Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Clinical Medicine Insights: Geriatrics

Hip Fracture After Stroke in the Elderly: Trends in the Beginning of the 21st Century and Projections into the Future in Australia

Alexander A. Fisher[1,3], Jodie Martin[3], Wichat Srikusalanukul[1] and Paul N. Smith[1,3]

Departments of [1]Geriatric Medicine and [2]Orthopaedic Surgery, The Canberra Hospital and [3]Australian National University Medical School, Canberra ACT.

ABSTRACT

AIMS: To estimate age- and sex-specific incidence rates and time trends of post-stroke hip fracture (HF) in the Australian Capital Territory (ACT) and to present projections of future post-stroke HF incidence in Australia until 2051.

METHODS: Analysis of annual age- and sex-specific standardized (to 2006 Australian population) post-stroke HF incidence rates in older stroke survivors (aged ≥60 years) over an 11 year period (between 1999/2000 and 2009/2010). Projections of number of post-stroke HF in 2021 and 2051 are based on demographic predictors obtained from the Australian Bureau of Statistics.

RESULTS: Over the study period among 1784 stroke survivors HF was recorded in 61 (3.42%) subjects (40 women and 21 men), indicating a HF incidence rate of 6.31 per 1000 stroke person-years. The standardized annual post-stroke HF incidence rate (per 100,000 person-years) in women was 1.7 times higher than in men (18.9 vs. 11.1 per, p = 0.008), and in the oldest group (>80 years) compared to aged 60–69 years was 10 times higher for women (47.54 vs. 4.73) and 4 times higher for men (26.65 vs. 6.50). Post-stroke HF occurred on average within the first 2.3 years, about 2 times more often in women aged ≥75 years (p = 0.033) and in survivors after an ischaemic stroke (p = 0.052), but age *per se* did not affect the time to HF. During the 11-year period the incidence rates of post-stroke HF decreased annually in total by 17.9%.

CONCLUSIONS: Post-stroke HF is relatively common, prevalent in women and occurs on average within 2.3 years after the stroke. The incidence of post-stroke HF in elderly people is decreasing. However, because of population ageing and increasing number of stroke survivors, the absolute number of post-stroke patients sustaining a HF and their proportion among the total HF population could be expected to increase.

KEYWORDS: hip fracture, stroke, epidemiology, trends, projections, elderly, Australia

CITATION: Fisher et al. Hip Fracture After Stroke in the Elderly: Trends in the Beginning of the 21st Century and Projections into the Future in Australia. *Clinical Medicine Insights: Geriatrics* 2014:7 1–14 doi:10.4137/CMGer.S13572.

RECEIVED: November 5, 2013. **RESUBMITTED:** November 24, 2013. **ACCEPTED FOR PUBLICATION:** November 24, 2013.

ACADEMIC EDITOR: David Simar, Editor in Chief

TYPE: Original Research

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: alex.fisher@act.gov.au

Introduction

Osteoporotic hip fractures (HF) and stroke in the aged represent two major health problems globally with an increasing burden on the health care systems as the ageing population rises. Stroke is recognized as an important risk factor for HF, but the available data on post-stroke HF epidemiology remains limited and controversial. The reported increase in incidence of HF after stroke (compared to the general population) varied between 1.5 and >7 times.[1–4] However, this was not observed in other studies.[5–7] The data on time course of post-stroke HF also ranges significantly. HF occurred mainly within the first year of hospitalisation in one study,[2] but 5.4 ± 6.4 years after stroke (median 2.9 years) in another.[8] Some previous epidemiologic studies of post-stroke HF were based on self-reported history of stroke[5,6] and the type of stroke often was not analyzed.[1,2,4]

The topic is further complicated by the large geographical variations in incidence rates and temporal trends of both HF[9–15] and stroke.[16–24] In the last decade in different Australian states and territories, the age-standardized osteoporotic HF incidence rates decreased, although the absolute number of HF cases has continued to rise.[25–29] For stroke, there was an annual reduction of 4.0% in mortality rate,[30] resulting in an increase of stroke survivors.[31] In order to obtain comprehensive data on post-stroke HF trends and to estimate future burden, it is important to analyze and compare changes in both stroke survivors and HF standardized incidence rates, but no such studies have been performed.

Despite increasing evidence of shared risk factors and a pathophysiological link between bone metabolism and the vasculature,[32–35] including an increased risk of stroke,[32,36–38] and the documented twin epidemic (HF and stroke), studies on post-stroke HF, the most common fracture location (33%[39]–45%[1]) and the most serious and disabling post-stroke complication, are rare. Data regarding incidence rates, temporal trends, and time course of post-stroke HF in relation to age, gender and stroke type remain scarce and controversial. The analysis of temporal trends and projections of post-stroke HF incidence may provide better understanding of the contributing factors, indicate preventive strategies, predict the health care burden and help in health care planning and provision of resources in coming decades. However, to our knowledge, no studies have presented projections of future trends in post-stroke HF.

The aims of this study were to (1) estimate age- and sex-specific incidence rates and time trends of post-stroke HF in the population of 60 years and over in a 11-year period between 1999/2000 and 2009/2010 in the Australian Capital Territory (ACT) and provide standardized rates of post-stroke HF, (2) evaluate the role of gender, age and stroke type in temporal trends and (3) present projections of future post-stroke HF incidence in Australia until 2051.

Methods

Study sample. All patients with HF occurring in the ACT are hospitalized only in the Canberra public hospital, and all stroke patients are treated only in the Canberra and Calvary public hospitals. This provides a unique opportunity for population-based epidemiologic research. We utilized administrative databases to identify patients discharged with a diagnosis of stroke. We performed a retrospective screening of medical records of all suspected stroke cases. Separations with a principal diagnosis of International Classification of Diseases, 10th Revision (ICD-10-AM) codes 160 through 164 were included in the dataset. HF was defined by the following codes: S72.0–S72.05, S72.08, S72.10, S72.11 and S72.2. Criteria for exclusion were pathological (malignancy-associated, multiple myeloma or Paget's disease) and multi-trauma related (e.g., motor vehicle accident) HF. In this study only cervical (neck, intracapsular) and trochanteric (extracapsular) fractures of the proximal femur were included while subtrochanteric and shaft fractures were excluded. To prevent double counting inter- and intra-hospital transfers for the same event and readmission were identified by matching date of birth, patient ID number and admission and separation dates and were excluded from this analysis. Thus, each stroke and each HF was counted only once and for stroke cases only if the patient was alive at the time of discharge. Although both patients with first-ever and recurrent strokes were included in the primary database, only the first event was included in the final analysis. Patients aged <60 years were excluded in the present study. A "stroke survivor" was defined as a person discharged after a non-fatal stroke.

We used the World Health Organization (WHO) standard definition of stroke. All stroke cases were identified with the first-listed ICD code. Cases were further categorized into subarachnoid haemorrhage (SAH, ICD-10-AM 160), intracerebral haemorrhage (ICH, ICD-10-AM 161–162), cerebral infarction (ICD-10-AM 163), ill-defined (unspecified) stroke (ICD-10-AM 164). Patients with post-stroke HF were grouped according to their age: 60–69, 70–79, and ≥80 years.

Population data. Population estimates were obtained from the Australian Bureau of Statistics.[40] The ACT in 2006 (the time of census) had a total population of 334,119 people (1.75% of 19.9 million Australians), of whom 96.3% were white, 1.2% indigenous and 2.6% Asian, with 13.8% aged 60 years and over. Our study covered the period from July 1, 1999 until June 30, 2010. Over this 11-year period there was a 13.5% increase in the total ACT population (females +13.8%, males +13.3%) with a shift toward higher age: a 50.4% increase in people aged ≥60 years (females +48.3%, males +53.0%) and a 86.8% increase in people aged ≥80 years (females +73.5%, males +113.1%). Population estimates from 2011 onwards were obtained from the ABS population projection Series B that is based on the 2011 census and trends in fertility rates, life expectancy at birth, and migration, and most closely reflects recent trends.

Statistical analysis. Annual sex- and age-specific incidence rates (per 100,000 person-years) were determined using the population data obtained from population census of the ABS. In non-census years, population estimates from ABS were used. The annual age- and sex-specific incidence rates of stroke survivors and HFs were based on the numbers in 5-age groups. Then we calculated incidence rates of post-stroke HF for three age groups: 60–69, 70–79 and ≥80 years. The rates were also determined for haemorrhagic and ischaemic stroke subtypes. Assuming a Poisson distribution of the number of post-stroke HFs, 95% confidence intervals (CI) for the rates were calculated and the difference between incidence rates was tested.

To look into the overall trend in post-stroke HF incidence rates, sex-specific age-standardized incidence rates were calculated by the direct method using the Australian 2006 population aged ≥60 years as the standard. We also estimated in each calendar year the post-stroke HF sex-specific standardized incidence rate as a percentage of the stroke survivors incidence rate and calculated the mean over the 11-year period (1999/2000–2009/2010). Group differences were analyzed using Student's t-test for continuous variables and chi-squared tests for categorical variables. The analyses on the association of age, gender and stroke type with time to post-stroke HF were also performed using Kaplan-Meier analysis and log-rank statistics. In addition we performed survival analyses using Cox proportional hazards with correction for age, gender and stroke type.

The secular changes in post-stroke HF incidence over the study period were examined with a Poisson regression model in which time was considered an independent variable, whereas age and sex were covariates. The Poisson regression model used to estimate the number of post-stroke HF (PSHF) was:

$$\text{PSHF}(x_1; x_2) = e^{a + b_1 x_1 + b_2 x_2}$$

where x_1 is the age in years and x_2 the year of post-stroke HF occurrence.

To project the number of post-stroke HF in 2021 and 2051 we applied age- and sex-specific post-stroke HF incidence rates to the Australian population projections (ABS Series B "medium" data) assuming that incidence rates would remain stable at the average level in the first decade of the 21st century. Separate predictions for males and females and for three age groups (60–69, 70–79, and ≥80) were made.

The data were analyzed using the Stata software version 10 (StataCorp, College Station, TX, USA). All statistical tests were 2-sided and the level of significance was $P < 0.05$.

The study was approved by the ACT Health Human Research Ethics Committee.

Results

Epidemiology of post-stroke hip fracture. Over the studied period (from 1999/2000 to 2009/2010), in the ACT, there were 2228 first-ever stroke hospitalized patients (1111 men, 1117 women) aged 60 years and over; 150 recurrent stroke events which occurred in 131 patients (2–5 stroke events in each person) were not included. From the analysis we also excluded 444 (19.93%) subjects who died (205 men and 239 women). The final sample included 1784 discharged alive first-ever stroke patients aged ≥60 years (9662 patient-years). The cases were classified as cerebral infarction (74.9%) and intracerebral (21.5%) or subarachnoid (3.6%) haemorrhage. No difference in incidence of cerebral infarction and haemorrhagic stroke subtypes between genders was observed. The distribution of stroke subtypes did not change over time.

The total mean duration of follow-up was 5.1 ± 3.1 (SD) years: in females 5.2 ± 3.1 years and in males 5.1 ± 3.1 years. There were 878 (49.2%) females and 906 (50.8%) males providing a female to male (F:M) ratio of 0.97. However, amongst 60–69 year old survivors 62.3% were men (F:M ratio 0.60), while in the ≥80 years old group 55.0% were woman (F:M ratio 1.22). The mean age at stroke in the study population was 77.2 ± 8.7 years. Females were significantly older (78.6 ± 8.7 vs. 75.9 ± 8.6 years, $p < 0.001$).

In total, over the study period among 1784 stroke survivors HF was recorded in 61 (3.42%) subjects, in 40 women and 21 men, indicating a HF incidence rate of 6.31 (95% CI 6.02–6.70) per 1000 stroke person-years. Table 1 displays in the aged ≥60 years the standardized incidence rates of post-stroke HF compared to the rates of stroke survivors and HF for the whole study period. Although the total incidence rates for stroke survivors and HF in the elderly were comparable, men exhibited a 1.74 times higher rate for stroke, while women had a 1.60 times higher rate for HF. The F:M ratio for incidence rates among the stroke survivors was 0.83, and among subjects with HF was 2.31. The average annual incidence rate of HF among stroke survivors was 1.45 times higher than in the general population (631.3 vs. 436.5 per 100,000 person-years). The standardized annual post-stroke HF incidence rate in women was 1.7 times higher than in men (18.9 vs. 11.1 per 100,000 person-years, $p = 0.008$). The average annual post-stroke HF incidence rate as a percentage of the total stroke survivors incidence rate was 3.9%, for males 2.6% and for females 5.1%. On the other hand, the average annual post-stroke HF incidence rate as a percentage of the total HF incidence rate was 3.5%, for males 4.3% and for females 3.2%. These indicate that in the elderly post-stroke population the incidence (and risk) of HF is about 2 times higher in females than in men, but among the older subjects with HF the relative incidence rate of stroke survivors is higher for men. The Kaplan-Meir survival analysis showed that the risk of post-stroke HF in females is significantly higher than in men (Fig. 1A) and the Cox proportional hazard analysis confirmed that it is 2 times higher (HR = 1.96, 95% CI 1.15–3.32, $p = 0.013$).

The incidence rates of stroke survivors (per 100,000 person-years) increased exponentially with advancing age

Table 1. Age- and sex-adjusted and standardized (to 2006 Australian population) incidence rates (per 100,000 person-years) of stroke survivors, hip fractures (HF) and post-stroke HF in the elderly population (≥60 years) of ACT (1999/2000–2009/2010).

PATIENTS GROUP	MALES	FEMALES	TOTAL	P VALUE (M-F)
Stroke survivors	447.5 ± 56.9	371.3 ± 62.8	402.1 ± 50.1	0.002
Hip fracture	257.0 ± 43.2	594.5 ± 128.3	436.5 ± 86.4	0.001
Post-stroke HF	11.1 ± 10.6	18.9 ± 16.5	15.3 ± 13.1	0.016
*Post-stroke HF, %	2.6 ± 2.5	5.1 ± 4.4	3.9 ± 3.3	0.008

*The average annual post-stroke HF incidence rate as a percentage of the stroke survivors incidence rate.
Data presented as mean ± SD.
Abbreviation: HF, hip fracture.

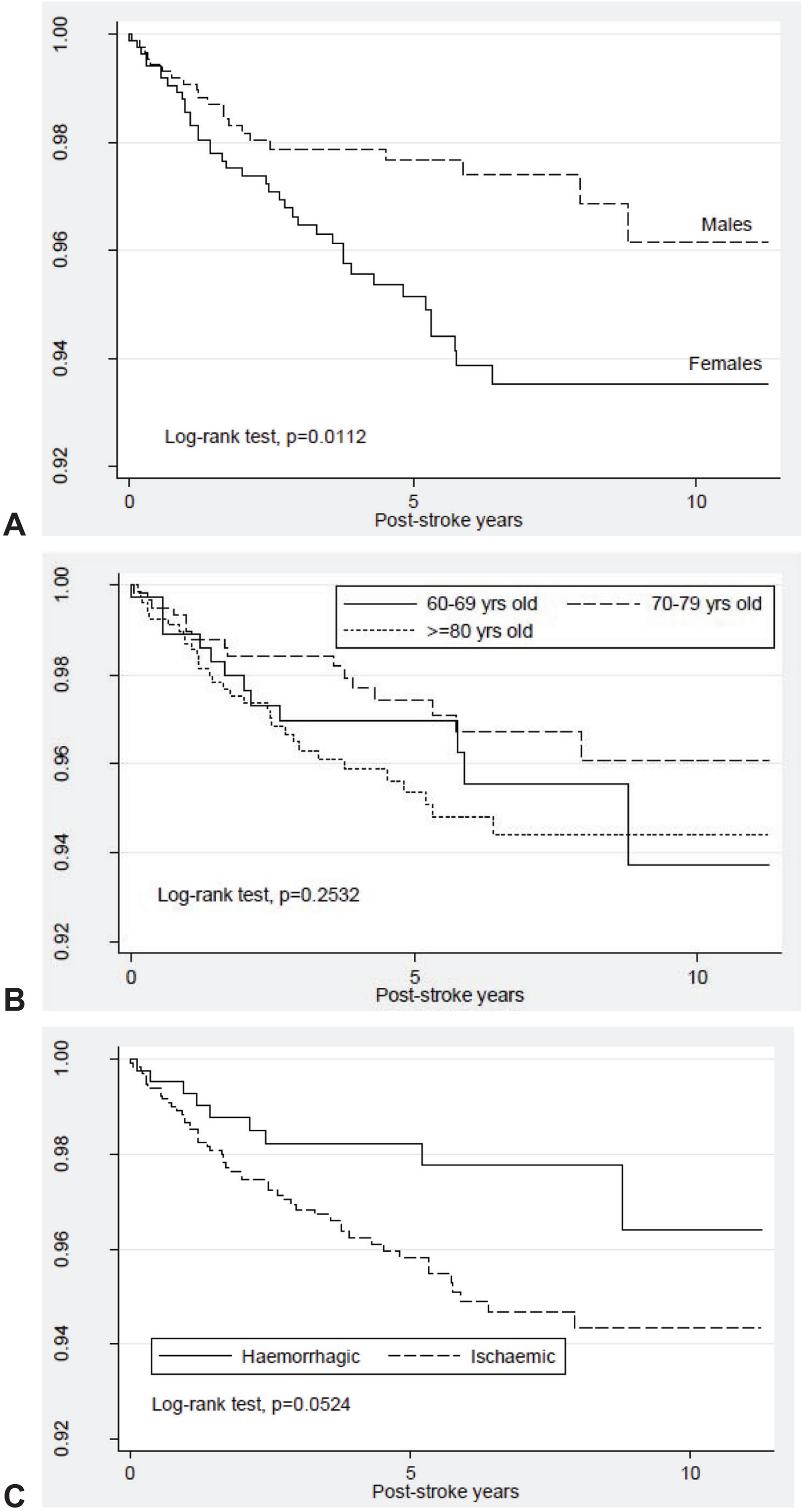

Figure 1. Kaplan-Meier analysis [survival curves of time to HF] of post-stroke hip fracture by gender (**A**), age (**B**) and stroke type (**C**).

in both sexes from 154 in 60–69 year old to 406 in aged 70–79 years and to 1000 in the ≥80 years old. In all three age groups the incidence rates were significantly greater in men than in women (F:M ratio 0.58, 0.82 and 0.70, respectively). While among stroke survivors men dominated, there were more women among subjects with post-stroke HF aged 70–79 years (F:M ratio 1.71) and aged ≥80 years (F:M ratio 1.78), suggesting that at younger ages post-stroke women are protected from HF (F:M ratio 0.73). As shown in Table 2, the standardized incidence rates of post-stroke HF in both sexes were low before 70 years of age, rose exponentially with increasing age, and in the oldest group compared to the aged

Table 2. Standardized incidence rates of post-stroke hip fracture (per 100,000 person years) in the elderly by age and sex.

AGE GROUP (YEARS)	FEMALES		MALES		P VALUE
	MEAN	95% CI	MEAN	95% CI	
60–69	4.73	3.61–5.86	6.50	5.06–7.95	<0.001
70–79	12.50	10.17–14.83	7.32	5.29–9.35	<0.001
≥80	47.54	42.39–52.69	26.65	21.45–31.85	<0.001

60–69 years the incidence in females was about 10 times higher, while in males only 4 times higher. Cox proportional hazards analysis showed that age ≥75 years was associated with near 2 times higher HF occurrence (HR = 1.89, 95% CI 1.05–3.38, p = 0.033). More than one-half (52.5%) of post-stroke HFs occurred in the aged ≥80 years, and three forth of these age group patients were women.

Post-stroke HF occurred within the first year in 32%, within two years in 59.0%, within three years in 72.1%, within 5 years in 85.3% and within 7 years in 96.7%. The mean time of HF occurring after the stroke was 2.34 ± 2.08 years and it did not differ significantly by age of stroke survivors neither in women, nor in men (Table 3). There was no significant difference in the mean time to post-stroke HF between patients with an ischaemic (2.30 ± 1.96 years) and haemorrhagic stroke (2.51 ± 2.79 years, p = 0.790), but the Kaplan-Meir survival analysis (Fig. 1C) indicated that risk of HF was possibly greater for survivors after an ischeamic stroke compared with haemorrhagic one (p = 0.052), and did not differ by age (Fig. 1B).

In order to investigate whether age, gender and stroke type were independently associated with time to post-stroke HF, we performed Cox proportional hazards analysis. When all data were entered in a single model, female gender (HR = 1.93, 95% CI 1.13–3.30, p = 0.016) was associated with time to post-stroke HF and ischaemic stroke (HR = 1.98, 95% CI 0.97–4.02, p = 0.059) tended to be associated with this outcome, but age was not associated when analyzed either as a continuous (p = 0.728), or as a categorical variable (p = 0.078).

Taken together, post-stroke HF occurs on average within the first 2.3 years, in total about 2 times more often in women, in the aged 75 years and above, and in survivors after an ischaemic stroke, but age *per se* does not affect the time to HF.

Table 3. Mean time (years) to post-stroke hip fracture by age and gender.

AGED GROUP (YEARS)	FEMALES (n = 40)	MALES (n = 21)	BOTH SEXES (n = 61)
60–69	2.19 ± 2.17	2.78 ± 3.00	2.55 ± 2.63
70–79	2.86 ± 1.96	2.20 ± 3.25	2.65 ± 2.34
≥80	2.26 ± 1.79	1.60 ± 1.40	2.09 ± 1.71
Total	2.41 ± 1.85	2.19 ± 2.50	2.34 ± 2.08

Temporal trends. Since survival after stroke is an important factor in determining the trends in post-stroke HF, data on the standardized annual incidence rates of stroke survivors and HF in those aged ≥60 years during the 11-year observation period are given in Figure 2. During the 11-year period, despite annual variations, there was a trend for the incidence of HF to decline in both women and men (mean annual decrease: in total −4.0%, in women −4.7% and men −3.8%) and for the incidence of stroke survivors to increase (annually +1.9% in total, +1.3% for women and +2.4% for men). Because of an increase in stroke survivors it could be expected to result in an increase in post-stroke HF incidence. In contrast to such expectation, the absolute number of post-stroke HF, in general steadily decreased among both men and women. In the last three years studied (2007/2008–2009/2010) compared to the first three (1999/2000–2001/2002), the temporal sex-specific age-adjusted standardized incidence rates substantially declined: in total by 77.2% (from 29.65 to 6.77 per 100 000 person-years), in females by 77.7% (from 38.77 to 8.65 per 100 000 person-years), in males by 75.1% (from 18.80 to 4.67 per 100 000 person-years).

The influence of age and calendar stroke year on the number and incidence rates of post-stroke HF in the 11-year period was further examined by Poisson regression analyses (Tables 4 and 5). These models explore the combined effects of age (in 10-year intervals) and the calendar period of stroke onset. Generally, the absolute number of post-stroke HF increased with increasing age (b_1) and decreased with time of stroke (b_2) by 4.6% and 14.0%, respectively (Table 4). However, stratification for sex revealed that changes related to these factors were statistically significant only in women but not in men. In women, the absolute number of post-stroke HF increased by 7.3% with each 10 years of age (p = 0.001), and decreased by 15.7% (p = 0.003) with each calendar year of stroke (b_2). The lack of significance in men (who demonstrated a similar direction of changes with calendar period) may be due to fewer cases and insufficient statistical power (rather than indicating gender difference).

In other words, in women the decreased number of post-stroke HF during the study period was influenced by the calendar year of the stroke, despite the increases with increasing age, while in men both factors (especially the year) have negative effects, which, however, were not statistically significant.

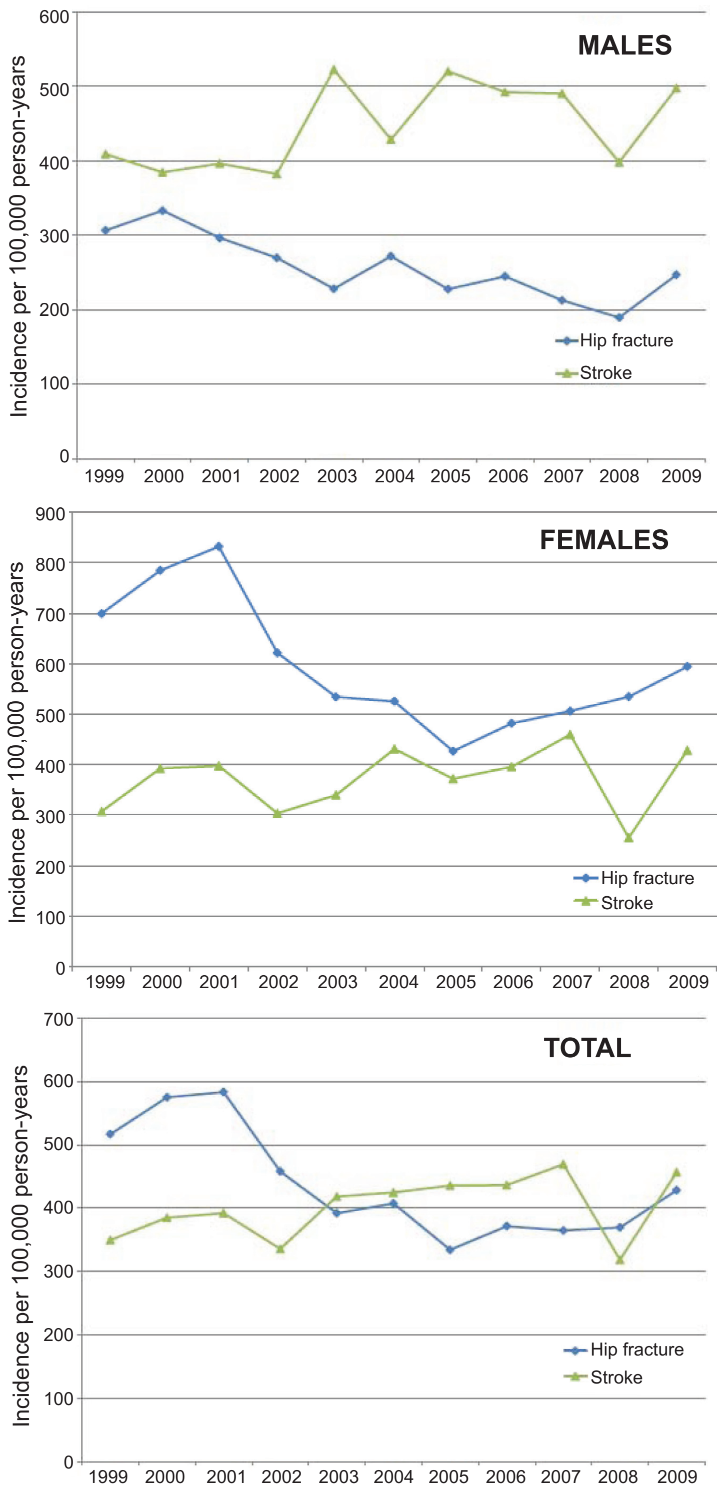

Figure 2. Secular trends in stroke survivors and hip fracture incidence rates. Age- standardised (to the 2006 Australian population) incidence rates (per 100,000 person-years) in males (**1**), females (**2**) and total (**3**) in the elderly ACT population (≥60 years), 1999–2000 to 2009–2010.

The incidence rates of post-stroke HF in both sexes increased with ageing but decreased to a larger degree with stroke year, in total by +11.4% and –17.9%, respectively, in females by +12.4% and –18.8%, in males by +9.0% and –15.8% (Table 5). According to the model for the sex-specific incidence rates, explained variances were moderate (R^2 0.28 –0.46).

Post-stroke hip fractures forecasts and economic impacts in Australia. These data were generated under the assumptions that the post-stroke HF incidence rates for those aged ≥60 years in the ACT region are reflective of the national Australian stroke survivors' incidence rates and that age- and sex-specific post-stroke HF incidence rates would remain the

Table 4. Influence of age and calendar year on the number of hip fractures in stroke survivors during the 11-year period (1999/2000 to 2009/2010) in men and women (Poisson regression analysis).

	FEMALES	MALES	TOTAL
Intercept	309.8294	314.2914	276.9193
Age (b_1)	0.0734	−2.4600	0.0458
SE (b_1)	0.0220	0.0267	0.0165
P value	0.001	1.000	0.006
Year (b_2)	−0.1574	−0.1072	−0.1397
SE (b_2)	0.0538	0.0714	0.0429
P value	0.003	0.133	0.001
R^2	0.1905	0.0322	0.1342

same over next 40 years (average for 1999/2000–2009/2010 period for each age group). The numbers of projected post-stroke HFs for the years 2021 and 2051 are based only on demographic changes (Table 6). These forecasts suggest that in Australia, compared to 2011, the total number of post-stroke HF patients aged ≥60 years may increase by 32.4% in 2021 (+30.2% in females and +36.7% in males) and by 162.5% in 2051 (+161.9% in females and +163.8% in males), of which 83.8% in 2021 and 86.6% in 2051 will be aged ≥70 while 55.2% and 67.4% will be ≥80 years, respectively. The gender distribution of post-stroke HF patients indicates that the F:M ratio among 60–69 (on average 3 women for every four men) and 70–79 year old (2 women for every man) post-stroke HF patients will not change, but among those aged 80 and above the F:M ratio will decrease from 2.76 in 2011 to 2.48 in 2021 and to 2.30 in 2051.

In 2021 post-stroke HF patients aged 70–79 years are predicted to have the largest increase (+55.6% in men and +50.6% in women), while in 2051 the greatest increase will occur in the ≥80 years old (+250.5% and +192.4%, respectively). This is likely due to the fact that the baby boom generation will reach age >70 at year 2021. Figure 3 shows the projected changes in absolute number of post-stroke HFs in 2021 and 2051 as a percentage to the numbers in 2011.

Table 5. Influence of age and calendar year on the incidence rates of post-stroke hip fractures (per 100,000 person-years) during the 11-year period (1999/2000 to 2009/2010) in men and women (Poisson regression analysis).

	FEMALES	MALES	TOTAL
Intercept	369.6300	313.0109	352.1499
Age (b_1)	0.1236	0.0899	0.1137
SE (b_1)	0.0061	0.0066	0.0063
P value	<0.001	<0.001	<0.001
Year (b_2)	−0.1878	−0.1584	−0.1788
SE (b_2)	0.0126	0.0152	0.0134
P value	<0.001	<0.001	<0.001
R^2	0.4643	0.2806	0.4588

To evaluate the potential social and economic burden of the number of post-stroke HF we tried to quantify the costs. Currently no Australian data on the costs of post-stroke HF are available. However, it was reported that mean cost per hospital episode of HF ranges between AU $13,012[25]–AU $15,984[41] and AU $26,023,[42] on average AU $15,500–AU $19,500 for procedures such as partial joint replacement.[25] No significant difference in costs between men and women was found.[41] It has also been estimated that direct hospital costs comprised only about 32% of the total cost. Assuming that hospital treatment of one post-stroke HF on average is also costing AU $13,012 (lowest estimated mean value), and this comprises 32% of total annual costs, each additional HF translates to an increase of AU $40,662 per year. Extrapolation of these data and applying the estimates to our projections suggest that the predicted annual post-stroke HF costs in Australia may reach AU $32,042,050 in 2021 and AU $65,710,600 in 2051. It should be, however, noted that these estimates are minimal as they do not account the history of stroke and that a significant percentage of these patients require long term residential care.

Although our data demonstrated a trend of marked annual decrease in post-stroke HF incidence rates for women and men, we did not use these results for the future forecasts because the number of cases each year was low, with substantial random variation; obviously, studies of larger populations are required before average annual percent change can be used for projections of future HF among the stroke survivors. If the incidence trends observed in Australia in the beginning of the 21st century continues, a levelling off or even decrease in the absolute number of post-stroke HF among the older adults may be expected, despite population ageing and increases in the number of stroke survivors; under such tendency scenario the health care costs should be revised.

Discussion

Main findings. This study has demonstrated that in the ACT, over the past decade in older (>60 years) stroke survivors HF was common, occurred on average 2.3 years after the stroke and tended to develop more often and earlier after an ischaemic stroke. The standardized incidence rate of post-stroke HF was near 2 times greater in women compared with men, and in the oldest group (>80 years) compared to aged 60–69 years was 10 times higher for women and 4 times higher for men. The overall incidence of post-stroke HF in the elderly has decreased. In coming decades, the total number of post-stroke HF patients and their proportion among all subjects sustaining a HF could be expected to increase due to ageing of the population (assuming that the average age- and sex-specific incidence rates of post-stroke HF observed during the study period remain unchanged).

Post-stroke hip fracture incidence rates in the first decade of the 21st centure. Stroke increases the risk of falls,

Table 6. Forecast number of post-stroke hip fracture patients aged ≥60 years in Australia to 2021 and 2051 (incidence rates unchanged, similar to the average from 1999/2000 to 2009/2010).

AGE GROUP	FEMALES			MALES			TOTAL			F:M RATIO		
	2011	2021	2051	2011	2021	2051	2011	2021	2051	2011	2021	2051
60–69	52	67	89	71	88	121	123	155	210	0.73	0.76	0.74
70–79	85	128	193	45	70	106	130	198	299	1.89	1.83	1.82
≥80	251	310	734	91	125	319	342	435	1053	2.76	2.48	2.30
Total	388	505	1016	207	283	546	595	788	1562	1.87	1.78	1.86

accelerates muscle weakness, bone loss and subsequently leads to fractures.[43–55] Not surprisingly, during the 11-year study period the incidence rate of HF in our cohort of stroke survivors was 1.4 times the rate in the general population. This is comparable with a 1.7 times increase in post-stroke HF incidence observed in Scotland,[1] 1.7–2.3 in Taiwan,[15] 1.9 in the North Carolina,[5] 2.0 in The Netherlands[3] and 2–4 in Sweden,[4] but much lower than a >7-fold increase reported in another Swedish study.[2] On the other hand, no statistically significant difference in fracture rates between post-stroke patients and controls or between persons with and without self-reported history of stroke[5] were observed in Minnesota, US[7] and in Iowa, US.[5]

The post-stroke HF incidence of 6.31 per 1000 person years in our study is comparable to 7.0 per 1000 person-years reported by Dennis et al,[1] but lower than 17,[4] 19.8[2] and 32[56] per 1000 person-years reported by others.

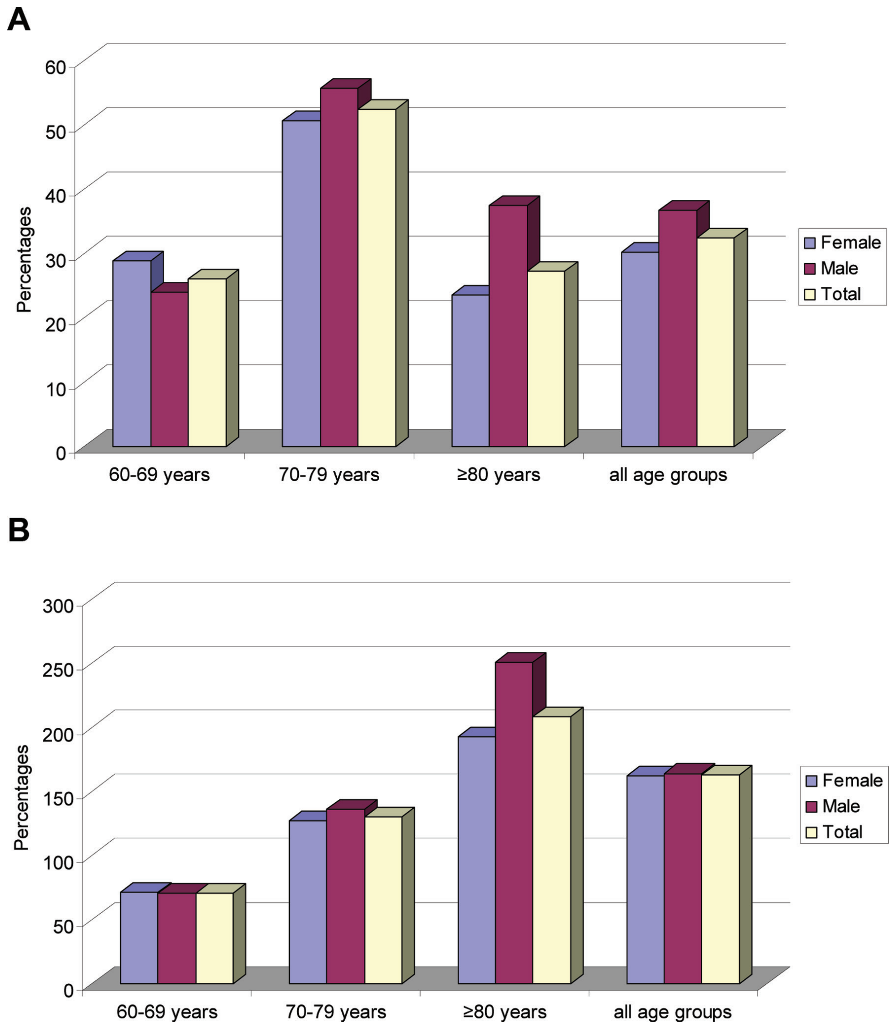

Figure 3. Projected trends [change] between 2011 and 2051 of the number of post-stroke hip fracture patients in Australia by gender and age (percentages in relation to 2011). **A**–2021, **B**–2051.

In published studies, the cumulative incidence of HF at 3 years post-stroke was about 3%,[39,48,54] at 5 years 9.5%–10%[39,57] and by 10 years 10.6%.[1] These differences in reported fracture rates might be explained by case selection, patients' age, rehabilitation and prevention schemes, medication used and environmental factors. Looked at another way, in Australian older adults, age- and sex-adjusted and standardized incidence rates of post-stroke HF (per 100,000 person-years) is 15.3 ± 13.1 (SD) which corresponds to 3.9% of stroke survivors incidence rate and 3.5% of HF incidence rate. It has to be mentioned that in addition to the differences in study design and case ascertainment methods, the high SD and wide confidence interval may explain, at least partly, the reported "differences" in incidence rates in the literature. Therefore, these figures, although confirming the markedly higher risk of HF after stroke, should be interpreted cautiously in respect to its magnitude. More importantly, the incidence rates should be considered in regard to age and gender: breakdown by age and sex demonstrates the marked increase with age and the predominance of women.

In our study, the mean time of HF occurring after the stroke was 2.34 ± 2.08 years and it did not differ significantly by age of stroke survivors neither in women, nor in men. About ¾ of post-stroke HFs occurred within the first three years: 32% in the first year, 59.0% at two years and 72.1% at three years. This is in accordance with other data showing higher HF incidence throughout the first 2–3 years after the stroke,[1,39,54,56,58] although some studies reported the highest incidence within the first year with a rapid decrease thereafter.[2,3]

Post-stroke HF, as shown in ours and other studies,[1,3,15,39,54] is 2-times more common among females, although in general stroke is more common in males (at least among <80–84 years of age),[59–62] and in our sample as in some others[63,64] the incidence rates of stroke survivors in males were higher than in female across all age groups. Interestingly, the gender distribution of HF following a stroke mirrors HF distribution in the general population: in both cohorts roughly 70% of HF occurs in women. Moreover, in this study the influence of age on post-stroke HF incidence was greater in women than in men. Post-stroke patients aged >80 years, compared to the 60–69-year-old, showed an increased incidence rate of HF of 10 times in women and 4 times in men. In previous studies older age was also associated with increased risk of post-stroke HF.[39,56] However, in some reports, HF rate after stroke compared with that in the general population was highest in patients <69 years of age,[1] patients younger than 70 had a 23-fold increased risk for HF[3] and women aged 50 to 54 years at time of stroke had a 12-fold risk of HF in the first post-stroke year.[2]

Our observations of female preponderance in post-stroke HF among those aged >70 years and a greater age effect in females than in males are in line with higher F:M ratio in the general population as age increases, higher falls rates,[65] lower bone mineral density (BMD) and higher prevalence of osteoporosis in women compared with men,[37,66] as well as with increased bone loss following stroke in women compared to men, especially with prolongation of the post-menopause period.[43,67,68] The data indicates that the development of low-energy post-stroke HF in women and men is influenced by different mechanisms and provides evidence that the phenomenon of lower BMD/osteoporosis in females at stroke onset and more severe bone loss thereafter results from the effects of altered sex hormone exposure and factors intrinsic to the sex chromosomes, suggesting that this group of stroke survivors requires specific interventions. Although postmenopausal hormone therapy for osteoporosis is controversial and the use of estrogens is supported only by some groups,[69] recent publications provide new evidence of the protective effects against HF of hormone therapy and these are augmented by calcium and vitamin D supplementation.[70] The critical role of α-oestrogen receptors in bone homeostasis and the preventive effect of selective agonists of these receptors have been shown in ovariectomized rats.[71,72] Both low serum free oestradiol levels[73–75] and α-oestrogen receptor-mediated activity are associated with osteoporotic HF.[75] On the other hand, while debate on risks and benefits of menopausal hormone therapy for stroke prevention continued over the last decade,[76,77] emerging data emphasized the neuroprotective effect of oestrogens[78] and increased risk of cerebral ischaemia in animal models with long-term oestrogen deprivation and loss of α-oestrogen receptor.[79–81] This complex issue deserves further intensive research to determine timing of initiation, safety and efficacy of formulation, dose (e.g. low-dose transdermal hormone therapy, selective oestrogen receptors modifiers) and duration. In this context in the meantime, exogenous oestrogens such as soy phytoestrogens,[82] although less effective than hormone therapy,[83] may be considered, among other interventions, in treatment of post-menopausal women. Notably, at the end of the study period, in 2010, the age group of ≥80 years comprised 4.04% of the total ACT population (3.20% among men and 4.85% among women), accounted for 44.5% of stroke survivors (39.4% among men and 49.8% among women) and 52.5% of post-stroke HFs (three quarters of whom were women).

Analyzing time of HF after the stroke in regards to the age, gender and stroke type (multivariate Cox regression), we found that gender (females) and possibly stroke type (ischaemic) but not the age of stroke survivors predict earlier occurrence of HF. In one recent study, post-stroke risk of HF did not differ by stroke type, but risk of any fracture was significantly greater for haemorrhagic compared with ischaemic strokes;[39] this association was not reported by others.[1,54]

Temporal trends. Time trends of post-stroke HF should be considered in relation to the trends in incidence rates of both HF and stroke survivors. Changes in survival rates may, obviously, contribute to HF incidence rate, especially in the elderly susceptible to osteoporosis before the stroke. Large geographic variations in incidence rates and divergent temporal trends of both HF and stroke further emphasize the importance of an integrative analysis in order to obtain comprehensive data. However, the few previous epidemiologic studies evaluated post-stroke HF separately, and comparable time trends of age- and sex-specific standardized post-stroke HF incidence rates are currently not available.

Our results show that in the ACT during the 11-year period there was a significant trend for the incidence rates of HF (in the general population) to decline (annually in total by 4.0%) and for the incidence of stroke survivors to increase (annually by 1.9% in total), but the first trend was more pronounced in females (4.7% vs. 3.8%), while the second in males (2.4% vs. 1.3%). The incidence rates of post-stroke HF decreased in total by 17.9% (in females by 18.8%, in males by 15.8%). Our data on declining HF incidence rates and a greater decrease in age-standardized HF incidence among females compared with males are comparable to those reported in other Australian states[25,26,28,29,84] and New Zealand,[85] as well as in many developed countries,[10,14,86–97] although a levelling off or even an increase was observed in other countries,[15,88,98–105] especially in the oldest.[106,107] A sex-specific difference in HF incidence trends (decrease in women but not in men) was observed in some studies.[90,108]

Similarly, data on secular trends of stroke incidence rates are also conflicting[17] with declining,[23,109–116] stable[23,24,117–119] or increasing incidence[21,120,121] reported. Some[122,123] found sex-specific changes in stroke incidence rates (decreased in men but unchanged in women), other demonstrated trends for older age and toward milder strokes.[124] In Australia, over recent decades the number of hospitalisations for stroke remained stable, and there was an annual reduction of 4.0% in mortality rate.[30] The decline in stroke mortality, which was also observed in Western Europe and North America,[24,118,125] together with population ageing may explain the rise of the number and incidence rates of stroke survivors observed in this study. Therefore, an increase in the proportion of stroke survivors among the HF population can be expected.

Our study has encouragingly shown that in the new millennium the standardized incidence rates for stroke survivors tended to increase and rates for HF (total) significantly declined. In this circumstance, one would expect an increase of post-stroke HF. However, we found that the incidence rates of post-stroke HF were declining. This may seem especially puzzling given that stroke is frequently associated with limb weakness, spasticity and cognitive decline, accelerates bone and muscle loss,[44,126–129] increases the risk of falls,[8,45,130,131] and subsequently leads to fractures. While increased survival reflects success of stroke treatment, the decreasing incidence of post-stroke HF may indicate improvement in post-stroke management of HF risks (secondary prevention). However, the divergent time trends in the incidence rates of stroke survivors and HF makes a definitive explanation for the rates of post-stroke HF difficult indicating the complexity of the interactions between biological, behavioural, environmental and socioeconomic factors in development of HF after a stroke. Of interest, in The Netherlands, a remarkable decline in ischaemic stroke mortality after 2000 (in all age-sex groups, except for young men) was not matched by a decline in the number of stroke survivors which slightly increased.[23]

Potential explanations for the decrease in HF incidence[26,29,132] include increase in antiosteoporotic pharmacotherapy,[89,96,133] changes in lifestyle risk factors (reduced prevalence of smoking), and a cohort effect (improved nutrition, the protective effect of raised body mass index [BMI], reduction in falls risk.[14,85,134] Of note, the osteoporotic treatment does not fully explain the temporal reduction in HF incidence,[10,92,94,96] especially in men, indicating the significant contribution of other factors, which are still unknown, and should be identified in further research.

Of modifiable risk factors (diagnosis and treatment of hypertension and diabetes, reduction in cigarette smoking, and general improvements in lifestyle) attributed to decline in stroke incidence and mortality rates in high-income countries,[17,125] improvements in blood pressure control at the population level has been recognized as a consistent and powerful in some[135,136] but not all studies.[123] Although stroke and HF share several risk factors (older age, cigarette smoking, BMI), it should be acknowledged that the prevalence and importance of these factors may be different for the two diseases as the magnitude and direction of current changes are different for men and women (for instance, smoking rates decrease more in males, while systolic blood pressure trends are associated with stroke trends in women, but not in men,[122,123]) and the benefits of controlling some of the risk factors (hypertension, smoking) might be negated by increasing incidence of other (increased BMI).

Projections. The worldwide burden of stroke from 2002 to 2030 is predicted to increase due to population ageing and increased life expectancy.[137] In Australia in coming decades a significant increase in older stroke survivors is predicted.[31] Assuming that the average age- and sex-specific incidence rates of post-stroke HF observed during the study period remain unchanged and adopting population projections, in Australia in 2021 and in 2051, compared to 2011, there will be a 32.4% and 162.5%, respectively, increase in the number of patients with post-stroke HF. Based on our previous estimates and forecasts for osteoporotic HF in older Australians,[138] the proportion of post-stroke HF among all HF between 2011 and 2021 may increase from 5.0% to 7.8% (7.7% for females and 8.1% for males). It is predicted that post-stroke patients will represent a substantial and growing component among the elderly with HF. Importantly, while in Australia as in other developed countries, HF rates over the last two decades have decreased for both men and women, the number of fractures continues to rise as the population ages. Our data indicates that post-stroke patients will represent a substantial and growing segment among the total population of elderly with HF.

Economic impacts. Worldwide, despite the variability in estimates, HF was identified as the most expensive fracture type,[139–142] especially high for the elderly, with medical costs higher than for all other osteoporosis-related fractures combined.[143] A recent review found that in the year following a fracture, medical and hospitalization costs were 1.6–6.2 higher than pre-fracture costs and 2.2–3.5 times higher than those for matched controls.[140] The burden of HFs is comparable to that of strokes,[121] but no data on post-stroke HF costs is currently available. However, it was shown that HF patients with muscle atrophy/weakness had significantly higher total health care costs[144,145] and each increase in American Society of Anaesthesiologists (ASA) classification doubles the daily hospital costs for elderly patients with HF.[146] Our data show that due to demographic transition post-stroke HFs in 2021 and 2051, compared to 2011, may increase by 32.4% and 162.5%, respectively, with corresponding increases of the financial burden to the society. Based on the mean HF costs in Australia during the first year after the event (at least AU $40,662.5) we estimated that annual costs for post-stroke HF in Australia may reach AU $32,042,050 in 2021 and AU $65,710,600 in 2051. These cost estimates are minimal as they do not account the patients' pre-fracture stroke-related disability, comorbidities and the often need of long term residential care (as disability may persist permanently), factors that significantly increase the total health care costs. Of note, Australian cost estimates per HF patient appear to be consistent with international reports, which considered hospitalization costs between $US 8,358 and $US 32,195[140] and average cost in the first year following a HF Canadian $46,664.[147]

The reported results and projections highlight the need of strategies to prevent post-stroke HF[148] and may have a potential of contributing to healthcare planning and resourcing for the elderly, in whom both HF and stroke remain major public health problems.

Strength/Limitations

This study is novel in that it analyzed data on incidence and secular trends for post-stroke HF, stroke survivors and HF (in total) in the population aged >60 years in ACT, Australia, a well-defined area, over the last 11 years. The population-based design, complete inclusion of all hospitalized stroke survivors and post-stroke HF patients and exclusion of transfers and readmissions provided the opportunity to minimize the selection bias. The case ascertainment should be near complete, because in Australia all cases of HF are hospitalized and the stroke admittance rate is also high.[30,149,150] There are, however, several limitations that should be considered. First, our findings are limited to one Australian territory with predominantly Caucasian population and may not be representative in other ethnic populations. Second, we were unable to investigate the possible contribution to post-stroke HF trends of stroke severity, cognitive status, co-morbidities, pre-fracture function, BMI, anti-osteoporosis medication or hip protectors use, as well as the socio-economic status. Third, although we used the entire ACT population, the number of post-stroke HFs each year was low, with substantial random variation. We were able to demonstrate a significant annual decrease in post-stroke HF throughout the 11-year period, but did not use these data for forecasts, because the statistical power of this study is limited by its small sample size indicating that larger populations are required.

Conclusions

Post-stroke HF is relatively common, prevalent in women and occurs on average within 2.3 years after the stroke. The incidence of post-stroke HF in elderly people is decreasing. However, because of population ageing and increasing number of stroke survivors, the absolute number of post-stroke patients sustaining a HF and their proportion among the total HF population could be expected to increase.

Author Contributions

Conceived and designed the experiments: AF. Analysed the data: AF, JM, WS. Wrote the first draft of the manuscript: AF. Contributed to the writing of the manuscript: WS, PS. Agree with manuscript results and conclusions: AF, JM, WS, PS. Jointly developed the structure and arguments for the paper: AF, JM, WS, PS. Made critical revisions and approved final version: AF, JM, WS, PS. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

REFERENCES

1. Dennis MS, Lo KM, McDowall M, West T. Fractures after stroke: frequency, types, and associations. *Stroke; a Journal of Cerebral Circulation*. 2002;33(3): 728–734.
2. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke; a Journal of Cerebral Circulation*. 2001; 32(3):702–706.
3. Pouwels S, Lalmohamed A, Leufkens B, et al. Risk of hip/femur fracture after stroke: a population-based case-control study. *Stroke; a Journal of Cerebral Circulation*. 2009;40(10):3281–3285.
4. Ramnemark A, Nyberg L, Borssen B, Olsson T, Gustafson Y. Fractures after stroke. *Osteoporos Int*. 1998;8(1):92–95.

5. Colon-Emeric CS, Pieper CF, Artz MB. Can historical and functional risk factors be used to predict fractures in community-dwelling older adults? development and validation of a clinical tool. *Osteoporos Int.* 2002;13(12): 955–961.
6. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *The New England Journal of Medicine.* 1995;332(12):767–773.
7. Melton LJ, 3rd, Brown RD, Jr., Achenbach SJ, O'Fallon WM, Whisnant JP. Long-Term fracture risk following ischemic stroke: a population-based study. *Osteoporos Int.* 2001;12(11):980–986.
8. Ramnemark A, Nilsson M, Borssen B, Gustafson Y. Stroke, a major and increasing risk factor for femoral neck fracture. *Stroke; a Journal of Cerebral Circulation.* 2000;31(7):1572–1577.
9. Barbier S, Ecochard R, Schott AM, et al. Geographical variations in hip fracture risk for women: strong effects hidden in standardised ratios. *Osteoporos Int.* 2009;20(3):371–377.
10. Cooper C, Cole ZA, Holroyd CR, et al. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos Int.* 2011;22(5):1277–1288.
11. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. *Indian Journal of Orthopaedics.* 2011; 45(1):15–22.
12. Johnell O, Borgstrom F, Jonsson B, Kanis J. Latitude, socioeconomic prosperity, mobile phones and hip fracture risk. *Osteoporos Int.* 2007;18(3):333–337.
13. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int.* 2012;23(9):2239–2256.
14. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Nationwide decline in incidence of hip fracture. *J Bone Miner Res.* 2006;21(12):1836–1838.
15. Wu CH, Liou TH, Hsiao PL, Lin YC, Chang KH. Contribution of ischemic stroke to hip fracture risk and the influence of gender difference. *Archives of Physical Medicine and Rehabilitation.* 2011;92(12):1987–1991.
16. Bejot Y, Rouaud O, Durier J, et al. Decrease in the stroke case fatality rates in a French population-based twenty-year study. A comparison between men and women. *Cerebrovascular Diseases (Basel, Switzerland).* 2007;24(5):439–444.
17. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurology.* 2009;8(4):355–369.
18. Hata J, Kiyohara Y. Epidemiology of stroke and coronary artery disease in Asia. *Circ J.* 2013;77(8):1923–1932.
19. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurology.* 2009;8(4):345–354.
20. Kim AS, Johnston SC. Global variation in the relative burden of stroke and ischemic heart disease. *Circulation.* 2011;124(3):314–323.
21. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology.* 2012;79(17):1781–1787.
22. Mukherjee D, Patil CG. Epidemiology and the global burden of stroke. *World Neurosurgery.* 2011;76(6 Suppl):S85–90.
23. Vaartjes I, O'Flaherty M, Capewell S, Kappelle J, Bots M. Remarkable decline in ischemic stroke mortality is not matched by changes in incidence. *Stroke; a Journal of Cerebral Circulation.* 2013;44(3):591–597.
24. Benatru I, Rouaud O, Durier J, et al. Stable stroke incidence rates but improved case-fatality in Dijon, France, from 1985 to 2004. *Stroke; a Journal of Cerebral Circulation.* 2006;37(7):1674–1679.
25. AIHW. Health expenditure Australia 2008–09. Health and welfare expenditure series no. 42. Cat. no. HWE 51. http://www.aihw.gov.au/publication-detail/?id=6442472450. 2010.
26. Crisp A, Dixon T, Jones G, et al. Declining incidence of osteoporotic hip fracture in Australia. *Archives of Osteoporosis.* 2012;7(1–2):179–185.
27. Fisher AA, Goh SL, Srikusalankul W, Southcott EN, Davis MW. Serum leptin levels in older patients with hip fracture—impact on peri-operative myocardial injury. *The American Heart Hospital Journal.* Summer 2009;7(1):9–16.
28. Pasco JA, Brennan SL, Henry MJ, et al. Changes in hip fracture rates in south-eastern Australia spanning the period 1994–2007. *J Bone Miner Res.* 2011; 26(7):1648–1654.
29. Cassell E, Clapperton A. A decreasing trend in fall-related hip fracture incidence in Victoria, Australia. *Osteoporos Int.* 2013;24(1):99–109.
30. Thrift AG, Tong B, Senes S, Waters AM, Lalor E. No evidence for an epidemic of stroke with the ageing of the population. *Neuroepidemiology.* 2012;38(4):268–273.
31. Fisher A, Martin J, Srikusalanukul W, Davis M. Trends in Stroke Survival Incidence Rates in Older Australians in the New Millennium and Forecasts into the Future. *J Stroke Cerebrovasc Dis.* 2013 Aug 5. doi:pii: S1052-3057(13)00264-4. 10.1016/j.jstrokecerebrovasdis.2013.06.035. [Epub ahead of print]. PMID:23928347.
32. Fisher A, Srikusalanukul W, Davis M, Smith P. Cardiovascular diseases in older patients with osteoporotic hip fracture: prevalence, disturbances in mineral and bone metabolism, and bidirectional links. *Clinical Interventions in Aging.* 2013;8:239–256.
33. Khosla S, Melton LJ, 3rd, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner Res.* 2011;26(3):441–451.
34. McFarlane SI. Bone metabolism and the cardiometabolic syndrome: pathophysiologic insights. *Journal of the Cardiometabolic Syndrome.* Winter 2006;1(1):53–57.
35. Sennerby U, Melhus H, Gedeborg R, et al. Cardiovascular diseases and risk of hip fracture. *Jama.* 2009;302(15):1666–1673.
36. Lee SB, Cho AH, Butcher KS, Kim TW, Ryu SY, Kim YI. Low bone mineral density is associated with poor clinical outcome in acute ischemic stroke. *Int J Stroke.* 2013;8(2):68–72.
37. Jorgensen L, Engstad T, Jacobsen BK. Bone mineral density in acute stroke patients: low bone mineral density may predict first stroke in women. *Stroke; a Journal of Cerebral Circulation.* 2001;32(1):47–51.
38. Mussolino ME, Armenian HK. Low bone mineral density, coronary heart disease, and stroke mortality in men and women: the Third National Health and Nutrition Examination Survey. *Annals of Epidemiology.* 2007;17(11): 841–846.
39. Lisabeth LD, Morgenstern LB, Wing JJ, et al. Poststroke fractures in a bi-ethnic community. *J Stroke Cerebrovasc Dis.* 2012;21(6):471–477.
40. Statistics ABo. 3101.0—Australian Demographic Statistics, June. *http://www.abs.gov.au/ausstats/abs@.nsf/mf/3101.0/.* 2012.
41. Randell A, Sambrook PN, Nguyen TV, et al. Direct clinical and welfare costs of osteoporotic fractures in elderly men and women. *Osteoporos Int.* 1995;5(6): 427–432.
42. Ireland AW, Kelly PJ. Total length of stay, costs and outcomes at final discharge for admitted patients with hip fracture: linked episode data for Australian veterans and war widows. *Intern Med J.* 2012 Dec 24. doi: 10.1111/imj.12071. [Epub ahead of print]. PMID:23279612.
43. Bainbridge NJ, Davie MW, Haddaway MJ. Bone loss after stroke over 52 weeks at os calcis: influence of sex, mobility and relation to bone density at other sites. *Age and Ageing.* 2006;35(2):127–132.
44. Beaupre GS, Lew HL. Bone-density changes after stroke. *American journal of physical medicine & rehabilitation/Association of Academic Physiatrists.* 2006;85(5):464–472.
45. Ashburn A, Hyndman D, Pickering R, Yardley L, Harris S. Predicting people with stroke at risk of falls. *Age and Ageing.* 2008;37(3):270–276.
46. Brown DL, Morgenstern LB, Majersik JJ, Kleerekoper M, Lisabeth LD. Risk of fractures after stroke. *Cerebrovascular Diseases (Basel, Switzerland).* 2008; 25(1–2):95–99.
47. Eng JJ, Tang PF. Gait training strategies to optimize walking ability in people with stroke: a synthesis of the evidence. *Expert Review of Neurotherapeutics.* 2007;7(10):1417–1436.
48. Kerse N, Parag V, Feigin VL, et al. Falls after stroke: results from the Auckland Regional Community Stroke (ARCOS) Study, 2002 to 2003. *Stroke; a Journal of Cerebral Circulation.* 2008;39(6):1890–1893.
49. Lazoura O, Groumas N, Antoniadou E, et al. Bone mineral density alterations in upper and lower extremities 12 months after stroke measured by peripheral quantitative computed tomography and DXA. *J Clin Densitom.* 2008;11(4):511–517.
50. Marsden J, Gibson LM, Lightbody CE, Sharma AK, Siddiqi M, Watkins C. Can early onset bone loss be effectively managed in post-stroke patients? An integrative review of the evidence. *Age and Ageing.* 2008;37(2):142–150.
51. Myint PK, Poole KE, Warburton EA. Hip fractures after stroke and their prevention. *Qjm.* 2007;100(9):539–545.
52. Paker N, Bugdayci D, Tekdos D, Dere C, Kaya B. Relationship between bone turnover and bone density at the proximal femur in stroke patients. *J Stroke Cerebrovasc Dis.* 2009;18(2):139–143.
53. Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in individuals with stroke. *Journal of Rehabilitation Research and Development.* 2008;45(8): 1195–1213.
54. Whitson HE, Pieper CF, Sanders L, Horner RD, Duncan PW, Lyles KW. Adding injury to insult: fracture risk after stroke in veterans. *Journal of the American Geriatrics Society.* 2006;54(7):1082–1088.
55. Feigin VL, Barker-Collo S, Parag V, et al. Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years post-stroke. *Neurology.* 2010;75(18):1597–1607.
56. Andersson AG, Seiger A, Appelros P. Hip fractures in persons with stroke. *Stroke Research and Treatment.* 2013;2013:954279.
57. Lakshminarayan K, Schissel C, Anderson DC, et al. Five-year rehospitalization outcomes in a cohort of patients with acute ischemic stroke: Medicare linkage study. *Stroke; a Journal of Cerebral Circulation.* 2011;42(6):1556–1562.
58. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. *Calcified Tissue International.* 2009;84(2):103–111.
59. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke; a Journal of Cerebral Circulation.* 2009;40(4):1032–1037.
60. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurology.* 2008;7(10):915–926.

61. Sealy-Jefferson S, Wing JJ, Sanchez BN, et al. Age- and ethnic-specific sex differences in stroke risk. *Gender Medicine.* 2012;9(2):121–128.
62. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation.* 2012;125(1):188–197.
63. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. *Journal of Neurology, Neurosurgery, and Psychiatry.* 2003;74(3):317–321.
64. Lewsey JD, Jhund PS, Gillies M, et al. Age- and sex-specific trends in fatal incidence and hospitalized incidence of stroke in Scotland, 1986 to 2005. *Circulation.* 2009;2(5):475–483.
65. Morrison A, Fan T, Sen SS, Weisenfluh L. Epidemiology of falls and osteoporotic fractures: a systematic review. *Clinicoecon Outcomes Res.* 2013;5:9–18.
66. Sigurdsson G, Aspelund T, Chang M, et al. Increasing sex difference in bone strength in old age: The Age, Gene/Environment Susceptibility-Reykjavik study (AGES-REYKJAVIK). *Bone.* 2006;39(3):644–651.
67. Selby P. Postmenopausal osteoporosis. *Current Osteoporosis Reports.* 2004;2(3): 101–106.
68. D'Amelio P. The immune system and postmenopausal osteoporosis. *Immunological Investigations.* 2013;42(7):544–554.
69. de Villiers TJ, Gass ML, Haines CJ, et al. Global consensus statement on menopausal hormone therapy. *Climacteric.* 2013;16(2):203–204.
70. Robbins JA, Aragaki A, Crandall CJ, et al. Women's Health Initiative clinical trials: interaction of calcium and vitamin D with hormone therapy. *Menopause New York, N.Y.* 2013.
71. Hertrampf T, Ledwig C, Kulling S, et al. Responses of estrogen sensitive tissues in female Wistar rats to pre- and postnatal isoflavone exposure. *Toxicology Letters.* 2009;191(2–3):181–188.
72. Seidlova-Wuttke D, Prelle K, Fritzemeier KH, Wuttke W. Effects of estrogen receptor alpha- and beta-selective substances in the metaphysis of the tibia and on serum parameters of bone and fat tissue metabolism of ovariectomized rats. *Bone.* 2008;43(5):849–855.
73. Devine A, Dick IM, Dhaliwal SS, Naheed R, Beilby J, Prince RL. Prediction of incident osteoporotic fractures in elderly women using the free estradiol index. *Osteoporos Int.* 2005;16(2):216–221.
74. Kuchuk NO, van Schoor NM, Pluijm SM, Smit JH, de Ronde W, Lips P. The association of sex hormone levels with quantitative ultrasound, bone mineral density, bone turnover and osteoporotic fractures in older men and women. *Clinical Endocrinology.* 2007;67(2):295–303.
75. Lim VW, Li J, Gong Y, et al. Serum free estradiol and estrogen receptor-alpha mediated activity are related to decreased incident hip fractures in older women. *Bone.* 2012;50(6):1311–1316.
76. Billeci AM, Paciaroni M, Caso V, Agnelli G. Hormone replacement therapy and stroke. *Current Vascular Pharmacology.* 2008;6(2):112–123.
77. Lisabeth L, Bushnell C. Stroke risk in women: the role of menopause and hormone therapy. *Lancet Neurology.* 2012;11(1):82–91.
78. Brann D, Raz L, Wang R, Vadlamudi R, Zhang Q. Oestrogen signalling and neuroprotection in cerebral ischaemia. *Journal of Neuroendocrinology.* 2012;24(1): 34–47.
79. Liu R, Yang SH. Window of opportunity: estrogen as a treatment for ischemic stroke. *Brain Research.* 2013;1514:83–90.
80. Schreihofer DA, Ma Y. Estrogen receptors and ischemic neuroprotection: who, what, where, and when? *Brain Research.* 2013;1514:107–122.
81. Scott E, Zhang QG, Wang R, Vadlamudi R, Brann D. Estrogen neuroprotection and the critical period hypothesis. *Frontiers in Neuroendocrinology.* 2012;33(1):85–104.
82. Fitzpatrick LA. Phytoestrogens—mechanism of action and effect on bone markers and bone mineral density. *Endocrinology and Metabolism Clinics of North America.* 2003;32(1):233–252, viii.
83. Chiechi LM, Secreto G, D'Amore M, et al. Efficacy of a soy rich diet in preventing postmenopausal osteoporosis: the Menfis randomized trial. *Maturitas.* 2002;42(4):295–300.
84. Watson WL, Mitchell R. Conflicting trends in fall-related injury hospitalisations among older people: variations by injury type. *Osteoporos Int.* 2011;22(10):2623–2631.
85. Langley J, Samaranayaka A, Davie G, Campbell AJ. Age, cohort and period effects on hip fracture incidence: analysis and predictions from New Zealand data 1974–2007. *Osteoporos Int.* 2011;22(1):105–111.
86. Nymark T, Lauritsen JM, Ovesen O, Rock ND, Jeune B. Decreasing incidence of hip fracture in the Funen County, Denmark. *Acta Orthopaedica.* 2006;77(1):109–113.
87. Bjorgul K, Reikeras O. Incidence of hip fracture in southeastern Norway: a study of 1,730 cervical and trochanteric fractures. *International Orthopaedics.* 2007;31(5):665–669.
88. Hernandez JL, Olmos JM, Alonso MA, et al. Trend in hip fracture epidemiology over a 14-year period in a Spanish population. *Osteoporos Int.* 2006; 17(3):464–470.
89. Jaglal SB, Weller I, Mamdani M, et al. Population trends in BMD testing, treatment, and hip and wrist fracture rates: are the hip fracture projections wrong? *J Bone Miner Res.* 2005;20(6):898–905.
90. Chevalley T, Guilley E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R. Incidence of hip fracture over a 10-year period (1991–2000): reversal of a secular trend. *Bone.* 2007;40(5):1284–1289.
91. Melton LJ, 3rd, Kearns AE, Atkinson EJ, et al. Secular trends in hip fracture incidence and recurrence. *Osteoporos Int.* 2009;20(5):687–694.
92. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* 2009;302(14):1573–1579.
93. Stevens JA, Rudd RA. The impact of decreasing U.S. hip fracture rates on future hip fracture estimates. *Osteoporos Int.* 2013;24(10):2725–8. doi: 10.1007/s00198-013-2375-9. Epub 2013 Apr 30. PMID:23632827.
94. Leslie WD, O'Donnell S, Jean S, et al. Trends in hip fracture rates in Canada. *Jama.* 2009;302(8):883–889.
95. Holt G, Smith R, Duncan K, Hutchison JD, Reid D. Changes in population demographics and the future incidence of hip fracture. *Injury.* 2009;40(7):722–726.
96. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997–2006. *Osteoporos Int.* 2010;21(3):373–380.
97. Maravic M, Taupin P, Landais P, Roux C. Change in hip fracture incidence over the last 6 years in France. *Osteoporos Int.* 2011;22(3):797–801.
98. Lonnroos E, Kautiainen H, Karppi P, et al. Increased incidence of hip fractures. A population based-study in Finland. *Bone.* 2006;39(3):623–627.
99. Vestergaard P, Rejnmark L, Mosekilde L. [Strongly increasing incidence of hip fractures in Denmark from 1977 to 1999]. *Ugeskrift for Laeger.* 2008;170(8):621–623.
100. Icks A, Haastert B, Wildner M, Becker C, Meyer G. Trend of hip fracture incidence in Germany 1995–2004: a population-based study. *Osteoporos Int.* 2008; 19(8):1139–1145.
101. Shao CJ, Hsieh YH, Tsai CH, Lai KA. A nationwide seven-year trend of hip fractures in the elderly population of Taiwan. *Bone.* 2009;44(1):125–129.
102. Johansson H, Clark P, Carlos F, Oden A, McCloskey EV, Kanis JA. Increasing age- and sex-specific rates of hip fracture in Mexico: a survey of the Mexican Institute of Social Security. *Osteoporos Int.* 2011;22(8):2359–2364.
103. Piscitelli P, Gimigliano F, Gatto S, et al. Hip fractures in Italy: 2000–2005 extension study. *Osteoporos Int.* 2010;21(8):1323–1330.
104. Mann E, Meyer G, Haastert B, Icks A. Comparison of hip fracture incidence and trends between Germany and Austria 1995–2004: an epidemiological study. *BMC Public Health.* 2010;10:46.
105. Emaus N, Olsen LR, Ahmed LA, et al. Hip fractures in a city in Northern Norway over 15 years: time trends, seasonal variation and mortality: the Harstad Injury Prevention Study. *Osteoporos Int.* 2011;22(10):2603–2610.
106. Guilley E, Chevalley T, Herrmann F, et al. Reversal of the hip fracture secular trend is related to a decrease in the incidence in institution-dwelling elderly women. *Osteoporos Int.* 2008;19(12):1741–1747.
107. Bergstrom U, Jonsson H, Gustafson Y, Pettersson U, Stenlund H, Svensson O. The hip fracture incidence curve is shifting to the right. *Acta Orthopaedica.* 2009; 80(5):520–524.
108. Stoen RO, Nordsletten L, Meyer HE, Frihagen JF, Falch JA, Lofthus CM. Hip fracture incidence is decreasing in the high incidence area of Oslo, Norway. *Osteoporos Int.* 2012;23(10):2527–2534.
109. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *Jama.* 2006; 296(24):2939–2946.
110. Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Kiyohara Y. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. *Circulation.* 2008;118(25):2672–2678.
111. Harmsen P, Wilhelmsen L, Jacobsson A. Stroke incidence and mortality rates 1987 to 2006 related to secular trends of cardiovascular risk factors in Gothenburg, Sweden. *Stroke; a Journal of Cerebral Circulation.* 2009;40(8):2691–2697.
112. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999–2008: time-trend analysis from the General Practice Research Database. *BMJ Open.* 2011;1(2):e000269.
113. Morgenstern LB, Smith MA, Sanchez BN, et al. Persistent Ischemic stroke disparities despite declining incidence in Mexican Americans. *Ann Neurol.* 2013 Jul 19. doi: 10.1002/ana.23972. [Epub ahead of print]. PMID:23868398.
114. Hata J, Ninomiya T, Hirakawa Y, et al. Secular Trends in Cardiovascular Disease and its Risk Factors in Japanese: Half Century Data from the Hisayama Study (1961–2009). *Circulation.* 2013;128(11):1198-205. doi: 10.1161/CIRCULATIONAHA.113.002424. Epub 2013 Jul 31. PMID:23902756.
115. Modig K, Andersson T, Drefahl S, Ahlbom A. Age-specific trends in morbidity, mortality and case-fatality from cardiovascular disease, myocardial infarction and stroke in advanced age: evaluation in the Swedish population. *PloS One.* 2013;8(5):e64928.
116. Rosengren A, Giang KW, Lappas G, Jern C, Toren K, Bjorck L. Twenty-four-year trends in the incidence of ischemic stroke in sweden from 1987 to 2010. *Stroke; a Journal of Cerebral Circulation.* 2013;44(9):2388–2393.

117. Sturgeon JD, Folsom AR. Trends in hospitalization rate, hospital case fatality, and mortality rate of stroke by subtype in Minneapolis-St. Paul, 1980–2002. *Neuroepidemiology.* 2007;28(1):39–45.
118. Hallstrom B, Jonsson AC, Nerbrand C, Norrving B, Lindgren A. Stroke incidence and survival in the beginning of the 21st century in Southern Sweden: comparisons with the late 20th century and projections into the future. *Stroke; a Journal of Cerebral Circulation.* 2008;39(1):10–15.
119. Khellaf M, Quantin C, d'Athis P, et al. Age-period-cohort analysis of stroke incidence in Dijon from 1985 to 2005. *Stroke; a Journal of Cerebral Circulation.* 2010;41(12):2762–2767.
120. Medin J, Nordlund A, Ekberg K. Increasing stroke incidence in Sweden between 1989 and 2000 among persons aged 30 to 65 years: evidence from the Swedish Hospital Discharge Register. *Stroke; a Journal of Cerebral Circulation.* 2004; 35(5):1047–1051.
121. Piscitelli P, Iolascon G, Argentiero A, et al. Incidence and costs of hip fractures vs strokes and acute myocardial infarction in Italy: comparative analysis based on national hospitalization records. *Clinical Interventions in Aging.* 2012; 7:575–583.
122. Anderson CS, Carter KN, Hackett ML, et al. Trends in stroke incidence in Auckland, New Zealand, during 1981 to 2003. *Stroke; a Journal of Cerebral Circulation.* 2005;36(10):2087–2093.
123. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. *European Journal of Epidemiology.* 2012;27(4):287–295.
124. Teuschl Y, Brainin M, Matz K, et al. Time trends in patient characteristics treated on acute stroke-units: results from the Austrian Stroke Unit Registry 2003–2011. *Stroke; a Journal of Cerebral Circulation.* 2013;44(4):1070–1074.
125. Kunst AE, Amiri M, Janssen F. The decline in stroke mortality: exploration of future trends in 7 Western European countries. *Stroke; a Journal of Cerebral Circulation.* 2011;42(8):2126–2130.
126. Pang MY, Eng JJ, McKay HA, Dawson AS. Reduced hip bone mineral density is related to physical fitness and leg lean mass in ambulatory individuals with chronic stroke. *Osteoporos Int.* 2005;16(12):1769–1779.
127. Poole KE, Warburton EA, Reeve J. Rapid long-term bone loss following stroke in a man with osteoporosis and atherosclerosis. *Osteoporos Int.* 2005;16(3):302–305.
128. Sato Y, Iwamoto J, Honda Y. Beneficial effect of etidronate therapy in chronically hospitalized, disabled patients with stroke. *J Stroke Cerebrovasc Dis.* 2010; 19(3):198–203.
129. Schnitzer TJ, Harvey RL, Nack SH, Supanwanid P, Maskala-Streff L, Roth E. Bone mineral density in patients with stroke: relationship with motor impairment and functional mobility. *Topics in Stroke Rehabilitation.* 2012;19(5):436–443.
130. Jorgensen L, Engstad T, Jacobsen BK. Higher incidence of falls in long-term stroke survivors than in population controls: depressive symptoms predict falls after stroke. *Stroke; a Journal of Cerebral Circulation.* 2002;33(2):542–547.
131. Hyndman D, Ashburn A, Stack E. Fall events among people with stroke living in the community: circumstances of falls and characteristics of fallers. *Archives of Physical Medicine and Rehabilitation.* 2002;83(2):165–170.
132. Turkington P, McDonald S, Elliott J, Beringer T. Hip fracture in Northern Ireland, 1985–2010. Are age-specific fracture rates still rising? *The Ulster Medical Journal.* 2012;81(3):123–126.
133. Fisher A, Martin J, Srikusalanukul W, Davis M. Bisphosphonate use and hip fracture epidemiology: ecologic proof from the contrary. *Clinical Interventions in Aging.* 2010;5:355–362.
134. Stevens JA, Anne Rudd R. Declining hip fracture rates in the United States. *Age and Ageing.* 2010;39(4):500–503.
135. Herttua K, Tabak AG, Martikainen P, Vahtera J, Kivimaki M. Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study. *Eur Heart J.* 2013;34(38):2933-9. doi: 10.1093/eurheartj/eht219. Epub 2013 Jul 16. PMID:23861328.
136. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ Clinical Research ed.* 2009;338:b1665.
137. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine.* 2006;3(11):e442.
138. Fisher AA, O'Brien ED, Davis MW. Trends in hip fracture epidemiology in Australia: possible impact of bisphosphonates and hormone replacement therapy. *Bone.* 2009;45(2):246–253.
139. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *Journal of the American Geriatrics Society.* 2003;51(3):364–370.
140. Budhia S, Mikyas Y, Tang M, Badamgarav E. Osteoporotic fractures: a systematic review of U.S. healthcare costs and resource utilization. *Pharmaco Economics.* 2012;30(2):147–170.
141. Haentjens P, Lamraski G, Boonen S. Costs and consequences of hip fracture occurrence in old age: an economic perspective. *Disability and Rehabilitation.* 2005;27(18–19):1129–1141.
142. Nshimyumukiza L, Durand A, Gagnon M, et al. An economic evaluation: Simulation of the cost-effectiveness and cost-utility of universal prevention strategies against osteoporosis-related fractures. *J Bone Miner Res.* 2013;28(2):383–394.
143. Nurmi I, Narinen A, Luthje P, Tanninen S. Cost analysis of hip fracture treatment among the elderly for the public health services: a 1-year prospective study in 106 consecutive patients. *Archives of Orthopaedic and Trauma Surgery.* 2003;123(10):551–554.
144. Wu N, Chen SY, Lee YC, Zhao Y. Demographics and clinical and economic characteristics of patients receiving total hip arthroplasty with and without muscle atrophy/weakness. *Clinicoecon Outcomes Res.* 2013;5:271–280.
145. Zhao Y, Chen SY, Lee YC, Wu N. Clinical and economic characteristics of hip fracture patients with and without muscle atrophy/weakness in the United States. *Archives of Osteoporosis.* 2013;8(1–2):127.
146. Garcia AE, Bonnaig JV, Yoneda ZT, et al. Patient variables which may predict length of stay and hospital costs in elderly patients with hip fracture. *Journal of Orthopaedic Trauma.* 2012;26(11):620–623.
147. Bessette L, Jean S, Lapointe-Garant MP, et al. Direct medical costs attributable to peripheral fractures in Canadian post-menopausal women. *Osteoporos Int.* 2012;23(6):1757–1768.
148. Fisher A, Srikusalanukul W, Davis, Smith P. Poststroke hip fracture: prevalence, clinical characteristics, mineral-bone metabolism, outcomes, and gaps in prevention. *Stroke Res Treat.* 2013:641943. doi: 10.1155/2013/641943. Epub 2013 Sep 25.PMID:24187647.
149. Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. *Stroke; a Journal of Cerebral Circulation.* 2008;39(3):776–782.
150. Marsden DL, Spratt NJ, Walker R, et al. Trends in stroke attack rates and case fatality in the Hunter region, Australia 1996–2008. *Cerebrovascular Diseases (Basel, Switzerland).* 2010;30(5):500–507.