination compared with the joint reference category (90 percentile of sT and no depressive symptoms) had multiplicative effect on falls (ie, each exposures was independently associated with falls). In addition, using splines, we noted a continued increase in risk of falling among participants with relatively low testosterone levels; by definition, quartiles or quintiles cannot detect an increase in risk below the 25th centile or 20th centile of exposure, respectively.[25]

We believe that our findings here will influence the activities of physicians and health-policymakers for several reasons. First, both low testosterone levels and depressive symptoms are potentially modifiable risk factors for falls. Testosterone deficiency can be managed with testosterone replacement therapy, and depressive symptoms can be managed with a combination of cognitive behavioral therapy and antidepressants; individuals with both testosterone deficiency and depressive symptoms may be able to manage their condition with a combination of these therapies. Physicians who encounter individuals with suspected testosterone deficiency should, therefore, carefully assess the presence of depressive symptoms to reduce further risk of falls. An international survey conducted among physicians treating testosterone deficiency showed that depressive symptoms are considered to be one of the main symptoms, other than sexual problems, related to testosterone deficiency—a finding that supports the potential coexistence of depressive symptoms with testosterone deficiency.[14] Second, screening for low testosterone levels in the saliva using ELISA may be a reasonable health plan for community-dwelling older men to stratify the fall risk, as ELISAs are more cost-efficient ($5 per sample) and easier to perform than radioimmunoassay and liquid chromatography/mass spectrometry.[26] Third, any biological connection between low testosterone levels and falls may be independent of mobility function, as we estimated the relationship between testosterone and falls with adjustment for TUG, which reflects gait, balance, and mobility. For example, reduced cognitive function may be involved as a nonmobility-related intermediate pathway, as low testosterone levels may be associated with visuospatial ability or vigilance.[27,28]

Several strengths to the present study warrant mention. First, we demonstrated the relationship between testosterone and falls among community-dwelling older adults, adjusting for confounding variables such as depressive symptoms and TUG, which are potentially related to both testosterone and falls. Second, we showed that the strength of the association between combination of low testosterone level and depressive symptoms and falls might be larger than that of low testosterone or depressive symptoms alone; specifically, the strength of the association appears to be equal to the product of the 2 exposures in terms of OR. These findings provide a basis for thoughtful consideration of how to reduce risk of falls in older men with both testosterone deficiency and depressive symptoms.

However, several limitations to the present study also warrant mention. First, although sT is a reliable and suitable metric for evaluating testosterone levels in population-based studies,[29–31] the clinical guideline for the diagnosis of hypogonadism does not recommend its clinical use, as the methodology has not been standardized and adult male ranges are not yet available in most hospital or reference laboratories.[32] Therefore, in actual clinical practice, serum testosterone levels should be measured to diagnose hypogonadism. Further prospective studies are warranted to determine whether or not late-onset hypogonadism diagnosed via serum test and depressive symptoms are jointly associated with falls. The prevalence of late-onset hypogonadism is also known to rise with increasing body mass index (BMI) and number of coexisting illnesses. Median BMI in our population was much lower than mean values reported in western countries.[9–11,13] However, a study among Korean men aged 21–79 years showed that the participants' mean BMI was 24.5, and that even in the lowest quintile by serum testosterone level (113–378 ng/dL), BMI was 25.2.[33] Given these previous findings, hypogonadism among Asian people diagnosed by blood testing may be found among individuals with relatively low BMI more often than among Caucasians with BMI in the same range. Further, some endocrine specialists question the validity of sT measured by ELISA. However, previous studies have shown that sT levels obtained via ELISA share good correlation with those obtained via liquid chromatography/mass spectrometry,[26] and sT has also been shown to be closely correlated to serum free testosterone.[34] However, in addition to differences noted based on assay adopted, blood contamination in saliva might also influence testosterone concentration.[35] As such, in the present study, saliva with suspected blood contamination was excluded from analyses. Even taken together with these drawbacks, however, utilization of sT still facilitates easily conducted, minimally invasive screening methods for evaluating testosterone levels on a population basis. Second, nonprescriptional use of testosterone or methyl-testosterone could not be recorded. However, use of such medication in our population is unlikely, as these compounds require a physician's prescriptions and are not available as over-the-counter drugs in Japan. Third, the cross-sectional design of the present study means that we cannot attribute causality from the associations between testosterone and depressive symptoms and falls. Although we believe that low testosterone as a cause of falling is biologically plausible, association between low testosterone or depressive symptoms and falls might be explained by reverse causality. Fourth, we were unable to include other medication usage and all chronic conditions in our analyses, and given that use of antihypertensives, sedatives, or antidepressants are also potential risk factors for falls,[4,36] the association between salivary testosterone and falls in the present study might be confounded by these factors. To mitigate this limitation, we adjusted for individuals with hypertensive problems. Effect of depressive symptoms on falls might be mediated partly by sedatives or antidepressants, as individuals with depressive symptoms are often prescribed these agents. The literature suggests that use of serotonin selective reuptake inhibitor is indeed associated with increased salivary testosterone levels,[37] and that serotonin selective reuptake inhibitor is associated with falls.[36] However, given that we adjusted for depression symptoms, we, therefore, believe it unlikely that any association between sT and falls was confounded by antidepressants. Although arthritis (including osteoarthritis) is prevalent in elderly and is also a potential risk factor for falls,[38] its burden on functional mobility should be reflected by TUG. As such, we believe that these confounding factors had negligible effects on our analyses. Fifth, a high rate of missing data was noted in the primary analyses. In sensitivity analyses using 87.7% of the older men in the health check-up examination showed an association similar to, but slightly smaller than, that noted in primary analyses between low sT and falls (Supplementary Figure 1). We, therefore, cannot completely exclude the possibility that our findings in the primary analysis may suffer from selection bias.

Conclusions

In conclusion, both lower testosterone and depressive symptoms were found to be separately associated with any falls over a 1-month period among community-dwelling older men. Furthermore, having both low testosterone levels and depressive symptoms might imbue a greater likelihood of having falls than either metric alone. Causality of these associations should be confirmed in future prospective studies with adjustment for potential confounding by more numbers of chronic illnesses.

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Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2013.11.003.

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Overactive bladder symptom severity is associated with falls in community-dwelling adults: LOHAS study

Noriaki Kurita,[1] Shin Yamazaki,[1] Norio Fukumori,[1] Kenichi Otoshi,[2] Koji Otani,[2] Miho Sekiguchi,[2] Yoshihiro Onishi,[3] Misa Takegami,[4] Rei Ono,[5] Shigeo Horie,[6] Shin-ichi Konno,[2] Shin-ichi Kikuchi,[2] Shunichi Fukuhara[1]

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For numbered affiliations see end of article.

Correspondence to
Professor Shunichi Fukuhara; fukuhara.shunichi.6m@kyoto-u.ac.jp

ABSTRACT

Objectives: To examine the association between overactive bladder (OAB) symptom severity and falls and the contribution of OAB symptoms to falls in a community-dwelling population.

Design: Cross-sectional study.

Setting: 2 Japanese municipalities.

Participants: A total of 2505 residents aged over 40 years, who participated in health check-ups conducted in 2010. OAB symptom assessed via overactive bladder symptom score (OABSS) was divided into six categories based on distribution and Japanese clinical guidelines. Mobility problems and depressive symptoms were assessed via the Timed Up and Go test and the short form of the Center for Epidemiologic Studies Depression Scale, respectively.

Primary outcome measures: Self-reported any fall and frequent fall (≥2) over the 1-month period. Independent contributions to any fall and frequent falls were assessed via logistic regression to generate population-attributable fractions (PAFs), assuming separate causal relationships between OAB symptoms, mobility problems and depressive symptoms and any or frequent falls.

Results: Among the total 1350 participants (mean age: 68.3 years) analysed, any fall and frequent falls were reported by 12.7% and 4.4%, respectively. Compared with no OABSS score, moderate-to-severe OAB and mild OAB were associated with any fall (adjusted ORs 2.37 (95% CI 1.12 to 4.98) and 2.51 (95% CI 1.14 to 5.52), respectively). Moderate-to-severe OAB was also strongly associated with frequent falls (adjusted OR 6.90 (95% CI 1.50 to 31.6)). Adjusted PAFs of OAB symptoms were 40.7% (95% CI 0.7% to 64.6%) for any fall and 67.7% (95% CI −23.1% to 91.5%) for frequent falls. Further, these point estimates were similar to or larger than those of mobility problems and depressive symptoms.

Conclusions: An association does indeed exist between OAB symptom severity and falls, and OAB symptoms might be important contributors to falls among community-dwelling adults. Further longitudinal studies are warranted to examine whether or not OAB symptoms predict risk of future falls and fall-related injuries.

ARTICLE SUMMARY

Article focus

- An association has been reported between the mere presence of overactive bladder (OAB) and fall-related injuries in a US telephone-based survey study.
- Whether or not the severity of OAB symptoms is related to an increased likelihood of having falls in community-dwelling individuals and how much the OAB symptom impacts on falls remains unclear.
- We assessed the relationship between OAB symptom severity and falls and estimated the potential contribution of OAB symptoms on falls among community-dwelling individuals, assuming a causal relationship between OAB symptoms and falls.

Key messages

- OAB was associated with both any fall and frequent (≥2) falls over the 1-month study period in community-dwelling adults.
- An increasing trend was noted between OAB symptom severity and frequent falls over the 1-month period.
- Estimates of adjusted population-attributable fraction of OAB symptoms on falls were similar or larger than those of mobility problems and depressive symptoms.

Strengths and limitations of this study

- Strengths of our study include large sample size, population-based format, adjustment for many potential confounding factors and the robustness of the relationship between OAB symptom severity and falls based on sensitivity analyses.
- However, the following limitations should be considered: the cross-sectional design cannot attribute causality based solely on associations between OAB symptom and falls and the assessment of OAB symptoms based on self-reported questionnaire cannot exclude the presence of other urological disorders.

INTRODUCTION

Overactive bladder (OAB) is a urological syndrome representing a common public

health problem worldwide; the overall prevalence of OAB in adults aged over 40 years was reported to be 12.4% in Japan and 16.6% in European countries, with incidence increasing with age.[1 2] OAB is characterised by a primary symptom of urgency, with or without incontinence, usually accompanied by nocturia and increased frequency,[3] although OAB can be diagnosed even without reports of incontinence or nocturia. Separately, falls are also a serious public health problem, with one-third of community-dwelling individuals aged over 65 years falling at least once annually[4] and with 5–10% of falls resulting in fracture, head injuries or other serious injuries.[5] While studies examining incontinence as a risk factor for falls have been well investigated,[6 7] few have examined the relationship between OAB and falls, despite reported overlaps in symptoms between incontinence and OAB.[8]

While findings from one US telephone survey suggested an association between OAB and an increased likelihood of being injured in a fall in the previous year among adults aged over 18 years,[9] whether or not the degree of OAB symptom severity is related to the frequency of falls among community-dwelling older adults over a certain period of time is unclear. This previous study also failed to examine the extent to which OAB symptoms contribute to falls. Clarification of this potential influence of OAB symptom severity on falls may help health policy-makers decide how much attention OAB symptoms should receive to prevent falls among community-dwelling individuals.

Here, we investigated the relationship between OAB symptom severity and frequency of falls over a 1-month period using data from a large community-dwelling population. We also assessed the potential contribution of OAB symptom severity to falls in the population.

METHOD

Our cross-sectional study of the locomotive syndrome and health outcome in Aizu cohort study (LOHAS)—which aims to evaluate the risk of cardiovascular disease, quality of life, medical costs and mortality attributable to locomotive dysfunction[10]—was approved by the Research Ethics Committee of Fukushima Medical University School of Medicine. Locomotive syndrome is conceptualised as a condition characterised by a set of associated symptoms due to problems of the locomotive systems.[11] The locations involved are located in valleys surrounded by mountains, and the main industry in the region is agriculture. Our target population comprised the general population of two communities (Tadami and Minamiaizu Towns) in Fukushima Prefecture, Japan. Eligibility criteria were 'aged over 40 years' and 'participated in annual health check-ups conducted in 2010'.[10] Details of the design of the LOHAS have been reported previously.[10]

OAB symptoms, mobility problems and depressive symptoms

OAB symptoms were the main exposure and assessed based on the OAB Symptom Score (OABSS),[12] which is designed to quantify OAB symptoms over the previous week based on four items: daytime frequency, nighttime frequency, urgency and urgency incontinence (see online supplementary table S1). The OABSS has been psychometrically validated and has demonstrated reliability, discriminant validity and responsiveness among patients with OAB.[12 13] Able to be used as an alternative to a bladder diary,[14] which is considered the gold standard tool for the assessment of OAB symptoms, the OABSS is recommended in Japanese clinical practice.[15] A total OABSS score of 3 or more and an urgency score of 2 or more is the recommended cut-off for diagnosing OAB, and the severity is further divided into mild (total score of 3–5 points), moderate (6–11 points) and severe (12 or more points), according to Japanese clinical practice guidelines.[15] Therefore, individuals with a total OABSS score of 2 or less or an urgency score of 1 or less are considered to be 'non-OAB'. To assess the dose–response relationship of the strength of the association between OAB symptom severity and falls citing non-OAB individuals with a total score of 0 as reference, participants with and without OAB were divided into six categories based on the severity of total OABSS score and the distribution of the participants: non-OAB with 0, 1, 2 or 3 or more points; mild OAB; and moderate-to-severe OAB. The median and range of total OABSS score among the six groups are described in table 1, along with the number of participants.

In addition to accounting for the contribution of OAB symptoms to falls, we considered the contributions of mobility problems (ie, problems in gait, balance and mobility) and depressive symptoms as well, citing these parameters as secondary exposures in light of their prevalence in ageing societies and their predictability of fall risk in the literature.[6 16 17] Mobility problems were assessed using the Timed Up and Go (TUG) test, in which the individuals are timed with a stopwatch when rising from a chair, walking 3 m and turning to return to sit on the chair. The TUG test is considered to be a reflection of function in gait, balance and mobility[17] and is commonly used among older persons in geriatric clinics to evaluate physical performance,[18] with a greater score indicating more mobility problems. Given the findings from a meta-analysis suggesting that reference TUG values differ by age group (mean=8.1 s for 60 to 69, 9.2 s for 70 to 79 and 11.3 s for 80 to 99-year-olds),[19] specifying a uniform cut-off of TUG value to discriminate the presence of mobility problems was difficult, and the TUG value was therefore treated as a continuous variable. Although no reference TUG values have been established for persons aged 40–59 years, we believe that '5.5–8.1 s' is a feasible range, as a previous study

Table 1 Baseline characteristics of the analysis population

	Total (N=1350)			No falls over the previous month (N=1179)			Any fall over the previous month (N=171)		
	n	Per cent	Mean (SD); median (range)	n	Per cent	Mean (SD); median (range)	n	Per cent	Mean (SD); median (range)
Age (years)			68.3 (8.7)			68.0 (8.7)			70.4 (8.6)
Age group (years)									
40–59	196	14.5		180	15.3		16	9.4	
60–69	490	36.3		436	37		54	31.6	
70–79	585	43.3	—	499	42.3		86	50.3	
≥80	79	5.9		64	5.4		15	8.8	
Gender									
Women	746	55.3		637	54		109	63.7	
Men	604	44.7		542	46		62	36.2	
Body mass index (kg/m^2)									
<25	892	66.1	23.9 (3.0)	783	66.4	23.8 (3.1)	109	63.7	24.2 (3.0)
25–29.99	414	30.7		356	30.2		58	33.9	
≥30	44	3.3		40	3.4		4	2.3	
Exercise habit									
Present	607	45		532	45.1		75	43.9	
Absent	743	55		647	54.9		96	56.1	
Living arrangement									
Alone	217	16.1		175	14.8		42	24.6	
Cohabitating	1133	83.9		1004	85.2		129	75.4	
Hypertension									
Present	879	65.1		769	65.2		110	64.3	
Absent	471	34.9		410	34.8		61	35.7	
Cerebrovascular disease									
Present	68	5		51	4.3		17	9.9	
Absent	1282	95		1128	95.7		154	90.1	
Diabetes									
Present	135	10		113	9.6		22	12.9	
Absent	1215	90		1066	90.4		149	87.1	
OAB symptom severity*			2.6 (2.5); 2 (0–15)			2.5 (2.4); 2 (0–15)			3.4 (2.8); 3 (0–14)
OAB symptom severity groups†									
Non-OAB with 0 points	193	14.3	—	181	15.4		12	7	
Non-OAB with 1 point	360	26.7		324	27.5		36	21.1	
Non-OAB with 2 points	280	20.7		251	21.3		29	17	
Non-OAB with ≥3 points	247	18.3		204	17.3		43	25.2	
Mild OAB	114	8.4		94	8		20	11.7	
Moderate-to-severe OAB	156	11.6		125	10.6		31	18.1	

Continued

Table 1 Continued

	Total (N=1350)		No falls over the previous month (N=1179)			Any fall over the previous month (N=171)		
	n	Per cent	Mean (SD); median (range)	n	Per cent	Mean (SD); median (range)	n	Per cent	Mean (SD); median (range)
Timed Up and Go (s)	1350		7.5 (2.1); 7.1 (3.9–26.1)			7.4 (2.0); 7.0 (3.9–26.1)			8.4 (2.5); 8.0 (4.6–22.5)
Depressive symptoms									
Present	209	15.5		159	13.5		50	29.2	
Absent	1141	84.5		1020	86.5		121	70.8	
Any fall over the previous month									
Present	171	12.7							
Absent	1179	87.3							
Frequent (≥2) falls over the previous month									
Present	60	4.4							
Absent	1290	95.6							

OAB, overactive bladder.
*OAB symptom severity was derived from OABSS.
†Median (range): 3 (3–6) for non-OAB with ≥3 points, 4 (3–5) for mild OAB and 7 (6–15) for moderate-to-severe OAB.

found the mean TUG value to be 5.5 s in healthy young adults (mean age: 22.3 years) the mean TUG value in adults aged 60-69 years was 8.1 s as described above.[20]

Depressive symptoms were assessed using the 10-item version of the Center for Epidemiological Studies Depression Screening Index (CES-D), which is designed to quantify the number and frequency of symptoms of depression. Depressive mood was defined as a score of 10 or greater.[21]

Clinical outcomes

We examined two clinical outcomes of interest—'any fall over a 1-month period' and 'frequent (≥2) falls over a 1-month period'—based on subjects' answers to the question, 'Over the past year, have you fallen down?' to establish fall history. Participants who responded, 'Yes', were then asked the follow-up question, 'How many times have you fallen down over the past month?' with responses of 'zero', 'once', 'twice' or 'three or more times' allowed. Those who reported at least 'once' were considered to have had 'any fall' over the previous month. Those who reported at least 'twice' (≥2) were, in addition to 'any fall', further considered to have had 'frequent falls'.

Measurement of potential confounding variables

Potential confounding variables examined in the present study were sociodemographic characteristics including age, gender, exercise habit and living arrangement (alone or cohabitating), as well as the presence of cerebrovascular disease, all obtained via self-reported questionnaire; body mass index and blood pressure, as measured by local nurse practitioners; hypertension, defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or by individuals reporting attending a physician for treatment; and diabetes, defined as having glycosylated haemoglobin values ≥6.1%, as described by the Japanese Diabetes Society (equivalent to ≥6.5% described in National Glycohemoglobin Standardization Program (NGSP) values[22]) or by individuals reporting attending a physician for treatment. Individuals were considered to engage in exercise if they answered 'Yes' to the question concerning whether or not they had participated in moderate physical activity (making the individual breathe somewhat harder than normal and including situations such as carrying light loads, bicycling at a regular pace or doubles tennis) in the previous 7 days.

Statistical analysis

Participants with complete data were entered into the primary analyses. Statistical analyses were conducted using Stata V.11.0 (Stata Corp., College Station, Texas, USA). Sociodemographic characteristics, comorbidities, main (OAB symptom severity) and secondary exposures (TUG values and depressive symptoms) and outcomes (any fall and frequent falls over the previous month) were described.

Effect measures in the present study were ORs of the three exposures for any fall and frequent falls estimated using logistic regression models, with separate models applied for any fall and frequent falls over the previous month. To estimate adjusted ORs, the potential confounding variables described above were simultaneously forced into the models along with the three exposures. The goodness of fit of the models was assessed using the Hosmer-Lemeshow test.

The potential effect modification of gender difference, TUG and depressive symptoms on the association between OAB symptom severity and any fall or frequent falls over the previous month was tested by adding three interaction pairs (the product terms of OAB symptoms severity with gender, TUG or depressive symptoms) to the logistic regression models.

In addition, using the regression models based on a previously reported method, a test of linear trends across six OAB symptom severity categories was performed by treating the categories as a continuous variable using their median values.[23] To estimate the potential contribution of each of the exposures (OAB symptom severity, mobility problems or depression symptoms) to falls, we computed population-attributable fractions (PAFs). In general, in a cross-sectional study, PAF is the fraction of the prevalent outcomes that would be prevented if a certain exposure was removed. In other words, if the exposure was removed, then some fraction of the outcomes could be prevented, and that fraction is PAF. For this study, outcomes used were both 'any fall' and 'frequent falls', and exposures used were OAB symptom severity, mobility problems and depression symptoms. One assumption of this computation is that there is an unconfounded, causal relation between exposure(s) and outcome(s). PAFs were computed with the logistic regression models and the user-written command 'punaf' in Stata V.11.0.[24 25]

We also conducted sensitivity analyses by imputing missing covariate values. A multiple imputation approach using a chained equations method was used,[26 27] with results showing that 1037 participants (41.9%) had missing covariate values. $p<0.05$ was considered statistically significant.

RESULTS

Of the 2505 participants in the health check-up (figure 1), 2387 (95.3%) had both exposure and outcome variables. After excluding 1037 participants with at least one confounding variables missing, the remaining 1350 participants were ultimately entered into the primary analyses.

Baseline characteristics are presented in table 1. Participants tended to be older, with 85.5% aged over 60 years. The prevalence of hypertension and diabetes were 65.1% and 10.0%, respectively. The prevalence of OAB which met the criteria described in the Japanese clinical guidelines was 20.0%, with prevalence of moderate-to-severe OAB at 11.6%. Of note, the prevalence of non-OAB individuals with ≥3 points was 18.3%. Age-stratified prevalence of OAB in our participants was 9.7% for 40 to 59, 14.7% for 60 to 69, 27.0% for 70 to 79 and 26.6% for 80 to 89-year-olds, values similar to those noted in a previous study in Japan.[2] Mean TUG time in the present study was 7.5 s (SD 2.1 s), ranging from a minimum of 3.9 s to a maximum of 26.1 s. Age-stratified mean TUG values were 6.4 s for 40 to 59, 6.8 s for 60 to 69, 8.2 s for 70 to 79 and 9.8 s for 80 to 89-year-olds, values which were smaller than the reported reference.[19] The prevalence of depressive symptoms was 15.5%. The prevalence of any fall and frequent falls over the previous month was 12.7% and 4.4%, respectively, while age-stratified prevalence of any fall and frequent falls over the previous month were 8.2% and 2.0% for 40 to 59, 11.0% and 3.3% for 60 to 69, 14.7% and 5.6% for 70 to 79, and 19.0% and 8.9% for 80 to 89-year-olds, respectively.

Sociodemographic characteristics were similar between participants with and without missing confounding variables (see online supplementary table S2)

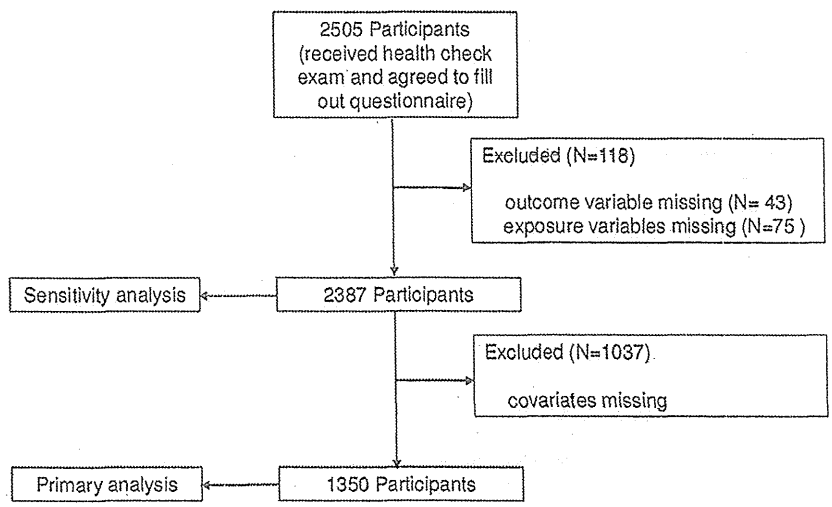

Figure 1 Flow chart of the study participants.

except for gender, as men were more likely to have missing variables. As a group, their OAB symptom severity, TUG value, proportion with depressive symptoms and proportions of any and frequent falls over the 1-month period examined were similar.

In crude analyses, the presence of OAB, increase in TUG, and the presence of depressive symptom indicated a greater likelihood of having both any and frequent falls (table 2), and ORs for these parameters were attenuated in adjusted analyses. Participants with moderate-to-severe OAB had a greater likelihood of having any fall and frequent fall than non-OAB individuals with 0 points (adjusted OR for any fall=2.37 (95% CI 1.12 to 4.98); and adjusted OR for frequent fall=6.90 (95% CI 1.50 to 31.6)). In addition, those with mild OAB and non-OAB individuals with ≥3 points had a similarly greater likelihood of having any fall (adjusted OR 2.51 (95% CI 1.14 to 5.52), and adjusted OR=2.46 (95% CI 1.23 to 4.92), respectively) than non-OAB individuals with 0 points. We noted no significant trends in likelihood of any fall across OAB severity categories (p=0.062), presumably because of similar strength of likelihoods among the top three categories of OAB severity. In contrast, we noted a significant increasing trend in the likelihood of frequent fall across OAB severity categories (p=0.015).

The adjusted ORs of TUG for any and frequent falls were 1.25 (95% CI 1.06 to 1.47) and 1.36 (95% CI 1.09 to 1.70), respectively, for each increase in SD of TUG, suggesting that the increase in TUG was associated with these outcomes. The adjusted ORs of depression for any and frequent falls were 1.96 (95% CI 1.31 to 2.94) and 1.98 (95% CI 1.06 to 3.71), respectively. The goodness-of-fit values of the covariate-adjusted logistic regression models for any fall and frequent falls were 0.217 and 0.364, respectively.

Overall, effect modification by gender difference, TUG and depressive symptoms on the association between the OAB severity and any fall or frequent falls was not apparent (data not shown). Therefore, PAF analyses and sensitivity analyses were performed without considering the effect modification. Analyses results indicated that, if OAB symptoms could have been reduced to OABSS 0 points (with all other parameters remaining the same), a sizeable proportion of any and frequent falls could have been prevented potentially (40.7% (95% CI 0.7% to 64.6%) and 67.7% (95% CI −23.1% to 91.5%), respectively), although of note—the lower CI of the proportion for frequent falls was already below 0% (table 3). Similarly, if TUG could have been improved up to 4 s (the second smallest value in this population), the estimated proportions of the any and frequent falls that could potentially have been prevented were 30.4% (95% CI 7.6% to 47.6%) and 45.8% (95% CI 13.1% to 66.2%), respectively. As for depressive symptoms, these estimated proportions were smaller, at 11.7% (95% CI 3.8% to 18.9%) and 15.3% (95% CI −1.3% to 29.1%) for any and frequent falls, respectively.

Table 2 Associations between OAB symptom severity, mobility problems and depressive symptoms and falls

		Any fall over the previous month		Frequent (≥2) falls over the previous month	
	Number of participants	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
OAB symptom severity groups					
Non-OAB with 0 points	193	1	1	1	1
Non-OAB with 1 point	360	1.68 (0.85 to 3.30)	1.61 (0.81 to 3.21)	3.29 (0.73 to 14.9)	2.97 (0.65 to 13.6)
Non-OAB with 2 points	280	1.74 (0.87 to 3.51)	1.46 (0.71 to 2.99)	3.17 (0.68 to 14.8)	2.17 (0.45 to 10.4)
Non-OAB with ≥3 points	247	3.18 (1.63 to 6.22)	2.46 (1.23 to 4.92)	4.88 (1.08 to 22.1)	3.35 (0.72 to 15.6)
Mild OAB	114	3.21 (1.50 to 6.85)	2.51 (1.14 to 5.52)	6.25 (1.28 to 30.6)	4.30 (0.84 to 22.0)
Moderate-to-severe OAB	156	3.74 (1.85 to 7.56)	2.37 (1.12 to 4.98)	12.5 (2.84 to 54.6)	6.90 (1.50 to 31.6)
		Trend p=0.018	Trend p=0.062	Trend p=0.006	Trend p=0.015
Timed Up and Go					
Per 1 s	1350	1.21 (1.13 to 1.29)	1.11 (1.03 to 1.20)	1.28 (1.17 to 1.39)	1.16 (1.04 to 1.29)
Per 1SD		1.49 (1.30 to 1.71)	1.25 (1.06 to 1.47)	1.67 (1.39 to 2.00)	1.36 (1.09 to 1.70)
Depressive symptoms					
Absent	1141	1	1	1	1
Present	209	2.65 (1.83 to 3.84)	1.96 (1.31 to 2.94)	3.16 (1.82 to 5.48)	1.98 (1.06 to 3.71)

OAB, overactive bladder.
*Estimated from logistic regression models adjusted for age, gender, body mass index, exercise habit, living arrangement, hypertension, cerebrovascular disease, diabetes and all variables in the table.

Table 3 Population-attributable fraction for falls*

	Any fall over the previous month Estimates (95% CI)	Frequent (≥2) falls over the previous month Estimates (95% CI)
OAB symptom	40.7% (0.7% to 64.6%)	67.7% (−23.1% to 91.5%)
Timed Up and Go†	30.4% (7.6% to 47.6%)	45.8% (13.1% to 66.2%)
Depressive symptoms	11.7% (3.8% to 18.9%)	15.3% (−1.3% to 29.1%)

OAB, overactive bladder; TUG, Timed Up and Go.
*Estimated from logistic regression models adjusted for age, gender, body mass index, exercise habit, living arrangement, hypertension, cerebrovascular disease, diabetes and all the variables in the table.
†Estimated assuming that all participants have TUG value of 4 s, the second smallest value in this population.

In sensitivity analyses using multiply imputed data for 2387 participants, similar associations were noted between OAB severity symptoms and increased ORs for both clinical outcomes (see online supplementary table S3).

DISCUSSION

In this large, cross-sectional study of community-dwelling adults, moderate-to-severe OAB and mild OAB were both associated with any falls over the 1-month study period. We also observed an increasing trend in OAB symptom severity with frequent falls, and moderate-to-severe OAB was strongly associated with frequent falls. In addition, OAB symptoms were found to likely experience similar or greater impact on falls than mobility problems and depressive symptoms. These findings may encourage health policy-makers and physicians to pay more attention to OAB symptoms than at present to help prevent falls among community-dwelling adults.

Our findings here agree well with those of a previous study, which showed that the presence of OAB increased the likelihood of being injured from a fall in the previous year (OR 2.26).[9] However, the present and previous studies differed in several respects. First, the mean age of the participants in our study was much higher than that in the previous study (68.3 vs 54.2 years), suggesting that our findings will be more applicable in ageing societies. Second, the previous study used matching to compare subjects with and without OAB; as such, their study design limited the accurate determination of prevalence of OAB symptom severity and estimation of PAF. Our use of PAF in the present study suggested the potential magnitude of reduction in falls that could theoretically be prevented in an ageing society such as the one examined here. PAF estimates of OAB symptoms in societies such as that involved in the present study with an unignorable proportion of falls would be of significant relevance to health policy-makers and physicians. Third, the telephone-based survey method hampered the determination of several biological measures in the previous study, such as body mass index and mobility problems (ie, TUG), which are potentially confounding variables that should be considered in the accurate assessment of the relationship between OAB and falls. Fourth, the dose–response relationship between OAB symptom severity and falls was not evaluated in the previous study; therefore, we feel that the logical connection between OAB and falls in the previous study is less convincing than that in the present study.

Several strengths to the present study warrant mention. First, we demonstrated the relationship between OAB symptom severity and falls in a large, community-dwelling population, adjusting for confounding variables such as body mass index and depressive symptoms, which are potentially related to both OAB and falls. Second, we showed that the contribution of OAB symptoms to falls might be similar or larger than that of mobility problems and depressive symptoms, according to PAF estimates. These findings provide a basis for considering the effective use of limited medical resources to prevent falls. Noted similarities in the relationship of OAB symptom severity and falls in our sensitivity analyses indicate that our results are robust.

However, several limitations to the present study also warrant mention. First, we were unable to include the medication usage and all chronic conditions in our analyses; given that use of antihypertensives or sedatives are also potential risk factors for falls, the association between OAB symptom severity and falls in the present study might be confounded by these factors. To mitigate this limitation, we adjusted for individuals with hypertensive problems. Effects of depressive symptoms on falls might be mediated partly by sedatives, as individuals with depressive symptoms are often prescribed sedatives to treat depressive emotion or sleep problems. However, we believe it unlikely that effects of OAB on falls are confounded by sedatives. While some specialists may express concern about whether or not antimuscarinics for OAB are associated with an elevated risk of falls among treated individuals, to date, little evidence has been generated which supports such an association.[28] Cognitive impairment and arthritis (including osteoarthritis) are also potential risk factors for falls[29 30]; however, individuals with cognitive impairment are unlikely to participate in epidemiological studies and complete self-reported questionnaires.[31] Regarding arthritis in particular, its burden on functional mobility should be reflected by TUG. As such, we believe that these confounding factors had negligible effects on our analyses. Second, given that the definition of OAB in this study used the criteria defined by the Japanese Urological Associations,[15] the presence of other urological

disorders (such as benign prostatic enlargement and urinary tract infection) cannot be ruled out. Third, the cross-sectional design of the present study means that we cannot attribute causality from the associations between any exposures and falls. While we believe that OAB being a cause of falling is possible and biologically plausible, some associations such as those between depressive symptoms and falls can be explained by reverse causality. Fourth, although sensitivity analyses using 95.2% of the participants in the health check-up exam showed an association similar to that noted in primary analyses between OAB symptom severity and falls, a high rate of missing data was noted in the primary analyses. Fifth, PAF of OAB symptom for frequent falls had low precision, although its point estimate suggested that a sizeable proportion of frequent falls might be preventable. Further, we were unable to estimate PAFs in the sensitivity analysis because, at present, statistical analyses are difficult to conduct using multiply imputed data. However, distributions of OAB symptom severity, TUG and depressive symptoms are similar between individuals with complete data and those with missing covariates. Therefore, it is unlikely that PAF estimates in the complete dataset would be starkly different from those in the target population.

We feel that the present findings will influence the activities of physicians and health policy-makers for several reasons. First, OAB symptoms are potentially modifiable risk factors for falls, able to be managed with a combination of behavioural therapy and antimuscarinics indicated for OAB. Indeed, well-designed clinical trials have shown that antimuscarinics such as solifenacin and tolterodine reduce the severity of OAB symptoms by more than 60%.[15] A further study is needed to clarify whether or not the treatment of OAB symptoms is associated with the reduction of falls. However, community-dwelling individuals may hesitate to consult physicians regarding OAB symptoms, in light of potential stigma attached to the disorder.[9] As such, when physicians encounter patients who have suffered falls, they should be sensitive when asking patients about their experiencing any OAB symptoms. This communication is applicable to both genders, as no gender differences were apparent in the relationship between OAB symptoms and falls. Second, the dose-response relationship between OAB symptom severity and frequent falls suggests that not only nocturia and incontinence but also urgency and frequency may contribute to the risk of fall. While previous fall-related studies have thus far focused primarily on nocturia and incontinence,[6 32] more frequent walking to the bathroom may raise the risk of falling. In addition, urgency may cause individuals to lose focus while walking due to nocturia or frequency, rendering them to be more susceptible to falling. Third, given the large PAF values for OAB symptoms for falls in our study, health policy-makers and physicians should consider OAB to be not only a mere syndrome reducing the health-related quality of life but also a large contributor to falls among community-dwelling individuals. As such, screening for OAB at health check-ups and appropriate referral may be a reasonable health plan to interact. We should also point out that physicians caring for fall victims and those treating OAB patients are usually different and may therefore not be communicating well. Compared with these physicians, primary care physicians and their team may provide better and care for the symptoms of the individuals.

In conclusion, OAB symptom severity in community-dwelling adults was found to be associated with any and frequent falls over a 1-month period. Further, OAB symptoms might have a similar or greater contribution to falls than mobility problems or depressive symptoms, both common in ageing societies. Further longitudinal studies are warranted to examine whether or not OAB symptoms predict future falls and fall-related injuries.

Author affiliations
[1]Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[2]Department of Orthopedic Surgery, Fukushima Medical University School of Medicine, Fukushima, Japan
[3]Institute for Health Outcomes & Process Evaluation Research (i-Hope international), Kyoto, Japan
[4]Department of Preventive Medicine and Epidemiologic Informatics, National Cerebral and Cardiovascular Center, Osaka, Japan
[5]Department of Community Health Sciences, Kobe University Graduate School of Health Sciences, Kobe, Japan
[6]Department of Urology, Juntendo University School of Medicine, Tokyo, Japan

Contributors NK had the idea for the study, participated in its design, performed the statistical analyses and drafted the manuscript. NF, KeO, KoO, MS, MT and RO participated in acquiring the data and helped in analysing the data. SY, YO, SKO, SKi are coordinators of the locomotive syndrome and health outcome in Aizu cohort study and participated in critical review of the manuscript. SH participated in the interpretation of the data and critical review of the manuscript. SF had the idea for the study and participated in the design of the study, interpretation of the data and critical reviewing and editing of the manuscript.

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