Exploring the role of biological factors in the male-female health-survival paradox using health claims data

Michael Nerius, Anne Fink, Gabriele Doblhammer

Introduction

Determinants of sex specific differences in health and mortality are widely debated. In terms of morbidity, studies suggest that men at advanced ages perform better in physical tests, report a higher self-rated health and show limitations in activities of daily living to a lesser extent compared to women [1]. Even though men tend to be healthier regarding these conditions, they have higher mortality rates at all ages than women. In selected European countries, the male to female differences in life expectancy ranges from 4.4 to 8.4 years in 200 2 [2]. This male-female health-survival paradox may be explained by behavioral and biological factors. On the behavioral level, men exercise more dangerous activities than women like smoking, alcohol consumption, more unhealthy diet, and are exposed to greater health risks at work [3]. On the biological level, the existence of the additional X chromosome and endogenous estrogens seem to be one of the main conditions for sex differences [1]. The presence of estrogens which is the focus of this study counteract aging processes of blood vessels, lead to a significant reduction of thrombosis in animals experiments, promote the production of high-density lipoprotein (HDL) and is able to capture free radicals which may prevent cell damages [4]. In consequence, these relations may protect women against the development of life-threatening diseases such as coronary heart disease [1, 4]. In order to test whether estrogens have a protective effect we chose Parkinson's disease (PD), because the majority of studies report a predominance of PD in men at all ages. Findings show male to female ratios with a range from 1.54 to 1.89 [5-9]. Estrogens seem to have favorable effects on processes preventing the development of PD. PD is more common among women affected by an early reduction of endogenous estrogens. For instance, women with an earlier menopause or women who underwent a bilateral oophorectomy were at a higher risk to develop PD [10]. Biologically, estrogens have an impact on the dopamine system. An increased amount of estrogens during menstrual cycle leads to an increased number of synaptic contacts. In addition, estrogens seem to have a protective effect on nigrostriatal neurons which are endangered by toxic influences. Estrogens also affect the stimulation of dopamine receptors which modifies the release of dopamine [11].

The aim of this study is to provide current sex specific incidence and mortality rates based on German Health Claims Data. We examine the role of the female sex hormone estrogen as a potential neuroprotective factor and explore its effect on PD incidence and mortality with PD. In this context, we use the occurrence of osteoporosis (OP) in women as a surrogate for the lack of estrogens leading to a higher risk of PD [12].

Studying women with OP, we hypothesize that their PD incidence should be higher than for OP-free women. Given the protective social factor influencing female mortality, they should still have lower or comparable mortality than their male counterparts.

Background

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder at higher ages (50+), causing disability and care dependency with increasing duration [13]. With ageing populations, the number of individuals affected by this incurable disease will almost double in Europe, USA, and Canada combined by 2050 [14]. PD lowers life expectancy, reduces quality of life for patients and relatives, and leads to substantial social and economic burdens. The prevalence of PD is about 1% for people aged 60 and above [15].

Data

We performed PD analyses using routine claims data from the years 2004-2013 of the largest German statutory health insurance, the "Allgemeine Ortskrankenkasse" (AOK). In Germany, about 70 million people are covered through statutory programs, one third of whom are members of the AOK. The AOK covers more than 50% of the population of higher ages [16]. We drew a randomized sample in the first quarter of 2004 containing a size of 250,000 persons ages 50 years and older, which was about 2% of all persons insured in the AOK. After data cleaning and validation processes, we arrived at an analysis sample for the first quarter 2004 of 236,045 individuals.

PD was identified based on the ICD-10 codes G20.0, G20.1, G20.2 and G20.9. We developed internal validation strategies to rule out false positive diagnoses. Thus, PD diagnoses are considered as valid if there is a confirmative diagnosis in at least one further quarter or a second diagnosis by another physician in the same quarter. OP was identified based on the ICD-10 codes M80-M82.

Methods

For estimating incidence rates, we used a longitudinal data set of the years 2004-2013. New cases of PD included all subjects who had a diagnosis-free period of at least six months but developed PD during the follow-up. Incidence rates are expressed as new PD cases per 100,000 person-years. 95% confidence intervals (95% CI) for incidence rates were calculated by assuming a Poisson distribution. For calculating the standardized incidence rate we used the age distribution of 2004 in Germany.

For estimating death rates, we divided the number of deaths among PD cases by the number of person-years with PDR. Rates are expressed as deaths per 100,000 person-years. 95% confidence intervals (95% CI) were calculated by assuming a Poisson distribution.

We used Cox proportional hazard models to examine whether PD was associated with the occurrence of OP; adjusting for age and major comorbidities.

Results

Transition to PD

A total of 5,210 new cases had their onset of PD during the follow-up, leading to a standardized incidence rate of 219 (95% CI 203-215). The mean age of PD onset was 77.1 years. Regarding sex, men had a higher standardized incidence rate (262; 95% CI 251-273) than women (179; 95% CI 171-186), and this was also true for the age-specific rates. Both male and female incidence rates peaked at ages 85-89 (men: 917; 95% CI 803-1,048; women: 580; 95% CI: 529-636) and declined thereafter.

We further did sex specific analyses and found higher incidences rates among women with OP compared to women without the disease. Standardized incidence rates for women affected by OP were 227 (95% CI 202-253) whereas women without OP showed a rate of 165 (95% CI 157-173). This relation was also true for men. The occurrence of OP led to a standardized incidence rate of 461 (95% CI 339-583) whereas men without the disease showed a rate of 254 (95% CI 243-265). Age specific rates incidence rates for PD are given in Figure 1.

Figure 1 PD incidence rates for men and women with/without OP stratified by age
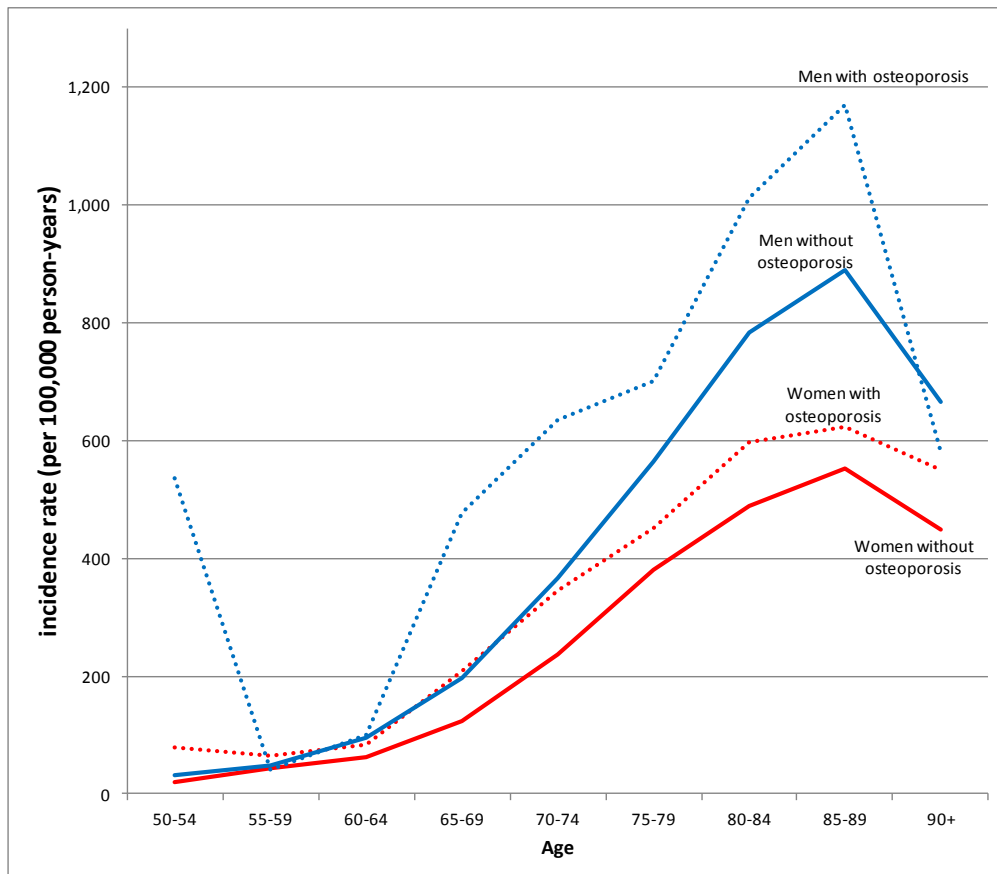
The relation between OP und PD remained after the adjustment for possible confounders (Table 1). Compared to women without OP, women with OP were faced by a significant increase of developing PD (HR=1.23, 95% CI 1.14-1.33). Men without OP also showed an elevated risk (HR=1.50, 95% CI 1.41-1.60) and men with OP had about twice the risk of suffering from PD (95% CI 1.79-2.37).

Table 1 Hazard ratios of PD

		Crude HR*	p≤	95% CI		Adj. HR**	p≤	95% CI	
Sex & OP	Women without OP	Reference				Reference			
	Men without OP	1.57	0.0001	1.47	1.67	1.50	0.0001	1.41	1.60
	Men with OP	2.40	0.0001	2.09	2.76	2.06	0.0001	1.79	2.37
	Women with OP	1.33	0.0001	1.23	1.44	1.23	0.0001	1.14	1.33

*Crude model controlled for age; ** Multivariate model controlled for age, diabetes mellitus, cerebrovascular diseases, hypertension, ischemic heart diseases, atrial fibrillation, hypercholesterolemia, COPD, chronic inflammatory bowel diseases, alcoholic liver disease

Transition to Death

After 9.5 years of follow-up, 2,329 (44.7%) of all incident PD cases had died. Among PD cases, standardized death rates were higher for men (3,186; 95% CI 2,970-3,402) compared to women (2,213; 95% CI 1,985-2,442). With respect to OP, we found no significant differences in women. Women with PD and OP showed standardized death rates of 2,674 (95% CI 1,932-3,418) which differ not significantly from those of OP-free women with PD (2,048; 95% CI 1,803-2,293). However, death rates for PD-Men with OP (4,526; 95% CI 3,786-5,265) were significantly higher compared to PD-Men without OP (3,029; 95% CI 2,806-3,252). Figure 2 illustrates these numbers by showing age specific death rates for each group.

Figure 2 Death rates for PD-Men and PD-Women with/without OP stratified by age
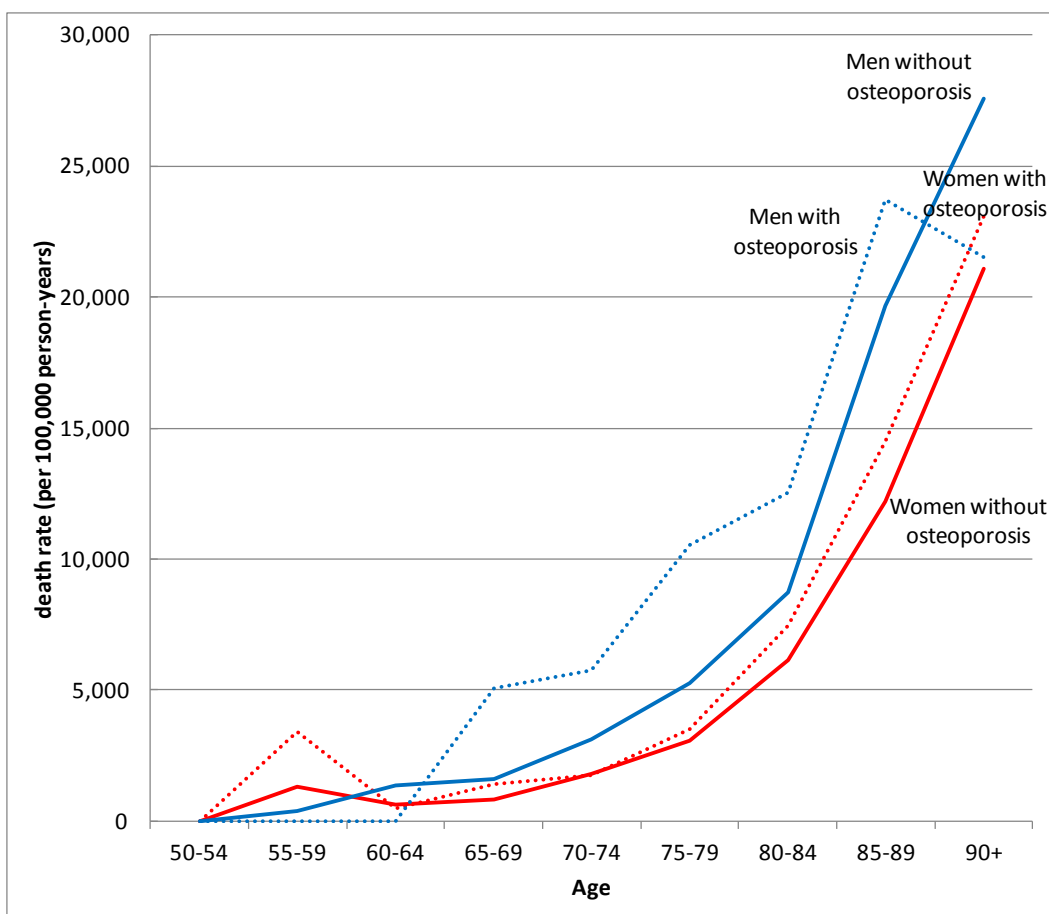
In the multivariate analyses, we found a significantly reduced risk of death for PD-Women with OP (HR=0.87; 95% CI 0.77-0.97). Table 2 further shows that men's excess mortality remained after the adjustment of major confounders. However, there were no significant differences in men according to OP.

Table 2 Hazard ratios of death

		Crude HR*	p≤	95% CI		Adj. HR**	p≤	95% CI	
Sex & OP	PD-Women without OP	Reference				Reference			
	PD-Men without OP	1.43	0.001	1.29	1.58	1.34	0.001	1.21	1.48
	PD-Men with OP	1.84	0.001	1.56	2.17	1.43	0.001	1.21	1.70
	PD-Women with OP	1.03	0.656	0.92	1.15	0.87	0.015	0.77	0.97

*Crude model controlled for age; **Multivariate model controlled for age, diabetes mellitus, cerebrovascular diseases, hypertension, ischemic heart diseases, atrial fibrillation, hypercholesterolemia, COPD, chronic inflammatory bowel diseases, alcoholic liver disease, hip and other fractures

Conclusion

Using a data sample from the largest German public health insurance, we present age and sex specific incidence and mortality rates of PD for Germany. We found increased incidence rates and HR of PD for women with OP which indicates that a lack of estrogens is connected to a higher risk of developing PD. In addition to that, OP in men was also associated with an elevated risk of PD. In this context, secondary OP (SOP) should be taken into account. SOP make up 20-30% of all OP diagnoses among women but 50-60% of the total OP diagnoses among men [17]. SOP is the result of having certain medical or lifestyle conditions, like exposure to glucocorticoids, hypogonadism (low testosterone), diabetes, alcohol abuse, smoking, gastrointestinal disease, low body weight, and immobility [18]. Some of these conditions were also risk factors for PD [19, 20] which may explain the increased risk among men with OP. Using health claims data, we are not able to differentiate between secondary and estrogen driven primary osteoporosis. Regarding mortality, PD women with OP were still at a lower risk of death than men which indicates protective social factors of women generally. However, PD-women with OP showed a lower risk of death compared to PD-women without OP. This effect occurred after adjusting for hip and other fractures and may be partly explained by OP therapy. Center et al. 2011 found a lower mortality risk for women with OP taking bisphosphonates which is one of the standard medications. They assume that the effect is reduced to the decrease in infection- and pneumonia related deaths (Center 2011). In addition to that, the recommended change of diet and movement therapies for people with OP may influence mortality positively.

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