society and the economy, which has led to discussion of the definition of old age [5], since the timing of old age is roughly equivalent to the age of retirement and receiving pension benefit.

The Survey on the Senior Citizens' Attitude toward Daily Life, conducted by the Cabinet Office of the Government of Japan in 2009, reported that the majority of respondents considered that the threshold for old age should be higher than the current one, 65 years, and more than 40% thought it should be 70 years [6]. This survey also showed that more than a quarter of the respondents answered that an even higher threshold of 75 years is appropriate for old age [6]. This may reflect the change in people's perception towards aging, and it is possible that the biological age, which involves multitudinous factors including not only elapsed time but also nutrition, living environment and medical conditions, may be going down compared with the chronological age. This hypothesis is compatible with the increase in healthy life expectancy that has occurred simultaneously with the increase in life expectancy [1, 3, 7].

Although both life expectancy and healthy life expectancy have been increasing, the gap between them has also been widening [1, 3]. In order to prevent disability and extend healthy life expectancy, a number of epidemiological studies have been conducted, and comorbid chronic medical conditions have been identified as significant risk factors for disability or the requirement for long-term care [8–13]. However, the prevalence of disability does not necessarily change in parallel with the prevalence of chronic medical conditions. Indeed, studies in some developed countries have reported an increase in the prevalence of chronic medical conditions but a stable or declining disability rate [14–17]. Therefore, examination of the trends in disability and chronic medical conditions in Japan, whose proportion of the old age population is the highest in the world, may facilitate our understanding of the relationship between chronic medical conditions and disability, and the medical and nursing care needs in the old adult population.

In this study, we aimed to characterize the trends in disability and chronic medical conditions over the age of 65 years, the current threshold for old age. We hypothesized that the prevalence of disability, along with the prevalence of chronic medical conditions, has been declining over time, consistent with increasing healthy life expectancy.

Materials and Methods

All the data analyzed in the current study are publicly available on the Japanese government's official website, and therefore ethical review is deemed not to be required [18].

We retrospectively analyzed three databases, Comprehensive Survey of Living Conditions, Patient Survey, and Vital Statistics, all of which are conducted by the Ministry of Health, Labour and Welfare and whose details and tabulated data are available on the website of the Statistics Bureau, Ministry of Internal Affairs and Communications [2, 19, 20].

The Comprehensive Survey of Living Conditions is a series of cross-sectional national surveys on a random stratified sample of households and their members [20]. A long-term care questionnaire has been administered every three years starting from 2001, covering persons requiring long-term care (approximately 6000 persons) in 2,500 districts from the National Census. Results from the long-term care questionnaire include the rate of persons certified for long-term care under the Long-Term Care Insurance System per 100,000 population (hereafter referred to as the disability rate), which is approximately equivalent to the prevalence of disability.

The Patient Survey is a series of cross-sectional national surveys on a random sample of medical institutions (including hospitals and outpatient clinics) [19]. All hospitals with more than 500 beds were included in the surveys. Data from medical institutions in Fukushima prefecture and the Ishinomaki and Kesennnuma medical areas of Miyagi prefecture were not included in the 2011 survey data due to the Tohoku earthquake and tsunami on March 11th, 2011. The surveys were conducted on one designated date set for each medical institution from three days in October. Physicians filled out the questionnaire and collected information on patients who attended the participating medical institutions on the date of the survey. Approximately 8 million patients were included in each survey. The International Statistical Classification of Diseases and Related Health Problems, ninth Revision (ICD–9), published by the World Health Organization, was applied to classify diseases and injuries in the surveys until 1996, and the ICD–10 thereafter, which prevented direct comparison of the data prior to and after 1996.

For each disease or injury, the rate of estimated number of patients per 100,000 population (hereafter referred to as the treatment rate) was calculated as the estimated number of patients divided by the estimated population x 100,000. The estimated number of patients who continuously received medical care was calculated using the following formula [19]:

Estimated number of patients receiving medical treatment = Estimated number of inpatients + Estimated number of initial visit outpatients + (Estimated number of return visit outpatients × Average interval since last visit × Adjustment factor (6/7))

Therefore, the estimated number of patients included those who did not receive medical care at medical institutions on the date of the survey, and the treatment rate can be considered a rough approximation of the prevalence.

Our analysis focused on the trends in the prevalence of medical conditions that can cause disability and lower healthy life expectancy. The Comprehensive Survey of Living Conditions in 2013 reported that the most common cause of disability was cerebrovascular accident, followed by dementia, frailty due to aging, joint disorders, bone fracture and cardiac disease [20]. These six categories accounted for more than 70% of causes of disability. In the current analysis, we chose to investigate cerebrovascular diseases, osteoarthritis, inflammatory polyarthropathies, fractures, osteoporosis, ischemic heart disease, diabetes mellitus, hypertension, pneumonia and malignant neoplasms based on their clinical significance, their potential to cause disability, and the availability of data. Osteoarthritis and inflammatory polyarthropathies were combined into a single category, joint disorders. We initially planned to investigate Alzheimer's disease as well, but our preliminary analysis suggested that the treatment rate had been much lower than the prevalence previously reported [21] despite recent increase in the treatment rate, presumably because of under-diagnosis (S1 Fig and S1 Table) [22]. We therefore decided not to include Alzheimer's disease in our analysis because our primary aim was to examine the actual prevalence of chronic medical conditions.

Vital Statistics is based on the Family Registry, and collects data on birth, marriage and death registrations [2]. The data on total mortality rate and mortality rates from specific causes (cerebrovascular diseases, heart diseases, pneumonia and malignant neoplasms) were obtained from Vital Statistics. The cause of death was obtained from the death certificate issued by physicians, and classified using ICD–9 until 1995, and ICD–10 thereafter, and therefore we included the data after 1995 in our analysis.

Statistical Analysis

We stratified the data by sex and examined the trends in disability rate, treatment rates of selected medical conditions and mortality rates in the four 5-year age strata over the age of 65 years (65–69, 70–74, 75–79 and 80–84 years). The overall increasing or decreasing trend in the rates in each sex was evaluated by the linear trend test using PROC GLM of SAS (SAS Institute, Inc., Cary, NC, USA) adjusted for the age groups. Provided the initial trend test was statistically significant, linear regression was performed to evaluate the trend in each age stratum. Two-sided $p<0.05$ was considered statistically significant.

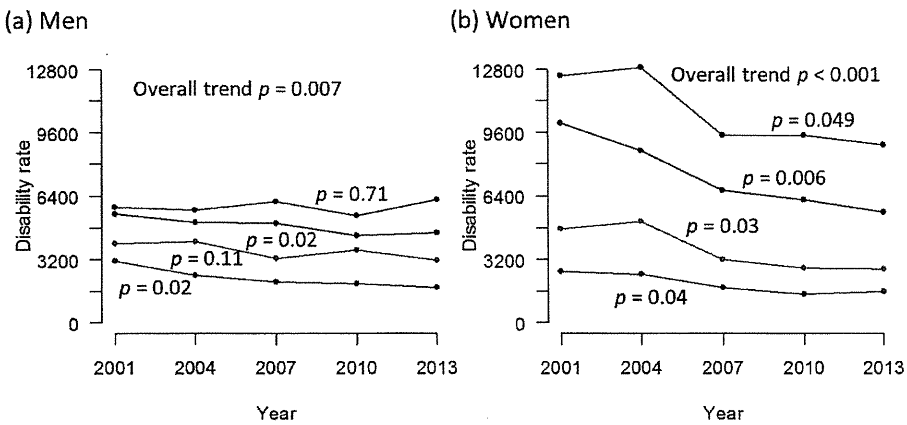

Fig 1. Trends in disability rate in men and women from 2001 to 2013. (a) men. (b) women. The disability rate is the rate of persons certified for long-term care under the Long-Term Care Insurance System per 100,000 population. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.

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Results

Trends in Disability

The trends in the disability rates from 2001 to 2013 are displayed in Fig 1 (Tabulated data available in S2 Table). The overall trend was downward and statistically significant in each sex. The trend in each age stratum was also statistically significant except for men aged 70–74 and 80–84 years.

Trends in Chronic Medical Conditions

Figs 2 and 3 show the trends in the treatment rates for the nine selected medical conditions from 1996 to 2011 (Tabulated data available in S3 Table). The overall treatment rate declined significantly for all medical conditions in each sex, except for fractures in women and pneumonia.

For cerebrovascular diseases, ischemic heart disease and osteoporosis, the downward trend was statistically significant for all age strata (65–69, 70–74, 75–79 and 80–84) in each sex.

For diabetes mellitus and hypertension, the treatment rate decreased over time with statistical significance for all age strata in women, but in men the downward trend was statistically significant in two younger age strata only (65–69 and 70–74).

For fractures and malignant neoplasms, the downward trend was statistically significant in two younger age strata of 65–69 and 70–74 years in men. In women, statistical significance was observed only in the age stratum of 70–74 years for malignant neoplasms.

For joint disorders, the downward trend was statistically significant in two younger age strata of 65–69 and 70–74 years in each sex, but the significance decline was not observed in older age strata except for the age stratum of 75–79 years in men.

Trends in Mortality

Figs 4 and 5 show the trends in total mortality rate and mortality rates from specific causes from 1995 to 2010 (Tabulated data available in S4 Table). Both total mortality rate and cause-specific mortality rates declined significantly in all age strata in both sexes, except for mortality

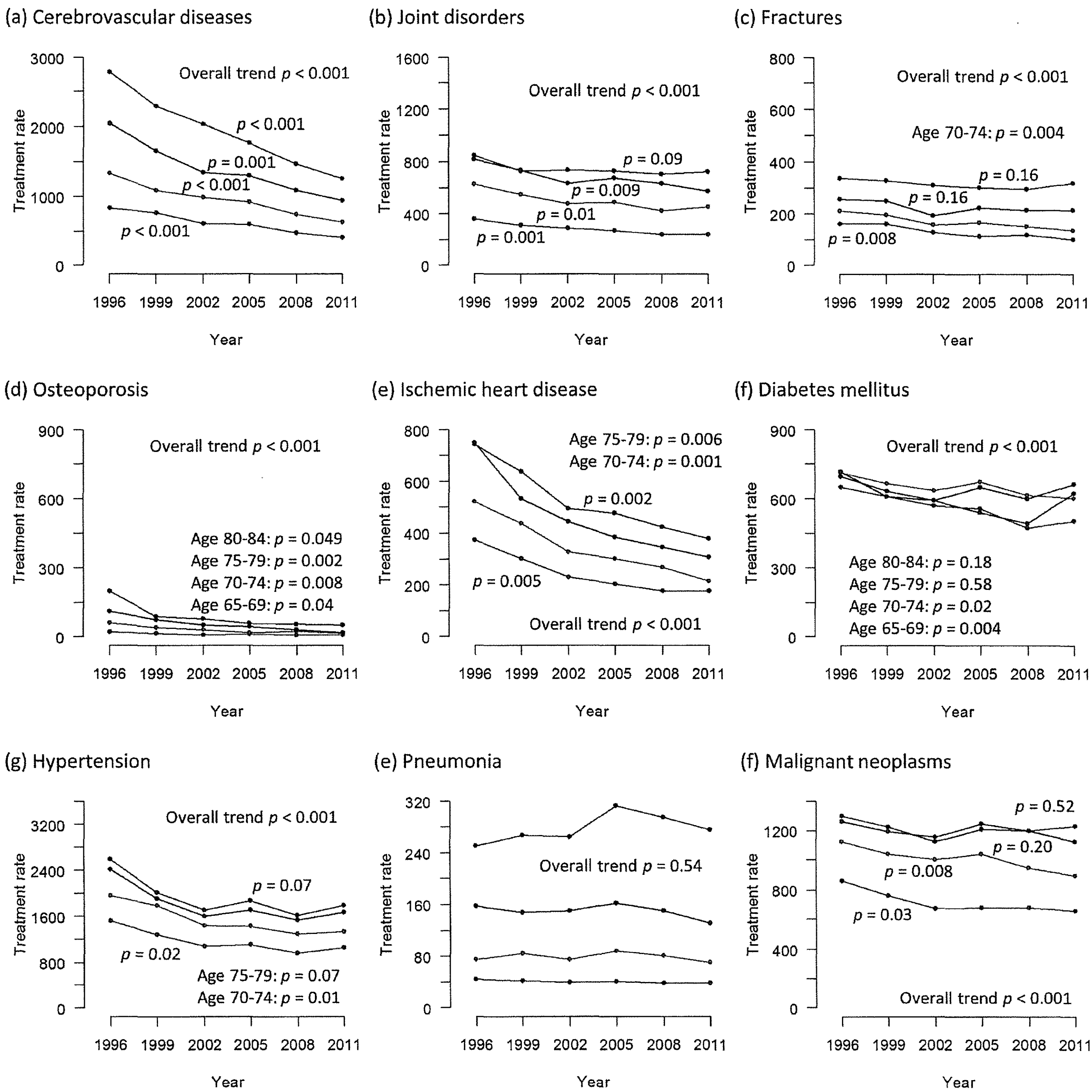

Fig 2. Trends in treatment rates of nine selected medical conditions in men from 1996 to 2011. (a) cerebrovascular diseases (b) joint disorders (c) fractures (d) osteoporosis (e) ischemic heart disease (f) diabetes mellitus (g) hypertension (h) pneumonia (i) malignant neoplasms The treatment rate is calculated as the estimated number of patients divided by the estimated population x 100,000. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.

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rate from malignant neoplasms in the age stratum of 70–74 years and heart diseases in the age stratum of 80–84 years in men in which the change was not statistically significant.

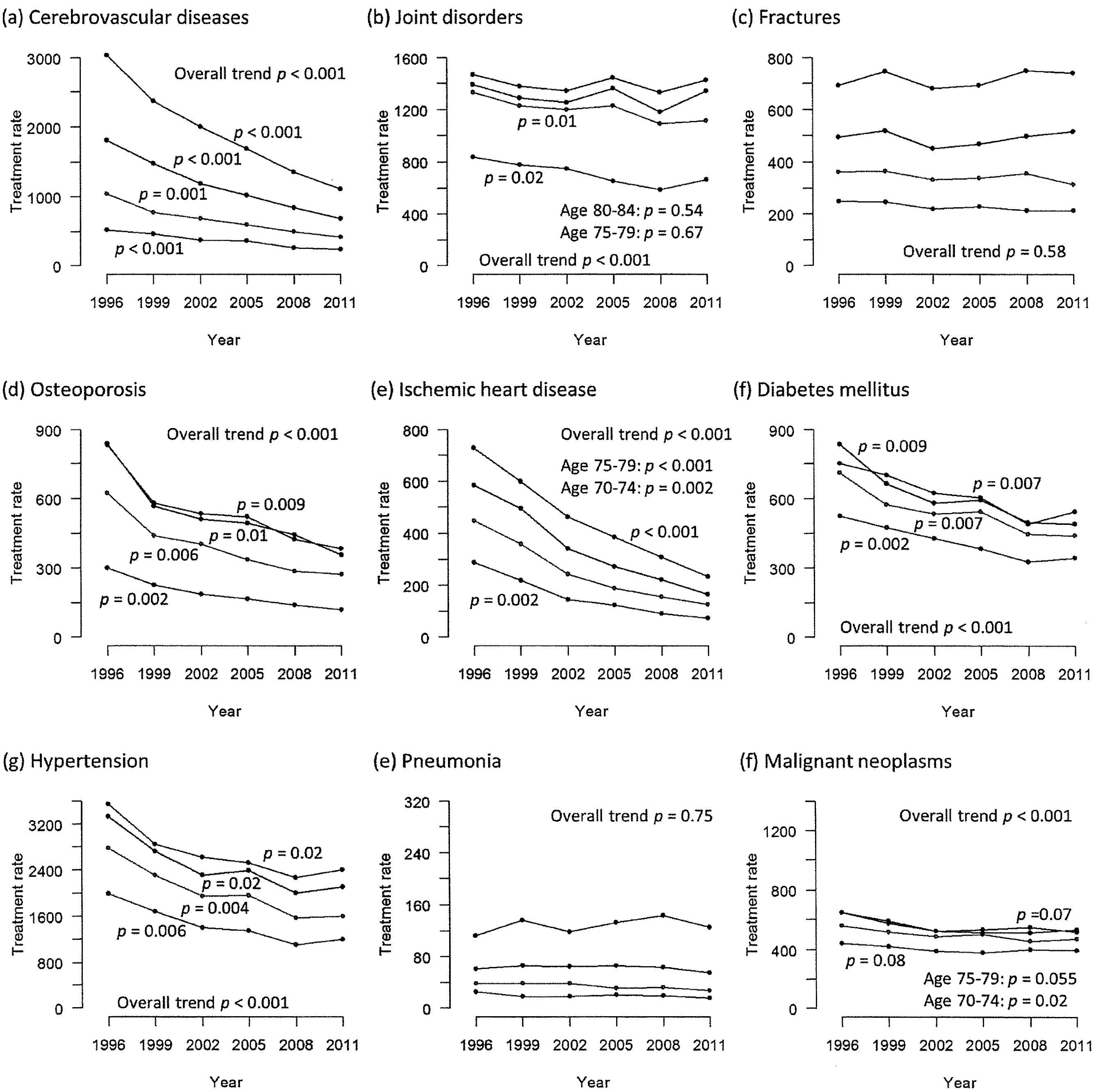

Fig 3. Trends in treatment rates of nine selected medical conditions in women from 1996 to 2011. (a) cerebrovascular diseases (b) joint disorders (c) fractures (d) osteoporosis (e) ischemic heart disease (f) diabetes mellitus (g) hypertension (h) pneumonia (i) malignant neoplasms The treatment rate is calculated as the estimated number of patients divided by the estimated population x 100,000. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.

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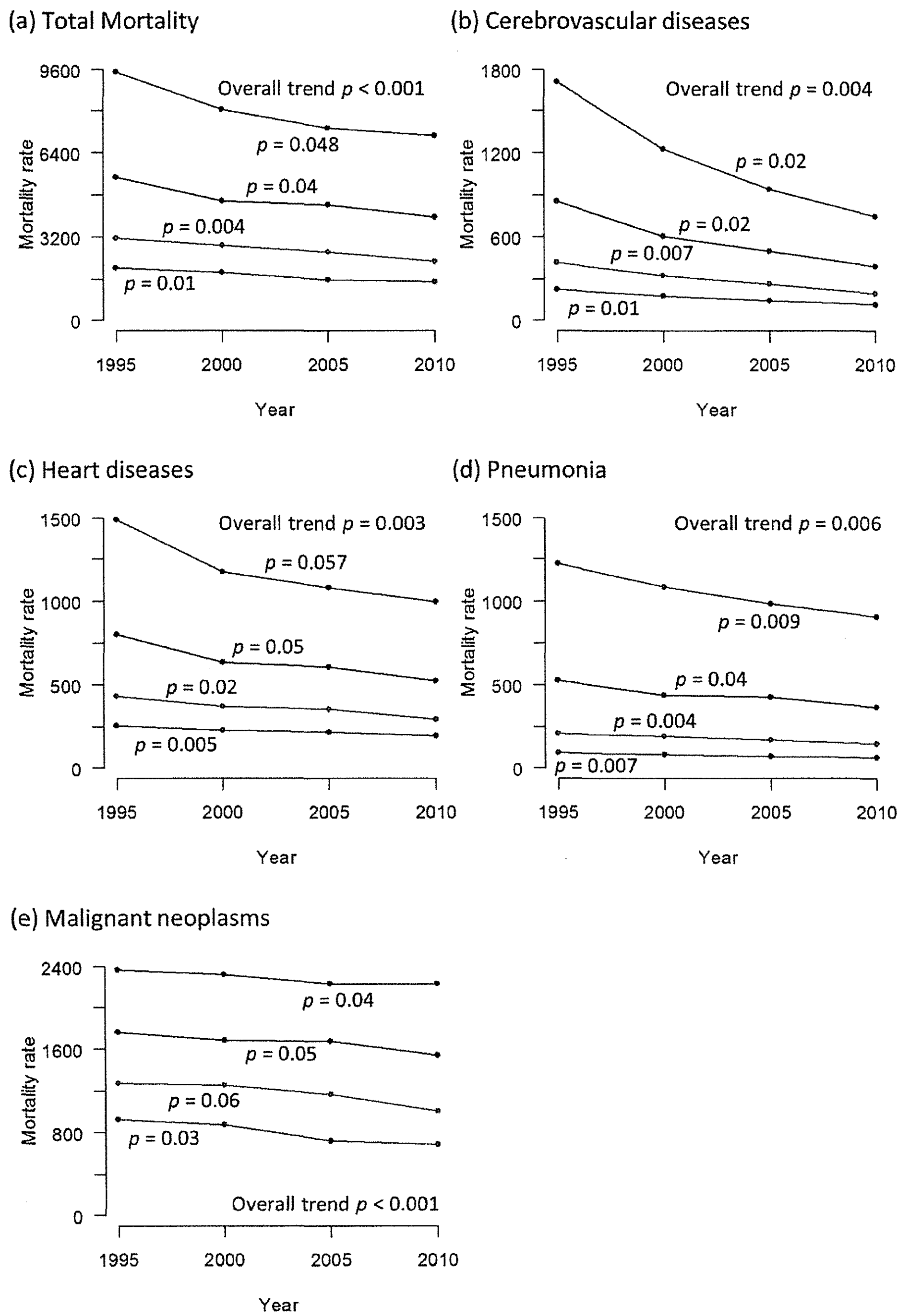

Fig 4. Trends in total mortality rate and mortality rates from specific causes in men from 1995 to 2010. (a) total mortality rate. Mortality rate from (b) cerebrovascular diseases (c) heart diseases (d) pneumonia (e) malignant neoplasms. The mortality rate is calculated as the number of deceased divided by the estimated population x 100,000. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.

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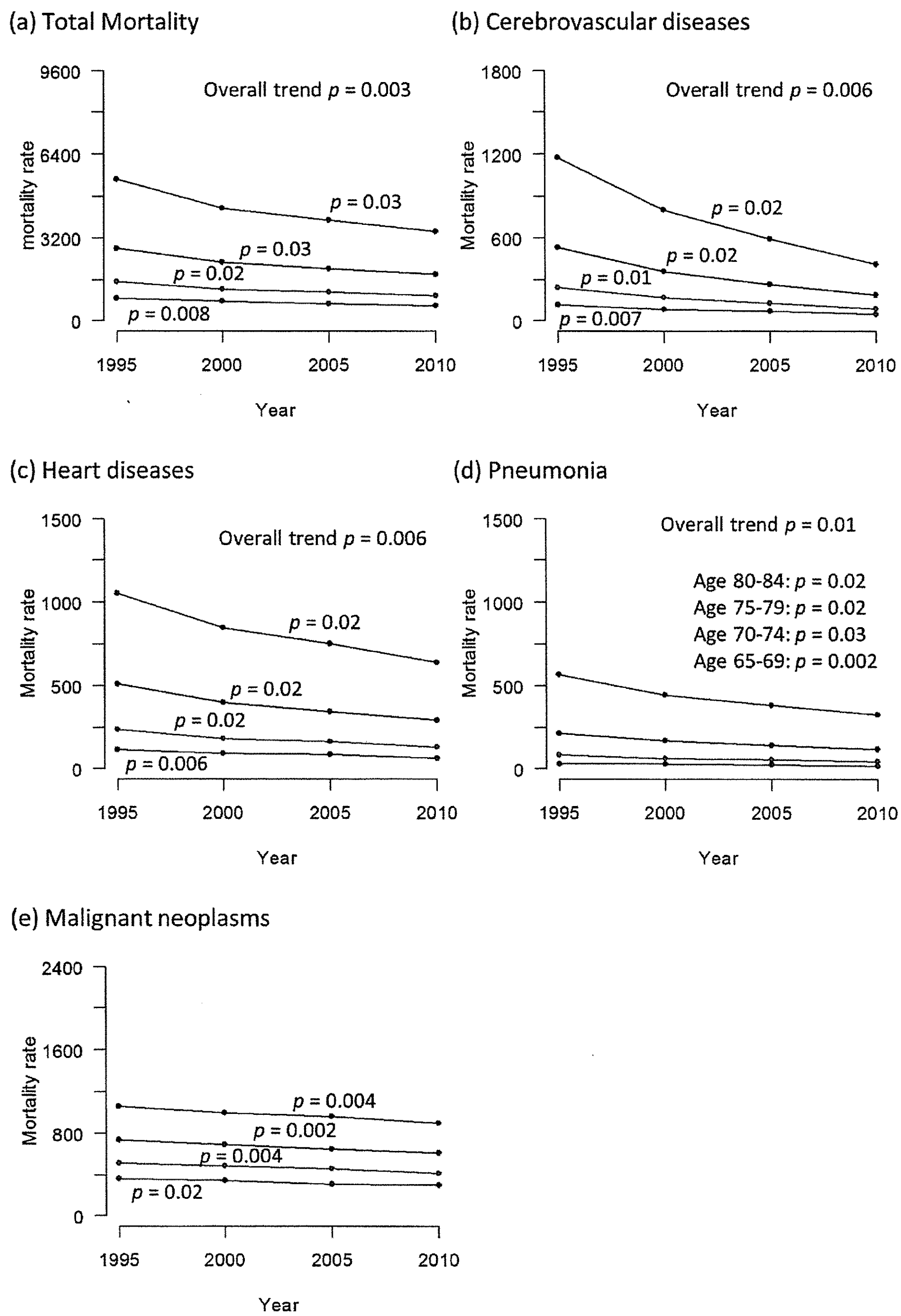

Fig 5. Trends in total mortality rate and mortality rates from specific causes in women from 1995 to 2010. (a) total mortality rate. Mortality rate from (b) cerebrovascular diseases (c) heart diseases (d) pneumonia (e) malignant neoplasms. The mortality rate is calculated as the number of deceased divided by the estimated population x 100,000. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.

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Discussion

In the analysis of nationally representative datasets, we demonstrated that the disability rate and mortality rate declined significantly over time in old adults aged between 65 and 84 in Japan. We also observed a decrease in treatment rates of many chronic medical conditions over approximately the same time period. This finding suggests a decline in the prevalence of these conditions, which is in concordance with the decline in disability rate. The concurrent decrease in mortality implies that the decrease in treatment rates is not attributable to attrition of sicker persons or survival bias. Hence, combined together, our findings indicate overall improvement in health conditions among adults entering "old age"; that is, people reaching the age of 65 years have recently enjoyed better health compared to preceding cohorts.

Among conditions whose treatment rates declined, three medical conditions, namely cerebrovascular diseases, ischemic heart disease and osteoporosis, showed a particularly substantial decline. The treatment rates of these medical conditions in each age group in 2011 were roughly equivalent to or even lower than the treatment rates of the group 5 years younger in 1996, and were consistent in each sex. Public health organizations have made efforts to increase people's awareness of the importance of a healthy lifestyle and avoiding major risk factors for these medical conditions, such as smoking, hypertension and diabetes. These efforts have gradually altered people's behavior. The smoking rate was 44.7% for men over 60 and 7.8% for women over 60 in 1996, but in 2011 it fell to 23.9% and 6.4%, respectively [23]. People, particularly those older than 60, exercise more than previously [23]. The Specific Health Checkup, which focuses on screening for metabolic syndrome and lifestyle-related diseases, was introduced in 2008 against a backdrop of increased awareness of such medical conditions, and led to early screening, diagnosis and treatment [24]. In addition, advances in medical technology, medication and care and an improving standard of living have helped facilitate prevention and management of these conditions. It should be noted that cerebrovascular diseases and ischemic heart disease are important causes of both mortality and disability.

Interestingly, the change in the overall treatment rate for fracture in women was not statistically significant, whereas the treatment rate for osteoporosis declined significantly. The observed disparity between the treatment rates of fractures and osteoporosis may be due to limited predictive ability of bone mineral density measurements, which have been widely used to diagnose osteoporosis. It is true that fracture is more likely to occur when bone mineral density is lower, but multiple factors play a role in determining fracture risk, and bone mineral density alone accounts for only 1.7 to 7.4 percent of fracture risk [25, 26]. Another possible explanation for the disparity may be under-diagnosis of osteoporosis. In primary care settings, osteoporosis is often undiagnosed and untreated. However, health checkups for old adults in Japan include screening for osteoporosis, and it is unlikely that the diagnostic rate of osteoporosis has significantly changed recently. The time gap between osteoporosis and fractures may also help explain the disparity. People tend to suffer fracture at an older age than the age when they receive a diagnosis of osteoporosis. Therefore, even though the treatment rate for osteoporosis has declined, the effects on the treatment rate of fracture may be delayed and take some more years to be observable.

The treatment rates for diabetes mellitus and hypertension declined significantly for all age strata in women, but the improvement in men was mostly restricted to those younger than 75 years. The reason for this apparent disparity between men and women is not clear, but it may reflect sex differences in age-related changes or a cohort effect. Those older than 75 years experienced the Second World War in their childhood when chronic malnutrition was widespread and started their occupational career in the period of rapid growth in 1960s when men were expected to earn their livings and women to stay home and raise a family.

An improvement in the treatment rate of pneumonia was not observed in each sex. Despite the largely unchanged treatment rate of pneumonia, pneumonia-specific mortality rate declined over time. This suggests stable occurrence of pneumonia, but possibly of a less severe form, and improved management of pneumonia. Because effective preventive measures for pneumonia, such as pneumococcal or influenza vaccination, are already widely available for old adults, further improvement in the prevention of pneumonia may be hard to achieve.

Only a few studies have provided descriptive epidemiological data on disability and chronic diseases among older adults in Japan. The Analysis of National Survey of Japanese Elderly, a nationally representative six-wave panel study, reported that six out of ten measures of Activity of Daily Living (ADL) and instrumental ADL improved significantly after adjustment for age from 1993 to 2002 [27]. A study of the Comprehensive Survey of Living Conditions reported that the number of expected years of life without activity limitation increased from 1995 to 2004 [7]. These studies reported data more than 10 years ago, but the results are consistent with our findings, implying that the improvement in health conditions started earlier than our data coverage.

Our study has some limitations that need to be acknowledged. First, the Patient Survey collected information on diseases and injuries from physicians, but the diagnostic criteria were not standardized and their severity was not included in the questionnaire. All medical conditions may not be captured by the questionnaire in the case of patients with multiple comorbidity, which is particularly concerning for older adults because older adults tend to have an increased number of comorbid conditions [28]. Second, the Patient Survey is conducted every three years in October, and therefore seasonal variation in the treatment rate is not accounted for. However, because each survey was conducted in a standardized manner at the same time of the year, the survey at least can provide valid estimates of the trends in the treatment rates over years. Third, some medical conditions may be underdiagnosed and not well captured by the survey. We did not include Alzheimer's disease in our analysis because it appears to be consistently underdiagnosed, and the change in the treatment rate of Alzheimer's disease does not seem to reflect the true change in prevalence. Last, the Patient Survey data in 2011 did not include data from medical institutions in Fukushima prefecture and the Ishinomaki and Kesennnuma medical areas of Miyagi prefecture. However, the populations in these areas comprised less than 3% of the population of Japan, and exclusion of data from these areas was unlikely to bias our findings and alter our conclusion.

Despite these limitations, our study has a number of strengths. The databases we utilized are nationally representative, containing large numbers of participants. The Vital Statistics in Japan is highly reliable, and the ascertainment of causes of death was based on death certificates issued by physicians. The data were collected in a standardized manner over a couple of decades, providing a unique opportunity to obtain descriptive epidemiological data of disability, comorbid medical conditions and mortality.

Our findings have several implications. First, even though our findings indicate overall improvement in health conditions in the population aged between 65 and 84, the absolute number of older adults with chronic medical conditions or disability will continue to increase as a result of increase in older adults [3]. This will be a great challenge for the National Health Insurance system and the Long-Term Care Insurance system in Japan. Second, considering the downward trajectory of the treatment rates observed in many medical conditions, it is important to keep raising the general public's awareness of taking preventive measures to help stave off these conditions. This is a particular priority when we consider the ramifications of the increasing number of older adults with disability. Third, the baby boomers, who were born after the Second World War, are now entering old age. It is important to carefully monitor their health conditions to see if the improvement in health conditions observed in this study will continue. Lastly, our findings do not explain the widening gap between life expectancy and healthy life expectancy. Further research focusing on very old adults is warranted.

We conclude that the prevalence of many chronic medical conditions has declined among old adults over time in Japan. Coupled with the decline in disability rate and mortality rate, our findings may signify overall improvement in health conditions among old adults. This is consistent with improving healthy life expectancy and supports the hypothesis that biological age may be getting lower compared with chronological age. Nonetheless, the increase in number of older adults will offset the improvement in health conditions, and older adults with chronic medical conditions or disability will continue to increase. Therefore, continuous public health efforts to prevent chronic medical conditions and a roadmap for a health care system to meet the increasing health care needs of older adults are still warranted.

Supporting Information

S1 Fig. Trends in treatment rates of Alzheimer's disease in men and women from 1996 to 2011. The treatment rate is calculated as the estimated number of patients divided by the estimated population x 100,000. The black line represents those aged 80–84 years, the blue line represents those aged 75–79 years, the green line represents those aged 70–74 years and the red line represents those aged 65–69 years. The p values signify statistical significance for the trends in each age stratum.
(TIF)

S1 Table. Trends in treatment rates of Alzheimer's disease in men and women from 1996 to 2011. The treatment rate is calculated as the estimated number of patients divided by the estimated population x 100,000.
(DOCX)

S2 Table. Trends in disability rate in men and women from 2001 to 2013. The disability rate is the rate of persons certified for long-term care under the Long-Term Care Insurance System per 100,000 population.
(DOCX)

S3 Table. Trends in treatment rates of nine selected medical conditions in men and Women from 1996 to 2011. The treatment rate is calculated as the estimated number of patients divided by the estimated population x 100,000.
(DOCX)

S4 Table. Trends in total mortality rate and mortality rates from specific causes in men and women from 1995 to 2010. The mortality rate is calculated as the number of deceased divided by the estimated population x 100,000.
(DOCX)

Author Contributions

Conceived and designed the experiments: SI MA. Analyzed the data: SI. Wrote the paper: SI. Reviewed the manuscript and provided advice and suggestions: MA SO SI.

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RESEARCH ARTICLE

Hypnotics and the Occurrence of Bone Fractures in Hospitalized Dementia Patients: A Matched Case-Control Study Using a National Inpatient Database

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Abstract

Background

Preventing falls and bone fractures in hospital care is an important issue in geriatric medicine. Use of hypnotics is a potential risk factor for falls and bone fractures in older patients. However, data are lacking on the association between use of hypnotics and the occurrence of bone fracture.

Methods

We used a national inpatient database including 1,057 hospitals in Japan and included dementia patients aged 50 years or older who were hospitalized during a period of 12 months between April 2012 and March 2013. The primary outcome was the occurrence of bone fracture during hospitalization. Use of hypnotics was compared between patients with and without bone fracture in this matched case-control study.

Results

Of 140,494 patients, 830 patients suffered from in-hospital fracture. A 1:4 matching with age, sex and hospital created 817 cases with fracture and 3,158 matched patients without fracture. With adjustment for the Charlson comorbidity index, emergent admission, activities of daily living, and scores for level walking, a higher occurrence of fractures were seen with short-acting benzodiazepine hypnotics (odds ratio, 1.43; 95% confidence interval, 1.19–1.73; $P<0.001$), ultrashort-acting non-benzodiazepine hypnotics (1.66; 1.37–2.01; $P<0.001$), hydroxyzine (1.45; 1.15–1.82, $P=0.001$), risperidone and perospirone (1.37; 1.08–1.73; $P=0.010$). Other drug groups were not significantly associated with the occurrence of in-hospital fracture.

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Conclusions

Short-acting benzodiazepine hypnotics and ultrashort-acting non-benzodiazepine hypnotics may increase risk of bone fracture in hospitalized dementia patients.

Introduction

Bone fracture following falls in hospitalized patients is an unresolved problem in geriatric medical management. Older patients, especially dementia patients, have higher risks of delirium, insomnia and day—night reversal with environmental changes related to hospital admission. Hypnotics and psychoactives are sometimes used to relieve these symptoms.

Studies have examined the risk of hypnotic drug use on fall and fracture. In a meta-analysis of 22 studies, fall was significantly associated with use of sedatives and hypnotics, neuroleptics and antipsychotics, antidepressants, and benzodiazepines, but was not associated with narcotics [1]. A retrospective analysis of 3683 patients demonstrated that fall was associated with use of hypnotics [2]. Several studies showed that zolpidem was significantly associated with a higher risk of fall and fracture [3, 4]. Another study showed a hip fracture risk associated with non-benzodiazepine hypnotics [5]. These previous studies were mostly performed in nursing homes or in the community in older patients. Falls in the acute care hospital setting occur at a higher rate than falls in nursing home settings [6–9]. Moreover, hospital falls are also most frequent in safety incident reports, and sometimes lead to negligence suits [10]. However, to our knowledge, there has been no study that simultaneously assessed various types of hypnotics and their risk of in-hospital fracture in a nationwide clinical setting. In this study, we performed a matched case-control study to analyze the association between use of various types of hypnotics and the occurrence of bone fracture in hospitalized dementia patients, using a national inpatient database in Japan. We focused on dementia for several reasons. First, older patients with dementia have a fall risk twice or more than that of older patients without dementia [11, 12]. Second, older patients with dementia also have three to eight times more injuries with falls and more often have a bad prognosis [13–15]. Third, wandering, as well as other behavioral and psychological symptoms of dementia, along with hypnotic and psychoactive agents used to relieve these symptoms, increases fall risks [16, 17]. The medications tend to become the problem in acute care hospitals in trying to prevent falls in dementia patients.

Methods

Setting and Participants

For this study, we used the Diagnosis Procedure Combination database. The details of the database have been described elsewhere [18–20]. Briefly, the database includes administrative claims data and discharge abstract data, collected from about 1000 participating hospitals across Japan. The database includes the following information: patient age and sex; main diagnoses, comorbidities at admission and complications after admission recorded according to the International Classification of Diseases, 10th Revision (ICD-10) and text data in Japanese; medical procedures; medicines and devices used; length of stay; activities of daily life (ADL) scores at admission; and discharge status. A unique identifier was used for each hospital. All patient identifiers were removed from this database. Because of the anonymous nature of the data, the Institutional Review Board of The University of Tokyo waived the need for written informed consent from the participants. Study approval was also obtained from the Institutional Review Board of The University of Tokyo.

Among approximately 7 million inpatients over 12 months between April 1, 2012 and March 31 2013, we identified patients aged 50 years or older. Of these, we selected patients who were diagnosed with dementia or dementia-related diseases, including dementia in Alzheimer disease (ICD-10 code, F00), vascular dementia (F01), dementia in Pick disease (F02.0, G31.0), dementia in Creutzfeldt—Jakob disease (F02.1, G810), dementia in Huntington disease (F02.2, G10), dementia in Parkinson disease (F02.3, G20), dementia in human immunodeficiency virus disease (F02.4, B220), dementia in other specified diseases classified elsewhere (F02.8), unspecified dementia (F03), alcoholic dementia (F107), dementia in cerebral lipidosis (F028, E756), Lewy bodies dementia (F028, G318), and mild cognitive disorder (F06.7).

We extracted data on the following 17 types of hypnotics (or sedatives used as hypnotics) for each patient: benzodiazepine anxiolytics; diazepam; ultrashort-acting benzodiazepine hypnotics; short-acting benzodiazepine hypnotics; middle- to long-acting benzodiazepine hypnotics; ultrashort-acting non-benzodiazepine hypnotics; melatonin-receptor agonists; hydroxyzine; phenothiazine antipsychotics; haloperidol; sulpiride; risperidone and perospirone; multi-acting-receptor-targeted antipsychotics used as a hypnotic; antidepressants used as a hypnotic; Japanese *kampo* herbal medicine used as a hypnotic and in the treatment of behavioral and psychological symptoms of dementia; and other neurological drugs used as hypnotics.

Comorbidities were assessed by ICD-10 codes and converted into scores to calculate the Charlson comorbidity index (CCI) based on Quan's algorithm [21]. ADL scores for walking on a flat floor were also extracted including bedridden (Score 0), totally assisted (Score 1), partially assisted (Score 2) and without disability (Score 3).

Outcomes

The outcome in this study was in-hospital fracture. In the database, comorbidities already present at admission are clearly differentiated from complications that occurred after admission. In-hospital fracture was defined as fracture that occurred after admission and was determined according to the following ICD-10 codes: fracture of skull and facial bones (S02); fracture of neck (S12); fracture of rib(s), sternum and thoracic spine (S22); fracture of lumbar spine and pelvis (S32); fracture of shoulder and upper arm (S42); fracture of forearm (S52); fracture at wrist and hand level (S62); fracture of femur (S72); fracture of lower leg, including ankle (S82); fracture of foot, except ankle (S92); fractures involving multiple body regions (T02); fracture of spine, level unspecified (T08); fracture of upper limb, level unspecified (T10); and fracture of lower limb, level unspecified (T12).

Statistical Analyses

We performed a matched case—control study. First, we identified cases with in-hospital fracture. For each case, we selected four controls of similar age (±5 years) and the same sex from the same hospital. When there were more than four matched-control candidates to each case, we randomly selected four control patients. Specifically, control cases were sorted by randomly generated values from a Microsoft SQL server and the top four were selected. There are two ways to conduct matching: matching with replacement; and matching without replacement [22]. Matching with replacement means that controls can be used as matches for more than one treated individual; matching without replacement signifies that controls cannot be used as matches for more than one treated individual. Though the statistical analysis becomes more complex, matching with replacement can often decrease bias because controls that resemble many treated individuals can be used multiple times [23, 24]. Moreover, the order of matching the treated individuals is immaterial in the case of matching with replacement. One methodological paper compared matching with and without replacement in three matching methods, and it found that matching with replacement had a smaller bias among all three methods [25]. Thus, we chose matching with replacement for the present study. If a control case was a candidate for more than one case, we included both matches. In the following analysis, one control was selected three times, 95 controls were selected twice, and they were weighted using frequency weights. If the number of matched-control candidates for each case was less than four, we also included both the corresponding case (62 cases) and control (138 controls) in the analytical group subset to avoid selection bias, unless no control subjects were assigned (13 cases).

Descriptive statistics were presented for the matched patients. Categorical variables were compared using the chi square test. We performed multivariable logistic regression for the occurrence of in-hospital fractures fitted with a generalized estimating equation to account for the clustered nature of the cases and controls. There are two ways to cluster in matched case-control studies: generalized estimating equations (GEEs) and conditional logistic analysis. Both methods can make consistent estimates. As GEE is more robust in terms of the specification of matching effect, we chose GEEs [26]. The dependent variable was in-hospital fracture, and independent variables included, emergent admission, ADL score for walking on a flat floor, CCI and 17 classes of drugs. All statistical analyses were conducted using IBM SPSS version 22.0 (IBM SPSS, Armonk, NY, USA).

Results

Among 140,494 eligible patients, 830 patients suffered from in-hospital fracture.

Using 1:4 matching, we obtained a case group of 817 patients and a control group of 3158 patients. Table 1 shows the baseline characteristics of the matched patients (n = 3975). As a result of matching, there was no significant difference in age ($P = 0.582$) or sex ($P = 0.728$) between the case and control groups. To exclude the possibility that controls may have been matched to cases with a larger age difference than to cases with a smaller age difference, we also compared the distribution of age in the case and control groups. Mean, median, standard deviation, range and interquartile range of age (years) in the case and control groups were 81.5 vs. 81.8, 82.0 vs. 82.0, 7.9 vs. 7.5, 50–103 vs. 50–103, 11.0 vs. 10.0, respectively. The age distributions of the case and control groups were also similar. No significant difference in CCI or emergent admission was present between the cases and controls. The ADL score for walking on a flat floor on admission was significantly different between the groups.

Table 2 shows 17 types of hypnotics (or sedatives used as hypnotics) used for the case and the control groups. The most frequently used drugs in both groups were ultrashort-acting non-benzodiazepine hypnotics, followed by short-acting benzodiazepine hypnotics. The proportion of patients who used any of the 17 types of drugs was significantly higher in the case than the control group (66.8% vs. 51.9%, $P<0.001$) (Table 2). The proportion of patients who used more than three types of hypnotics (or sedatives used as hypnotics) was also higher in the case than the control group (24.2% vs. 14.6%, $P<0.001$). The case group was significantly more likely to use benzodiazepine anxiolytics; ultrashort-acting benzodiazepine hypnotics; short-acting benzodiazepine hypnotics; middle- to long-acting benzodiazepine hypnotics; ultrashort-acting non-benzodiazepine hypnotics; melatonin-receptor agonists; hydroxyzine; phenothiazine antipsychotic; haloperidol; sulpiride; risperidone and perospirone; multi-acting-receptor-targeted antipsychotics used as a hypnotic; and an antidepressant used as a hypnotic. The proportion of patients who used Japanese *kampo* herbal medicine was not significantly different between the cases and controls.

Table 1. Characteristics of patients in the matched case and control groups.

		Cases (n = 817)		Controls (n = 3158)		P
Charlson comorbidity index	0	141	17.3%	526	16.7%	0.971
	1	264	32.3%	1013	32.1%	
	2	199	24.4%	805	25.5%	
	3	115	14.1%	435	13.8%	
	≥4	98	12.0%	379	12.0%	
Emergent admission		415	50.8%	1538	48.7%	0.286
ADL score (walking on flat floor)	0 (bedridden)	459	56.3%	1773	56.3%	0.001
	1 (totally assisted)	59	7.2%	208	6.6%	
	2 (partially assisted)	105	12.9%	382	12.1%	
	3 (without disability)	113	13.9%	588	18.7%	
	Unknown	81	9.9%	207	6.5%	

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Table 3 shows the results of the multivariable logistic regression analysis. A higher occurrence of in-hospital fracture was significantly associated with use of a short-acting benzodiazepine hypnotic, an ultrashort-acting non-benzodiazepine hypnotic, a hydroxyzine, risperidone and perospirone. Neither melatonin agonists nor Japanese *kampo* herbal medicine was associated with the occurrence of in-hospital fracture.

Table 2. Comparison of drug use between matched case and control groups.

	Case (n = 817)		Control (n = 3158)		P
benzodiazepine anxiolytic	98	12.0%	279	8.8%	0.006
diazepam	46	5.6%	171	5.4%	0.809
ultrashort-acting benzodiazepine hypnotic	24	2.9%	55	1.7%	0.029
short-acting benzodiazepine hypnotic	173	21.2%	460	14.6%	<0.001
middle- to long-acting benzodiazepine hypnotic	57	7.0%	159	5.0%	0.029
ultrashort-acting non-benzodiazepine hypnotic	194	23.7%	461	14.6%	<0.001
melatonin-receptor agonist	34	4.2%	83	2.6%	0.021
hydroxyzine	119	14.6%	288	9.1%	<0.001
phenothiazine antipsychotic	25	3.1%	58	1.8%	0.029
haloperidol	124	15.2%	314	9.9%	<0.001
sulpiride	26	3.2%	54	1.7%	0.008
risperidone and perospirone	144	17.6%	343	10.9%	<0.001
multi-acting-receptor-targeted antipsychotics used as hypnotic	77	9.4%	217	6.9%	0.013
antidepressant used as hypnotic	50	6.1%	103	3.3%	<0.001
Japanese *kampo* herbal medicine used as hypnotic and in treatment of BPSD	50	6.1%	192	6.1%	0.966
other neurological drugs used as hypnotic	31	3.8%	91	2.9%	0.178
Number of drugs					
0	271	33.2%	1519	48.1%	<0.001
1	201	24.6%	746	23.6%	
2	147	18.0%	433	13.7%	
≥3	198	24.2%	460	14.6%	

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Table 3. Generalized estimating equation analysis result.

	odds ratio	95% confidence interval			P
Type of admission					
Non-emergent	Reference				
Emergent	1.03	0.88	–	1.20	0.712
ADL score of walking on flat floor					
0 (bedridden)	Reference				
1 (totally assisted)	1.01	0.75	–	1.37	0.924
2 (partially assisted)	1.00	0.79	–	1.27	0.989
3 (without disability)	0.67	0.54	–	0.85	0.001
Unknown	1.42	1.08	–	1.86	0.011
Charlson comorbidity index					
0	Reference				
1	0.91	0.72	–	1.16	0.461
2	0.88	0.69	–	1.12	0.296
3	0.93	0.71	–	1.22	0.609
≥4	0.91	0.68	–	1.22	0.526
benzodiazepine anxiolytic	1.15	0.90	–	1.47	0.250
diazepam	0.91	0.65	–	1.29	0.608
ultrashort-acting benzodiazepine hypnotic	1.53	0.94	–	2.50	0.086
short-acting benzodiazepine hypnotic	1.43	1.19	–	1.73	0.000
middle- to long-acting benzodiazepine hypnotic	1.01	0.70	–	1.45	0.977
ultrashort-acting non-benzodiazepine hypnotic	1.66	1.37	–	2.01	0.000
melatonin-receptor agonist	1.25	0.84	–	1.88	0.273
hydroxyzine	1.45	1.15	–	1.82	0.001
phenothiazine antipsychotic	1.06	0.57	–	2.00	0.847
haloperidol	1.16	0.91	–	1.48	0.244
sulpiride	1.57	0.95	–	2.57	0.077
risperidone and perospirone	1.36	1.08	–	1.73	0.010
multi-acting-receptor-targeted antipsychotics used as hypnotic	1.07	0.79	–	1.44	0.654
antidepressant used as hypnotic	1.38	0.97	–	1.98	0.077
Japanese *kampo* herbal medicine	0.72	0.52	–	1.00	0.052
other neurological drugs used as hypnotic	1.10	0.62	–	1.96	0.736

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Discussion

The present study showed an increased risk for in-hospital fracture with several hypnotics and psychoactives used as hypnotics in dementia patients who were admitted to acute care hospitals. In-hospital fracture risk was associated with a short-acting benzodiazepine hypnotic, an ultrashort-acting non-benzodiazepine hypnotic, and risperidone and perospirone.

A previous US study of nursing home residents demonstrated a fracture risk with ultra-short-acting non-benzodiazepine hypnotics [5]. The present study also showed a risk with ultrashort-acting non-benzodiazepine hypnotics. A new finding in the present study is that shorter-acting drugs had relatively higher odds ratios for in-hospital fracture than longer-acting drugs. A possible explanation for this may be that patients are more likely to fall when drowsy soon after taking hypnotics. Another possible reason is that physicians may have avoided prescribing long-acting hypnotics for frail patients.

To our knowledge, the present study is the first to show that hydroxyzine may increase the risk of fracture in dementia patients. Hydroxyzine has been shown to be as effective as bromazepam, one of the benzodiazepines, in the treatment of generalized anxiety disorder [27]. Because hydroxyzine has a half-life of around 3 hours, it may act like a short-acting benzodiazepine.

Our results showed that a melatonin agonist was not significantly associated with the occurrence of in-hospital fracture. Melatonin-receptor agonists including ramelteon are new types of hypnotics. They act on the $GABA_A$ receptor-independent pathway in contrast to most of hypnotics that act on the $GABA_A$ receptor. The present study suggests that a melatonin agonist may be safer than other hypnotics in terms of fall and fracture risk.

Japanese *kampo* herbal medicines, which are often used as sedatives or hypnotics in Japan, have beneficial effects on the behavioral and psychological symptoms of dementia [28–30]. Our results suggest that these drugs would be good alternatives to conventional hypnotics or sedatives in dementia patients and may reduce fracture risk.

This study has several limitations. First, recorded diagnoses in an administrative claims database are less well validated than those in planned prospective studies. Second, the time interval between drug administration and related in-hospital fracture cannot be identified from the database and its causal relationship remains to be clarified. We have information on the timing and use of these agents, but not on the timing of fracture. Consequently, we are not certain as to whether the agent was prescribed before or after the fracture, or if it was not used for a short period of time for weeks to months prior to fracture. Third, it is difficult to distinguish the deleterious effect of hypnotic use itself from underlying conditions, including night delirium and insomnia requiring prescription of hypnotics. Fourth, there was no information about previous falls, and so we were unable to examine this relationship owing to the lack of data.

In light of these findings, it is preferable to avoid prescribing short-acting benzodiazepines and ultrashort-acting non-benzodiazepine hypnotics, risperidone or perospirone, hydroxyzine, or multi-acting-receptor-targeted antipsychotics to in-hospital dementia patients. Melatonin-receptor agonists or Japanese *kampo* herbal medicine may be preferable to these drugs.

Conclusion

Short-acting benzodiazepines and ultrashort-acting non-benzodiazepine hypnotics were associated with an increase in in-hospital fractures in dementia patients, while no significant association with an increase in in-hospital fractures was seen with middle- to long-acting benzodiazepine hypnotics, melatonin-receptor agonists, or Japanese *kampo* herbal medicine.

Author Contributions

Conceived and designed the experiments: HT HY SO. Performed the experiments: HT HY SO. Analyzed the data: HT HY SO. Contributed reagents/materials/analysis tools: HM KF HY. Wrote the paper: HT HY MA SO.

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