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Sociodemographic moderation of the association between depression and stroke incidence in a retrospective cohort of 0.4 million primary care recipients with hypertension

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Abstract:	Background. Previous research has suggested an association between depression and subsequent acute stroke incidence, but few studies have examined any effect modification by sociodemographic factors. In addition, no studies have investigated this association among primary care recipients with hypertension. Methods. We examined the anonymized records of all public general outpatient visits by patients aged 45+ during January 2007 – December 2010 in Hong Kong to extract primary care patients with hypertension for analysis. We took the last consultation date as the baseline and followed them up for four years (until 2011 – 2014) to observe any subsequent acute hospitalization due to stroke. Mixed effects Cox models (random intercept across 74 included clinics) were implemented to examine the association between depression (ICPC diagnosis or anti-depressant prescription) at baseline and the hazard of acute stroke (ICD-9: 430 – 437.9). Effect modification by age, sex, and recipient status of social security assistance was examined in extended models with

	respective interaction terms specified. Results. In total, 396,858 eligible patients were included, with 9,099 (2.3%) having depression, and 10,851 (2.7%) eventually hospitalized for stroke. From the adjusted analysis, baseline depression was associated with a 17% increased hazard of acute stroke hospitalization (95% CI: 1.03–1.32). This association was suggested to be even stronger among men than among women (hazard ratio = 1.29, 95% CI: 1.00–1.67). Conclusion. Depression is more strongly associated with acute stroke incidence among male than female primary care patients with hypertension. More integrated services are warranted to address their needs.

Sociodemographic moderation of the association between depression and stroke incidence in a retrospective cohort of 0.4 million primary care recipients with hypertension

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Abstract

Background. Previous research has suggested an association between depression and subsequent acute stroke incidence, but few studies have examined any effect modification by sociodemographic factors. In addition, no studies have investigated this association among primary care recipients with hypertension.

Methods. We examined the anonymized records of all public general outpatient visits by patients aged 45+ during January 2007 – December 2010 in Hong Kong to extract primary care patients with hypertension for analysis. We took the last consultation date as the baseline and followed them up for four years (until 2011 – 2014) to observe any subsequent acute hospitalization due to stroke. Mixed effects Cox models (random intercept across 74 included clinics) were implemented to examine the association between depression (ICPC diagnosis or anti-depressant prescription) at baseline and the hazard of acute stroke (ICD-9: 430 – 437.9). Effect modification by age, sex, and recipient status of social security assistance was examined in extended models with respective interaction terms specified.

Results. In total, 396,858 eligible patients were included, with 9,099 (2.3%) having depression, and 10,851 (2.7%) eventually hospitalized for stroke. From the adjusted analysis, baseline depression was associated with a 17% increased hazard of acute stroke hospitalization (95% CI: 1.03 – 1.32). This association was suggested to be even stronger among men than among women (hazard ratio = 1.29, 95% CI: 1.00 – 1.67).

Conclusion. Depression is more strongly associated with acute stroke incidence among male than female primary care patients with hypertension. More integrated services are warranted to address their needs.

Keywords

Chronic disease, cerebrovascular disease, mental disorder, multimorbidity, psychiatric comorbidity

Introduction

Depression is consistently associated with a heightened risk of subsequent adverse cardiovascular events (Barlinn et al., 2014; Dong, Zhang, Tong, & Qin, 2012; Gan et al., 2014; Wium-Andersen et al., 2019). A meta-analysis of 28 prospective cohort studies with 317,540 subjects has suggested that the hazard rate of stroke among individuals with depression is 45% greater than among those without (Pan, Sun, Okereke, Rexrode, & Hu, 2011). Likewise, a recent meta-analysis further suggested that the use of anti-depressants, a commonly adopted proxy of the presence of severe depression, is associated with a 41% elevated risk of stroke incidence (Trajkova, d'Errico, Soffietti, Sacerdote, & Ricceri, 2019).

The mechanisms underlying such an association, nevertheless, remains unclear (Bucciarelli et al., 2019; Pan et al., 2011). Proposed causal links in the literature include the neuroendocrine and inflammation effects of depression (Lindqvist et al., 2017), shared genetic determinants (Rutten-Jacobs et al., 2018; Wassertheil-Smoller et al., 2018), the non-compliance to medical advice and prescriptions (Kretchy, Owusu-Daaku, & Danquah, 2014; Spikes et al., 2019) and more unhealthy lifestyle and behaviors among individuals with depression (Sin, Kumar, Gehi, & Whooley, 2016), the presence of common comorbidities related to both depression and stroke, such as hypertension (Kretchy et al., 2014) and diabetes (Fiore et al., 2015), as well as the interactive effect of selective serotonin reuptake inhibitors (SSRIs) with nonsteroidal anti-inflammatory drugs (NSAIDs) on hemorrhagic stroke (Shin et al., 2015). Although it is apparently infeasible to capture every one of those factors in epidemiological studies to identify the relative importance of each pathway, a comparison of the strength of this association between different sociodemographic strata, such as men and women, may generate important implications for this inquiry, because some pathways

are known to be more relevant to specific strata and may thus manifest as a stronger statistical association, e.g. greater hazard ratio, between depression and stroke in the corresponding strata.

Nevertheless, given a limited sample size, few previous studies have conducted such a comparison (Cho et al., 2019; Hamano et al., 2015). Furthermore, there is a scarcity of research in realistic healthcare settings to inform clinical practices, in particular, for patients living with hypertension, who constitute a sizeable proportion of the primary care population and are known to be at a significantly elevated risk of stroke (Shah, Sutaria, & Vyas, 2019).

In this study, we took advantage of a large multicenter public general outpatient clinic database of 0.4 million patients with hypertension in Hong Kong to estimate the association of depression with subsequent acute hospitalization due to stroke over a follow-up period of four years, and more importantly, to compare this association across different sociodemographic strata.

Methods

Study design and sample selection

We adopted a retrospective cohort study design for this investigation which was extended from a broader project on health care for older people commissioned by the Hong Kong Government. The Hospital Authority (HA), a major provider of public outpatient services and the sole provider of public inpatient services in Hong Kong, provided anonymized data on patients aged 45 years or more for the retrospective data analysis, which was approved by the Survey and Behavioral Ethics Committee of the Chinese University of Hong Kong (dated 25 Aug 2015, Project Code: Elderly Care – CUHK). We examined the records of all patients who visited any of the 74 general outpatient clinics run by the HA during January 1st, 2007 – December 31st, 2010 for further data extraction to form the closed cohort. According to a population survey by the Hong Kong

Government (Department of Health, 2017), only 5.7% of the people living with hypertension were under the age of 45. Therefore, the effect of this age limit of 45 or above on the representativeness of this cohort, if any, should only be negligible.

We took the last visit by these patients during the period as the baseline and retrieved the corresponding outpatient clinical records over the 12 months prior to the baseline (including baseline visit records). Inclusion criteria included the diagnosis of hypertension (defined by International Classification of Primary Care (ICPC) codes K86 and K87) and the absence of previous admission to any public hospitals over the past 12 months. This criterion was motivated by our intended focus on the non-institutionalized, and typically community-dwelling, patients who represent a population with milder risks and thus receiving less attention than those who had been recently admitted to hospitals.

Patients were then followed up until they were admitted to any public hospitals through the Accident & Emergency Unit (A&E) due to stroke (coded as event) or any other reasons (coded as non-event, right censored) classified by the International Classification of Diseases, Ninth Revision (ICD-9), or until four years after the baseline (until 2011 – 2014).

The analysis of patient records has been approved by the Survey and Behavioral Ethics Committee of the Chinese University of Hong Kong (dated 25 Aug 2015).

Study outcome – time to acute hospitalization due to stroke

The time duration from the baseline visit to the first hospital admission through A&E with a primary diagnosis of stroke (defined by ICD-9) was used as the outcome of the analysis. The ICD-9 codes used to identify acute stroke ranged from 430 to 437.9 (down to two decimal places when applicable).

Independent variable – depression

Depression was the main independent variable in the analysis. It was defined by ICPC codes P03, P76, and P77 or at least two prescriptions of the following anti-depressants (generic drug name) over the 12 months prior to the baseline: amitriptyline, clomipramine, citalopram, dosulepin, doxepin, fluoxetine, imipramine, lofepramine, mirtazapine, moclobemide, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, tranylcypromine, trazodone, and venlafaxine.

Effect modifiers – biological age, sex, and receiving social security assistance

Biological age in years, sex (men or women), and recipient status of social security assistance (recipient or non-recipient), an indicator of lower socioeconomic status, were examined as effect modifiers of the effect of depression on time to acute hospitalization due to stroke.

Multivariable adjustment

We also included other baseline variables (according to the records over the 12 months prior to the baseline) to adjust for their potential confounding effects. First, baseline stroke diagnosis (ICPC code K89 and K90) were included in the model to adjust for the history of previous strokes. Second, common comorbidities including diabetes (ICPC codes T89 and T90), ischemic heart disease (ICPC codes K74, K75, and K76), atrial fibrillation (ICPC code K78) and lipid disorder (ICPC code T93) were also included. Third, we further included tobacco abuse (ICPC code P17) and alcohol abuse (ICPC code P15) to proxy lifestyle factors: smoking and alcohol consumption. Fourth, we included the prescription of statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, simvastatin, rosuvastatin) as a dichotomized variable (prescribed or not prescribed in the past 12 months). Last, to avoid the potential problem of incomplete multivariable

adjustment in the study of interaction terms (Keller, 2014), we further specified the interaction between the potential effect modifier and each of the confounders respectively.

Statistical analysis

We used a mixed effects Cox model (with random intercept across the 74 general outpatient clinics) to examine the hazard ratios of acute hospitalization due to stroke between patients with and without depression, with potential confounders adjusted. Based on this model, we further constructed three extended models in which the interaction between depression and age, depression and sex, and depression and receiving social security assistance was specified and examined respectively. Both the confounders and the interaction between confounders and the effect modifier were adjusted.

We also conducted two sets of sub-analyses. First, we adopted the leave-one-out approach to replicate the main analysis eight times, in each of which we removed patients admitted for a specific type of stroke (ICD-9: 430 – 437). Second, we replicated the analysis with the outcome replaced by time to stroke mortality in hospitals.

Following the recent recommendations on the use of statistical significance thresholds in research (McShane, Gal, Gelman, Robert, & Tackett, 2019), we refrained from taking the conventional approach to infer or conclude about the presence of interactions between depression and the sociodemographic factors using *P*-value thresholds alone but instead, provided an estimate of the hazard ratios with 95% confidence intervals for the readers' own interpretation.

The mixed effects Cox model was implemented using the 'coxme' package (Therneau, 2018) in R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). There were no missing data in the anonymized patient records.

Results

Descriptive results

During January 1st, 2007 – December 31st, 2010, a total of 15,054,785 general outpatient clinic visits by 1,312,229 patients aged 45 or above were recorded. We removed 808,507 patients without hypertension and then 106,864 patients with hospital admission history over the past 12 months. Eventually, 396,858 primary care patients with hypertension were included for analysis. The mean (standard deviation) follow-up period was 1146.4 (500.4) days. **Fig. 1** shows the procedures of data selection for this study.

Table 1 shows the descriptive statistics of the cohort. In total, there were 9,099 patients classified as having depression and 2.8% of them were admitted due to stroke through A&E within four years, compared similarly with 2.7% among those without depression. There was a lower proportion of men (28.5%) among those with depression compared with those without (42.7%). Twenty-five-point-three percent of those having depression received social security assistance, approximately double that among those without depression (12.6%). Interestingly, those having depression were less likely to have lipid disorder ($P = 0.001$) but were more likely to be prescribed a statin at least once over the past 12 months ($P = 0.010$). There were only 298 patients with an ICPC diagnosis of depression, thus, most patients with depression, i.e. 9,005, were identified using anti-depressant prescriptions.

Fig. 2 shows the stroke-free survival patterns across follow-up time by sex and the presence of depression. In general, depression and being male seemed to be associated with a greater risk of acute hospitalization due to stroke. Nevertheless, it is clearly shown that the difference between those having depression and those without is larger among men than among women.

Mixed effects Cox model

Table 2 shows the results of the mixed effects Cox models. According to Model 1 (without the specification of interaction), ten additional years of age was associated with a 74%-elevated hazard rate of acute stroke hospitalization, while being male, receiving social security assistance, and baseline stroke diagnosis were associated with 38%-, 19%-, and 143%-increased hazard rates respectively. Likewise, having comorbidities like ischemic heart disease (+26%), atrial fibrillation (+215%), and diabetes (+14%) was associated with increased hazard rates of acute hospitalization due to stroke. Having lipid disorder, on the other hand, was associated with a 13%-reduced hazard rate. In this model, depression was associated with 17%-heightened hazard rate of acute hospitalization due to stroke.

Among the three interactions (depression × age, depression × sex, and depression × receiving social security assistance) respectively examined in the extended models, the hazard ratio for the interaction between depression and sex was estimated with a 95% confidence interval (CI) which did not cross one (hazard ratio = 1.29, 95% CI: 1.00 – 1.67). Model 2 in **Table 2** shows the associations after fitting this interaction together with all interaction terms between male sex and each of the potential confounders. It is shown that the hazard ratio for the main effect of depression attenuated to 0.83 (95% CI: 0.57 – 1.21). This result suggests that the association of depression with a greater risk of acute hospitalization due to stroke might be stronger among men than among women. Notably, Model 2 also shows that the association of atrial fibrillation (hazard ratio = 0.58, 95% CI: 0.46 – 0.73) with stroke was estimated to be weaker among men.

All three interaction terms between depression and each of the three effect modifier, after Bonferroni correction for multiple comparisons, did not reach statistical significance ($P > 0.017$) using the conventional approach of statistical inference.

Sub-analysis

The replication of the analysis omitting patients admitted for each of the eight specific types of stroke (ICD-9: 430 – 437) estimated hazard ratios for the interaction between depression and being male, which fell within a reasonably small range except for occlusion of cerebral arteries (ICD-9: 434) (see **Table S1**). There was an attenuation of the hazard ratio (hazard ratio = 1.09, 95% CI: 0.75 – 1.59) associated with the omission of patients admitted for this condition and this may suggest a high relevance of this specific type of stroke in the observed effect modification by sex as reported above.

The replication of the analysis with the outcome replaced by stroke mortality in hospitals estimated a smaller hazard ratio for the interaction between depression and male sex (hazard ratio = 1.13, 95% CI: 0.54 – 2.37) compared with that estimated in the main analysis (see **Table S2**).

Discussion

In this study, we examined male sex as an effect modifier of the association between depression and subsequent acute hospitalization due to stroke among 0.4 million primary care patients with hypertension in Hong Kong, with the association estimated to be stronger among men than among women. Although there is a possibility of residual confounding effects from unobserved factors due to limited data availability, this effect modification essentially implies that the underlying mechanisms of the association between depression and subsequent acute stroke incidence operate more strongly among men than among women. This evidence derived from routine clinical records of a realistic healthcare setting in Hong Kong, a typical developed Asian population, should also inform integrated clinical practices and policies about the prevention of acute stroke incidence among patients with hypertension who also have depression. To the best of our knowledge, this is

the largest follow-up study on the association of depression with subsequent acute stroke incidence among patients with hypertension.

Relationship with the literature

Despite our focus on patients living with hypertension, the findings of a positive association identified between depression and subsequent acute stroke in this study are highly similar with previous meta-analyses and systematic reviews on more broadly defined populations (Barlinn et al., 2014; Dong et al., 2012; Pan et al., 2011). Of a comparable scale, there was only one existing Swedish study investigating effect modification by sex and other sociodemographic factors, but with a shorter follow-up period and a smaller sample of a non-disease-specific primary care population (Hamano et al., 2015). The authors also identified an interaction of depression with sex (being male) in relation to stroke incidence with an odds ratio for the interaction of 1.30 (95% CI: 1.01, 1.68), which represents a similar effect size as identified in our analysis (see **Table 2**).

Despite similar findings, several weaknesses of the Swedish study were addressed in our analysis. First, we confined our sample to only patients with hypertension who had not been hospitalized in the previous 12 months to minimize heterogeneity, with an adequately large sample size and statistical power retained. Second, we further adjusted for diabetes (Larsson et al., 2017), atrial fibrillation (Kamel, Okin, Elkind, & Iadecola, 2016), lipid disorder (Yaghi & Elkind, 2015), and statin prescription (Flint et al., 2017), which are known to be related to the risk of stroke. Third, we applied a survival model instead of a multivariable logistic regression to estimate the interaction to account for the follow-up time difference of stroke incidence.

Interpretation of findings

The observed difference in stroke risk associated with depression between men and women in our analysis could have a number of explanations. First, the observed association could be partly mediated through lifestyle factors, which have been shown to differ notably between the sexes among individuals with depression (Lundström, Jormfeldt, Hedman Ahlström, & Skärsäter, 2019). Like the previous Swedish study, we did not have access to lifestyle data and were not able to statistically identify specific behaviors that were related to stroke. One obvious behavioral risk factor missing from this and the previous study was smoking status (although coded tobacco abuse was adopted as a proxy in this study), which is one of the dominant predictors of stroke incidence worldwide (Peters, Huxley, & Woodward, 2013). Evidence showed a consistent association between smoking status and the presence of depressive symptoms (Lam et al., 2004). In addition, a large cohort study of 0.5 million Chinese adults estimated that the effect of depression on stroke incidence was stronger among smokers (Sun et al., 2016). Thus, given a typically much higher smoking prevalence among men than among women (ZHANG, OU, & BAI, 2011), we speculate that preexisting smoking status may be a reason for the observed effect modification. However, we suspect it may not fully explain the observation, as previous smaller studies have reported a persistent sex difference with smoking status statistically adjusted (Bos et al., 2008).

Second, the severity of depression among men in the primary care clinics, i.e. the first contact point between the patients and the healthcare system, may be greater than that among women because of the low help-seeking rate among men with undiagnosed depression (Seidler, Dawes, Rice, Oliffe, & Dhillon, 2016). As men may refrain from seeking help because of the stigma associated with mental illnesses (Chung & Wong, 2004), the majority of male patients with depression in primary care clinics may represent more serious cases and may have even more drastically increased risk of stroke compared with female patients. The low overall prevalence of

depression in this study may be a result of a combination of cultural factors (Fang et al., 2019) and prescription habits of clinicians (Rajaratnam et al., 2016) which warrant further research to clarify. Future studies may also include patients younger than 45 years, who were excluded in this analysis, and investigate how this sex difference may change to further reflect on the underlying mechanisms.

Finally, biological mechanisms linking depression and cardiovascular risk may vary by sex. For example, sex differences in the physiological relationship between depression and cardiovascular risks have been suggested in recent research, emphasizing the distinct roles of different biomarkers between men and women such as neuroendocrine allostatic loads (Gillespie et al., 2019) and atherosclerosis (Chirinos et al., 2015). The respective physiological pathways including inflammatory responses, deregulation of the autonomic nervous system, neuroendocrine alterations, and platelet reactivity and endothelial dysfunction should be comprehensively considered (Bucciarelli et al., 2019).

Another interesting observation in our study was the negative association between lipid disorder and stroke incidence, which is indeed consistent with some of the existing literature (Yaghi & Elkind, 2015), depending on the specific type of lipid disorders and specific type of stroke. We recommend future studies to include a more detailed categorization of lipid disorders to investigate the relationship.

Implications

Unlike previous large-scale studies (Cho et al., 2019; Hamano et al., 2015; Sun et al., 2016), we have confined our sample to only primary care patients with hypertension. Therefore, the implications of the findings of this study are clear: more efforts are needed to prevent stroke among

primary care patients with hypertension who also have depression, especially among men, as stroke is currently still one of the largest cause of life years lost due to disability (Abajobir et al., 2017). This challenge may require an integration of services and practices, for example, colocation of primary care and psychiatric services, or additional collaborative care that cuts across medical specialties to jointly address depression and cardiovascular risk factors (Gunn, 2015).

Limitations

Despite the reliable disease coding by registered physicians and the large sample size, there are several limitations to this study that warrant caution. First, we only had access to public healthcare records, which account for around 30% of the outpatient services and about 90% of the inpatient services in Hong Kong (Leung, Tin, & O'Donnell, 2009). Patients attending private primary care clinics and admitted to private hospitals were not recorded. Also, deaths happening outside public hospitals were not recorded in our database. Second, depression is likely under-coded in the primary care records with 96.7% of the individuals with depression in this study identified with the use of anti-depressants. Although this approach shares similarities with other previous works which used administrative databases and enhanced the comparability of our results with the literature (Doktorchik et al., 2019), it prevented us from conducting more analyses on the respective independent effects of the diagnosis of depression and the use of anti-depressants on stroke, as well as the interaction between SSRIs and NSAIDs (Trajkova et al., 2019). In addition, the use of anti-depressants to identify patients with depression in the clinical records had not been validated and there was a possibility that the anti-depressants were prescribed for conditions other than depression, such as anxiety disorder, although past research showed a large majority of anti-depressants were prescribed for depressive disorders (Chee et al., 2015). Third, we did not have data on a more detailed sociodemographic background of patients except whether they received

social security assistance and, thus, we were not able to examine further effect modifications by those factors to better profile the underlying mechanisms of the association between depression and stroke incidence. Fourth, we did not have lifestyle-related factors (e.g. physical activity and BMI) and only used ICPC codes for tobacco abuse and alcohol abuse as a proxy for more detailed data on lifestyle. Nevertheless, both smoking prevalence and alcohol consumption in Hong Kong are low compared with other populations (Chan & Leung, 2014), and thus the confounding effect may be weaker than if this study were conducted in other populations. Fifth, we did not conduct any analyses on the co-existing pharmacotherapy for hypertension. However, there was little variance in whether medications for hypertension was prescribed (94.8% were on medications). In addition, the prescription of medications may imply more severe conditions and higher risks despite the intended effect of the medications. This issue required propensity score matching procedures to address but we lacked further information for the calculation of propensity scores. Sixth, the follow-up period of four years may not be sufficient in length to observe long-term effects of depression on stroke incidence. Last, we did not have data on the severity of depression to verify our speculation on the possibly different degrees of severity of depression between men and women in primary care.

Conclusion

To conclude, we found that depression was associated with subsequent acute stroke incidence among 0.4 million primary care patients with hypertension, and this association was stronger among men than among women. Integrated or collaborative care may be warranted in prevention of stroke in these high-risk patients.

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Conflict of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figure legends

Fig. 1. Flow chart showing the procedures of sample selection for this study

Fig. 2. Stroke-free survival patterns (with 95% confidence intervals represented by shaded region) of primary care patients with hypertension

Table 1. Baseline characteristics of sample (N = 396,858)

	Patients with hypertension but not depression N=387,759		Patients with both hypertension and depression N=9,099		*P*-value
	n	%	n	%	
Sex					<0.001
Female	222,278	(57.3)	6,507	(71.5)	
Male	165,481	(42.7)	2,592	(28.5)	
Age					<0.001
45-54	63,209	(16.3)	1,776	(19.5)	
55-64	112,884	(29.1)	2,824	(31.0)	
65-74	102,511	(26.4)	1,946	(21.4)	
75-84	84,423	(21.8)	1,880	(20.7)	
85+	24,732	(6.4)	673	(7.4)	
Receiving social security assistance					<0.001
Non-recipient	305,890	(87.4)	7,387	(74.7)	
Recipient	48,702	(12.6)	2,301	(25.3)	
International Classification of Primary Care Diagnoses					
Stroke	9,956	(2.6%)	356	(3.9%)	<0.001
Lipid disorder	81,869	(21.1)	1,712	(18.8)	<0.001
Ischemic heart disease	9,591	(2.5)	210	(2.3)	0.331
Atrial fibrillation	2,692	(0.7)	53	(0.6)	0.227
Diabetes	106,609	(27.5)	2,371	(26.1)	0.003
Tobacco abuse	3,468	(0.9)	57	(0.6)	0.008
Alcohol abuse	252	(0.1)	5	(0.1)	0.870
Statin prescription	46,497	(12.0)	1,172	(12.9)	0.010
Depression diagnosis by ICPC	-	-	298	(3.3)	<0.001
Two or more prescriptions of anti-depressant in the past 12 months	-	-	9,005	(99.0)	<0.001
Acute hospitalization due to stroke within four years					0.528
Not hospitalized	377,167	(97.3)	8,840	(97.2)	
Hospitalized	10,592	(2.7)	259	(2.8)	

Note. P-values were derived from chi-square tests/Fisher's exact tests for the difference between patients with and without depression

Table 2. Mixed effects Cox proportional hazard model estimating the adjusted hazard ratios with 95% confidence interval (CI) of acute hospitalization due to stroke, 2011 – 2014

	Model 1	Model 2
	Hazard ratio [95% CI]	Hazard ratio [95% CI]
Age (measured in 10-year)	1.74 [1.71, 1.77]***	1.74 [1.71, 1.77]***
Male (female as referent)	1.38 [1.33, 1.44]***	1.41 [1.35, 1.49]***
Receiving social security assistance	1.19 [1.13, 1.25]***	1.19 [1.13, 1.25]***
Prior stroke	2.43 [2.25, 2.62]***	2.42 [1.90, 3.09]***
Lipid disorder	0.87 [0.82, 0.91]***	0.90 [0.76, 1.06]
Ischemic heart disease	1.26 [1.14, 1.40]***	1.17 [0.85, 1.61]
Atrial fibrillation	3.14 [2.80, 3.53]***	7.01 [4.95, 9.92]***
Diabetes	1.14 [1.09, 1.19]***	1.25 [1.09, 1.43]**
Tobacco abuse	1.12 [0.92, 1.36]	2.39 [0.75, 7.55]
Alcohol abuse	1.30 [0.68, 2.51]	-
Statin prescription	0.69 [0.64, 0.74]***	0.61 [0.49, 0.77]***
Depression	1.17 [1.03, 1.32]*	0.83 [0.57, 1.21]
Interaction with male sex:		
Male (female as referent) × Prior stroke		1.00 [0.86, 1.16]
Male (female as referent) × Lipid disorder		0.98 [0.88, 1.09]
Male (female as referent) × Ischemic heart disease		1.05 [0.86, 1.29]
Male (female as referent) × Atrial fibrillation		0.58 [0.46, 0.73]***
Male (female as referent) × Diabetes		0.94 [0.87, 1.03]
Male (female as referent) × Tobacco abuse		0.67 [0.37, 1.22]
Male (female as referent) × Alcohol abuse		-
Male (female as referent) × Statin prescription		1.09 [0.94, 1.25]
Male (female as referent) × Depression		1.29 [1.00, 1.67]*

Note. Estimates for alcohol abuse and its interaction with male sex in Model 2 omitted due to extremely wide confidence intervals. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

Fig. 1

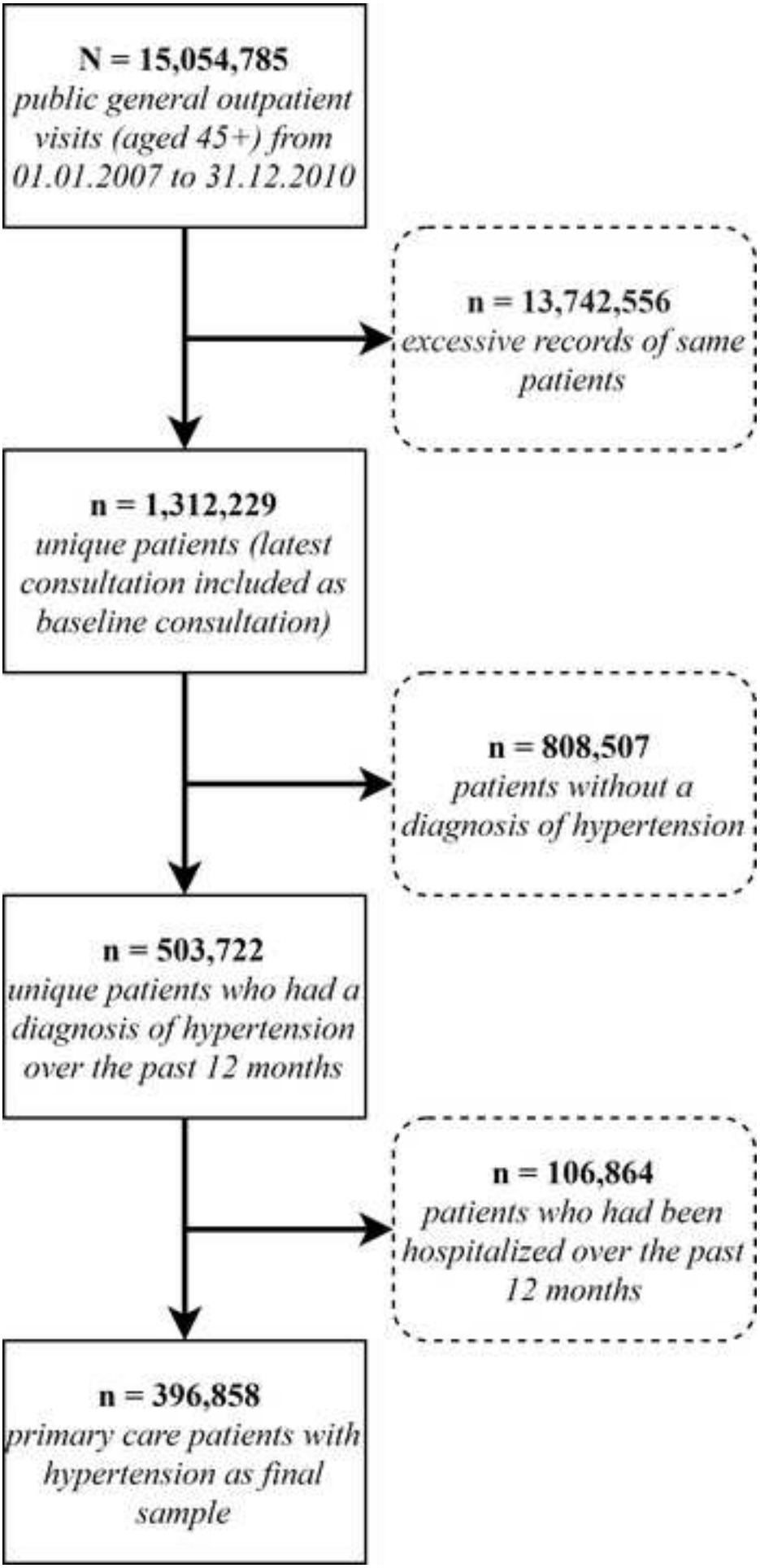

Fig. 2

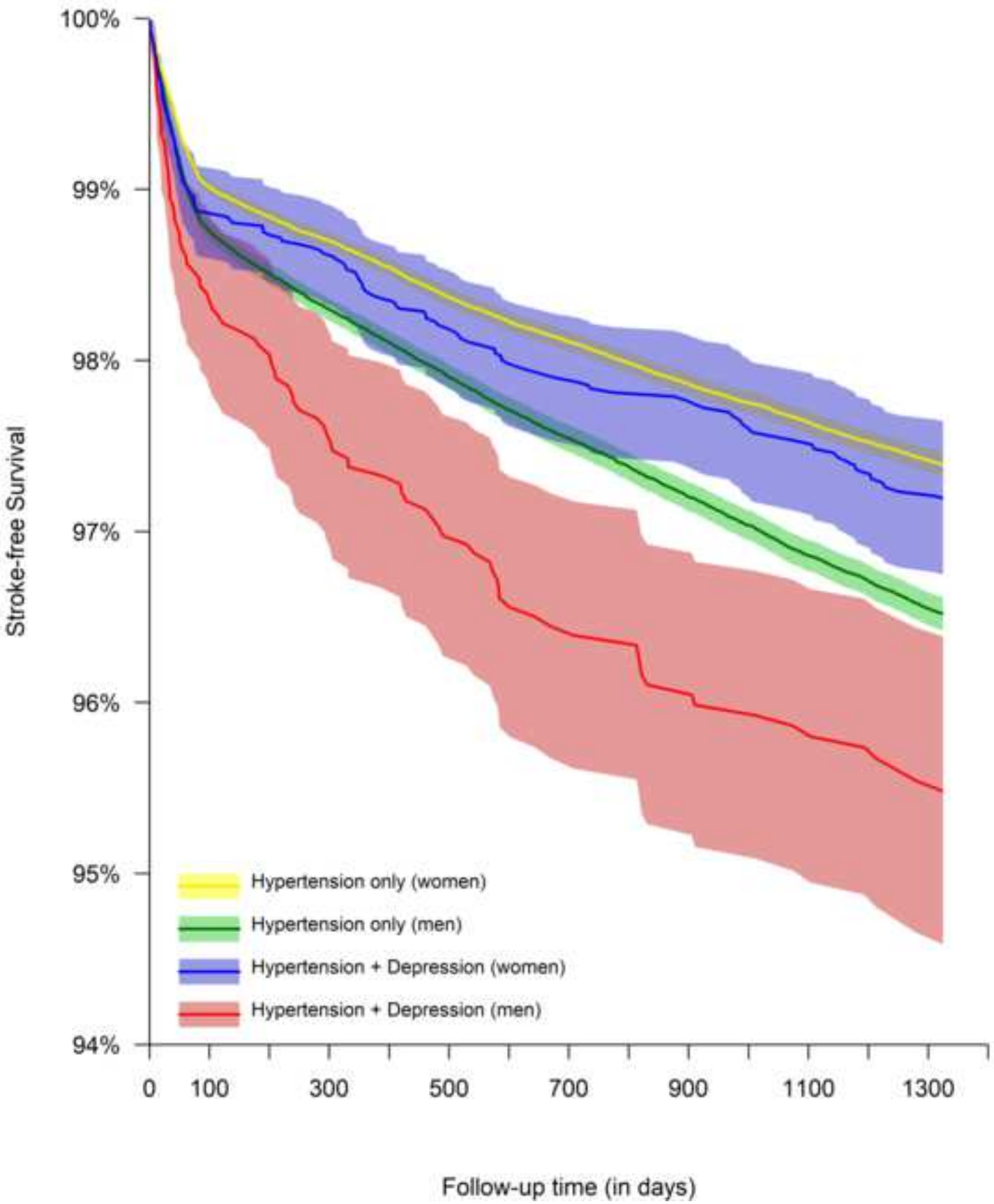

Table S1. Sub-analysis: adjusted hazard ratios with 95% confidence intervals (CI) of acute hospitalization due to stroke for the interaction between depression and being male excluding patients with admissions due to each specific type of stroke

Type of stroke being left out (ICD-9 code (3 digits))	Number of patients excluded	Hazard ratio [95% CI]
Subarachnoid hemorrhage (430)	429	1.26 [0.97, 1.63]
Intracerebral hemorrhage (431)	1,923	1.39 [1.05, 1.83]*
Other and unspecified intracranial hemorrhage (432)	581	1.29 [0.99, 1.68]
Occlusion and stenosis of precerebral arteries (433)	179	1.30 [1.00, 1.68]*
Occlusion of cerebral arteries (434)	8,454	1.09 [0.75, 1.59]
Transient cerebral ischemia (435)	1,326	1.31 [1.00, 1.73]*
Acute, but ill-defined, cerebrovascular disease (436)	2,166	1.31 [0.98, 1.73]
Other and ill-defined cerebrovascular disease (437)	116	1.29 [1.00, 1.68]*

Note. Estimates adjusted for age, sex, depression, previous stroke, lipid disorder, ischemic heart disease, diabetes, atrial fibrillation, tobacco abuse, alcohol abuse, receiving social security assistance.
* $P \leq 0.05$

Table S2. Sub-analysis: mixed effects Cox proportional hazard model estimating the adjusted hazard ratios with 95% confidence interval (CI) of stroke mortality in hospital, 2011 – 2014

	Model 1	Model 2
	Hazard ratio [95% CI]	Hazard ratio [95% CI]
Age (measured in 10-year)	2.22 [2.11, 2.35] ***	2.22 [2.11, 2.34]***
Male (female as referent)	1.44 [1.29, 1.60] ***	1.61 [1.40, 1.86]***
Receiving social security assistance	1.44 [1.27, 1.63] ***	1.44 [1.27, 1.64]***
Prior stroke	2.17 [1.78, 2.65] ***	2.14 [1.12, 4.08]*
Lipid disorder	0.71 [0.60, 0.84] ***	1.28 [0.77, 2.11]
Ischemic heart disease	1.43 [1.12, 1.84] *	1.17 [0.53, 2.56]
Atrial fibrillation	3.88 [2.99, 5.03] ***	9.87 [4.53, 21.51]***
Diabetes	1.01 [0.89, 1.14]	1.09 [0.74, 1.60]
Tobacco abuse	1.04 [0.58, 1.84]	11.35 [1.07, 120.73]*
Alcohol abuse	2.46 [0.61, 9.93]	-
Statin prescription	0.72 [0.58, 0.89] *	1.20 [0.63, 2.28]
Depression	1.12 [0.78, 1.59]	0.94 [0.33, 2.71]
Interaction with male sex:		
Male (female as referent) × Prior stroke		1.01 [0.68, 1.50]
Male (female as referent) × Lipid disorder		0.65 [0.46, 0.93]*
Male (female as referent) × Ischemic heart disease		1.15 [0.70, 1.89]
Male (female as referent) × Atrial fibrillation		0.52 [0.31, 0.89]*
Male (female as referent) × Diabetes		0.95 [0.74, 1.21]
Male (female as referent) × Tobacco abuse		0.27 [0.07, 1.02]
Male (female as referent) × Alcohol abuse		-
Male (female as referent) × Statin prescription		0.70 [0.46, 1.08]
Male (female as referent) × Depression		1.13 [0.54, 2.37]

Note. Estimates for alcohol abuse and its interaction with male sex in Model 2 omitted due to extremely wide confidence intervals. * $P \leq 0.05$, *** $P \leq 0.001$.