# Association of major depressive episodes with stroke risk in a prospective study of 0.5 million Chinese adults

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## Abstract

**Background and Purpose**—Although the relationship between depression and stroke risk has been investigated, findings in previous reports were conflicting. The aim of this study was to prospectively examine the effect of major depressive episodes (MDE) on stroke incidence and further assess the potential dose-response relationship between numbers of depression symptoms and subsequent stroke risk in Chinese population.

**Methods**—A total of 199 294 men and 288 083 women aged 30 to 79 years without a prior history of stroke, heart disease and cancer in the China Kadoorie Biobank cohort were followed from 2004 to 2013. A World Health Organization Composite International Diagnostic Interview-Short Form was used to access MDE according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Stroke events were ascertained through death certificates, medical records and health insurance data.

**Results**—Past year MDE was marginally associated with a 15% increased risk of stroke (adjusted hazard ratio = 1.15, 95% confidence interval = 0.99-1.33) in the fully-adjusted model, and the association was steeper and statistically significant in individuals aged <50 years, smokers, drinkers, those with higher education degree, BMI <24.0 kg/m$^2$ and no history of diabetes. Moreover, there was a positive dose-response relationship between the number of depression

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**Disclosures**
None.

symptoms and increased stroke risk ($P_{trend}$ = 0.011). Additionally, smoking status significantly interacted with MDE on stroke onset ($P$ for multiplicative interaction = 0.025).

**Conclusions**—Findings from this large prospective study suggest that the presence of MDE is a risk factor for stroke, especially in smokers.

## Keywords

depression; prospective study; stroke

## Subject Terms

Mental Health; Cerebrovascular Disease/Stroke

## Introduction

Stroke is the second most common cause of mortality worldwide and the first leading cause of death and disability in China.[1, 2] According to the World Health Organization report, the incidence of stroke in China is growing at an annual rate of 8.7 % and this trend will most likely continue over the next three decades.[3, 4] It is well known that early identification of risk factors for stroke would allow for effective preventive strategies and reduced economic burden. Some well-established stroke risk factors including hypertension, diabetes, coronary artery disease, smoking, physical inactivity and obesity have been identified;[5] however, it is also necessary to investigate more potential risk factors.

Major depression, a serious psychiatric disorder affecting ~16% of the general population,[6] is a known risk factor for vascular diseases such as coronary heart disease and myocardial infarction.[7, 8] It's worth noting that a number of researches including prospective studies have investigated the associations between depressive disorder and the occurrence of stroke, but they have yielded mixed results. For example, a recent large cohort study with 80 574 participants showed an increased stroke risk in women with a previous diagnosis of depression,[9] but other several studies found no evidence of depression being a significant risk factor for cerebrovascular diseases[10, 11] or showed an increased stroke risk only in persons younger than 65 years old.[12] These conflicting findings from the existing studies may be due to a limited sample size, a short follow-up duration or the use of self-reported symptom scales rather than diagnostic instruments to assess depressive disorder.[11–13] Moreover, the relationship between depression and stroke may differ in different countries and races, because of divergent medical, behavioral, or social responses to depressive disorder or differential prevalence of other cardiovascular risk factors.

Thus, we conducted a prospective study with a relatively rigorous design to investigate the relationship between major depressive episodes (MDE) and incidences of stroke and further examine the potential dose-response effect of depression symptoms on stroke risk in a large cohort-the China Kadoorie Biobank of 0.5 million people enrolled from 10 geographically defined regions of China.

# Methods

## Study population

Detailed information about the China Kadoorie Biobank cohort design, methods, participants and follow-up have been described previously.[14] Briefly, a total of 512 891 adults aged 30-79 years were enrolled into the cohort during 2004-08 from 10 diverse urban and rural areas in China and followed up ever since for cause-specific mortality as well as any episode of hospitalization, using routine mortality and health insurance data. In 10 study areas, the baseline survey was carried out by a Regional Coordinating Centre (RCC) and survey team, consisting of about 15 full-time staff with medical qualifications and fieldwork experience. Before the start of survey, all the staff underwent training including questioning technique, uniform methods of physical examination, standardized survey process, etc. At baseline, all the participants were face-to-face interviewed by trained staff using a standardized laptop-based questionnaire to collect detailed information, including demographic characteristics, socioeconomic status, medical history, personal behavior (e.g., smoking, alcohol and tea drinking), diet, physical activity and for women only, reproductive history. After the interview, a range of physical measurements were undertaken for each participant and a 10-ml blood sample was collected. All individuals provided written informed consent before the participation.

For the present study, participants who had a recorded implausible censoring date for loss to follow-up (n=1), or reported a prior history of stroke (n=8884), heart disease (n=15 472) and cancer (n=2577) at baseline were excluded, remaining a population of 487 377 individuals (men=199 294; women=288 083) eligible for analysis of the association between MDE and risk of stroke.

Our study was approved by the Ethics Review Committee of the Chinese Center for Disease Control and Prevention, Beijing, China, and the Oxford Tropical Research Ethics Committee, University of Oxford, Oxford, UK.

## Assessment of major depressive episodes

Past year MDE at baseline was defined using the Chinese version of computerized Composite International Diagnostic Inventory -Short form,[15] which produces similar population estimates of major depression to the Structured Clinical Interview for DSM (SCID).[16, 17] Compared with the full Composite International Diagnostic Interview, the MDE diagnoses using short form have shown sensitivity of 89.6%, specificity of 93.9% and overall classification accuracy of 93.2%.[15] Subjects were defined as having past year MDE if they had felt sad, blue, or depressed for 2 weeks or more during the past 12 months, and if they had at least three of seven additional symptoms including loss of interest and pleasure, loss of energy or fatigue, weight change, sleep problems, concentration problems, feelings of worthlessness, and thoughts of suicide.[18]

## Ascertainment of stroke

Each participant's vital status was ascertained through China's Disease Surveillance Point death registries[19] and residential records. Causes of death from official death certificates

were supplemented, if necessary, by a review of medical records. Linkage to national and local health insurance (HI) databases also helped to improve the accuracy of diagnosis and classification of reported conditions, outcome adjudication, and further data collection. Additionally, participants who were not included in the HI system were followed annually by dedicated staff members to ascertain their status including disease development, hospital admission, death and migration.

Stroke was defined as a focal neurological deficit of sudden or rapid onset lasting 24 hours or until death, confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). According to the International Classification of Diseases, 10th edition (ICD-10), strokes were coded as I60 (subarachnoid stroke), I61 (haemorrhagic stroke), I63 (ischaemic stroke) and I64 (other or unknown stroke type) by trained staff blinded to the baseline information. Stroke cases were further confirmed by a professional team consisting of 23 neurologists who received strict training including the recognition of CT/MRI imaging, application of uniform diagnostic criteria and standardized verification process.

## Assessment of variables

Demographic and socioeconomic characteristics including age, sex, region (rural or urban), marital status (married, widowed, separated/divorced, or never married), education level (no formal school, primary school, middle school, high school, college, or university and above) and annual household income (<20 000 Yuan or 20 000 Yuan) were collected at the baseline interview. Lifestyle factors included self-reported smoking status (never smoker, occasional smoker, ex-smoker, or current regular smoker), alcohol use (non-drinker, occasional drinker, ex-drinker, or current regular drinker) and total physical activity calculated as metabolic equivalent task hours (MET-hours/day) spent on work, transportation, housework, non-sedentary recreation and sedentary leisure. In addition, all participants were asked to report personal medical history, including hypertension, diabetes, chronic hepatitis or cirrhosis, peptic ulcer, etc.

At baseline, weight, height and blood pressure were measured using standard instruments and protocols by trained staff. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared. Prevalent hypertension was defined as measured systolic blood pressure 140 mmHg, measured diastolic blood pressure 90 mmHg, self-reported diagnosis of hypertension, or self-reported use of antihypertensive medication at baseline. Prevalent diabetes was defined as measured fasting blood glucose 7.0 mmol/L, measured random blood glucose 11.1 mmol/L, or self-reported diagnosis of diabetes.

## Statistical analysis

Person-years were measured from baseline (2004-08) until the date of stroke diagnosis, death of any other cause, or December 31, 2013, whichever occurred first. Comparisons between respondents with different baseline depression status were conducted using Student's T-test for continuous variables and Chi-squared test for categorical variables. Multivariate Cox proportional hazard regression analyses were then performed to estimate the relationship between MDE and stroke risk. Besides, stratification analysis was conducted

to investigate the association in different subgroups and the Chi-square-based Q test was used to test the heterogeneity. Interaction analysis was further carried out between MDE and selected exposures collected in the study. Data analyses were carried out by R software (Version 3.0.2, 2013-09-25; R Foundation for Statistical Computing, http://www.cran.r-project.org/). The significance level was set at $P < 0.05$ and $P$ values were given for two-sided tests.

## Results

Baseline characteristics of the study population stratified by depression status are summarized in Table 1. Individuals with past year MDE were more likely to be younger, female, rural residents and solitary (widowed, separated/divorced, or never married), and have lower education, household income and BMI, but less likely to be physically active, current regular smokers and drinkers, compared with those without a history of depression. Besides, the prevalence of diabetes was higher in depressed people, whereas hypertension was more prevalent in those without MDE. In addition, the associations between baseline characteristics and stroke risk were displayed in supplementary file Table I in the (online-only Data Supplement, http://stroke.ahajournals.org).

During 3 429 808 person-years of follow-up between 2004 and 2013 (median, 7.2 years), a total of 27 623 (5.67%) first-ever strokes occurred [5255 hemorrhagic (subarachnoid or intracerebral), 21 427 ischemic and 941 unknown type of strokes]. As shown in Table 2, past year MDE was marginally associated with a 15% increased risk of stroke with adjustment of age, sex, marital status, household income, education, region, smoking status, alcohol consumption, physical activity, BMI, history of hypertension and history of diabetes [adjusted hazard ratio (HR) = 1.15, 95% confidence intervals (95% CI) = 0.99-1.33]. Furthermore, analysis was also conducted to evaluate the cumulative effect of the seven depression symptoms on stroke occurrence. Intriguingly, we found a significantly positive dose-response association between the number of symptoms and stroke risk ($P_{trend} = 0.011$). Compared with individuals having "0-2" depression symptoms, those with more symptoms had higher risk of stroke, especially for the group with "6" and "7" symptoms [adjusted HRs of 1.33 (1.01-1.74) and 1.47 (1.04-2.08), respectively].

The stratification analysis for the association between MDE and incident stroke was then conducted by all aforementioned variables. In supplementary analyses (Table II in the online-only Data Supplement, http://stroke.ahajournals.org), steeper and statistically significant associations were observed in individuals aged <50 years (adjusted HR, 1.54; 95% CI, 1.16-2.03), smokers (adjusted HR, 1.51; 95% CI, 1.16-1.98), drinkers (adjusted HR, 1.62; 95% CI, 1.08-2.41), those with higher education degree (adjusted HR, 1.38; 95% CI, 1.10-1.73), BMI <24.0 kg/m$^2$ (adjusted HR, 1.23; 95% CI, 1.02-1.49) and no history of diabetes (adjusted HR, 1.18; 95% CI, 1.02-1.38). However, heterogeneity in every two strata was significant only for age ($P = 0.003$), education ($P = 0.047$) and smoking status ($P = 0.024$). Furthermore, stratification analysis by different stroke subtypes was also performed, but the association with stroke incidence was not statistically significant for either hemorrhagic stroke or ischemic stroke.

Then, a statistically significant multiplicative interaction between MDE and smoking status on stroke risk was identified (Figure 1, *P* for interaction = 0.025). Compared with nonsmokers with no prior depression, current smokers with MDE had a 1.71-fold increased risk of stroke (adjusted HR = 1.71, 95% CI = 1.31-2.24, *P* < 0.001) after adjusting for age, sex, marital status, household income, education, region, alcohol consumption, physical activity, BMI, history of hypertension and history of diabetes.

## Discussion

In the present study, we found past year MDE was marginally associated with an increased risk of stroke, independently of potential confounders. A positive dose-response association was also observed between the number of depression symptoms and stroke risk. Additionally, smoking status significantly interacted with MDE on stroke occurrence.

A variety of prospective studies have assessed the association between depression and stroke incidence, suggesting that depression could be a modifiable risk factor for stroke;[20] however, few researches have examined such relationship in Chinese population. Our finding showed a marginally positive association between MDE and stroke incidence and a positive dose-response relationship between the number of depression symptoms and increased stroke risk, which were consistent with results from several previous studies.[9, 13, 20–22] For example, Larson *et al.*[21] reported the prior depressive disorder was associated with a 2.6-fold increased risk of stroke during a 13-year follow-up and Jackson *et al.*[22] found a 1.9 times elevated risk of incident stroke associated with depression during a 12-year follow-up. Additionally, some studies have already evaluated the effect of single specific symptom of depression on stroke occurrence.[13, 23, 24] Liebetrau *et al.*[13] found that both of depressed mood and loss of interest or pleasure were related to an increased incidence of stroke among 401 Swedes. Glymour *et al.*[23] demonstrated that endorsement of any individual depressive symptom could predict subsequent stroke risk among 14 778 American whites. Since the number of symptoms is the reflection of the disease severity, it is reasonable that the risk of stroke could increase with the severity of depression in this study.

The association between depression and first-ever stroke may have several explanations. Firstly, depression has been found to be associated with cardiac arrhythmia,[25] enhanced insulin resistance,[26] more white matter lesions,[27] and increased levels of platelet activation,[28] fibrinogen[29] and C-reactive protein,[30] all of which might influence stroke risk. Secondly, depression could affect the occurrence of stroke by acting on risk factors related to health, including low physical activity,[31] smoking,[32, 33] heavy drinking,[31] obesity,[34] and certain comorbidities.[35] Nevertheless, when adjusting for baseline measures of smoking status, alcohol consumption, physical activity, BMI, hypertension and diabetes, the effects of MDE on stroke incidence remained stable in the present study, indicating the effect of depression on stroke risk was independent of these factors. Finally, it is really hard for patients with depressive disorder to follow prescribed medical regimens,[36] including antihypertensive drugs and lipid-lowering medications, which may be another explanation for the elevated stroke risk. Thus, specific mechanisms for the association between depression and incident stroke still need to be further explored.

Besides, it was worth mentioning that, in the stratification analysis, we found the significant association between MDE and stroke onset only existed in subjects younger than 50 years old but not in the elderly, similar with the findings in two previous studies.[12, 37] The Framingham Study suggested the antecedent depression was associated with a 3-fold increased risk of stroke in participants aged <65 years but not in those aged 65 years.[12] Likewise, another study showed an elevated stroke risk with depression in individuals aged 55 to 64 years but not in those 65 years old and above.[37] Some reasons may explain this result. On one hand, older people with depression have a considerably higher mortality,[38, 39] which could interfere with stroke occurrence through preventing its change into an observable event, thus altering the risk of stroke linked to depressive disorder. On the other hand, younger depressed individuals usually have greater life pressure and more daily hassles, which might increase stroke risk by aggravating the neuroendocrine effect of depression.[40] Meanwhile, our results provided statistical evidence on multiplicative interactions between baseline MDE and smoking status in relation to stroke risk. Both depressive disorder and tobacco smoking have been identified to independently increase the risk of stroke in the literature[41, 42] as well as in the present study. Additionally, increasing evidence has suggested that cigarette use may cause or worsen depressive symptoms,[43, 44] whereas the presence of depression could also increase the risk of daily smoking in some earlier reports.[32, 33] Taking together, these results suggested the effect of the two risk factors on stroke onset could be modified by each other, although the exact biological mechanism is unclear. Further studies with large samples and functional investigations may lead to important insights for such interactions.

The strengths of our study include its prospective design, markedly large sample size, long duration of follow-up, complete endpoint-data, and careful control of several confounding factors. However, some limitations should be considered. First of all, the relatively low prevalence of MDE at baseline could limit the capacity of the current study to detect associations between the depression and stroke risk. The potential bias arising from a 1-year period of retrospective recall for the MDE may provide an alternative explanation for the low prevalence. Another reason may be that the participants in this study usually have better mental health relative to general people. To more generally investigate the association between depression and stroke risk, we also compared the participants with negative emotions (feeling sad, blue or depressed, feeling useless, feeling exhausted or even numb, or losing interest in most things, n=13 601), instead of MDE (n=2988), with those who were not depressed at baseline, and a significantly positive association was observed between past year depression and stroke incidence (adjusted HR = 1.15, 95% CI = 1.07-1.24). Secondly, participants with minor stroke episodes may not be hospitalized and therefore not reported in the HI system, which could lead to the bias. Thirdly, some mental factors may potentially modify the real effect of depressive disorder on stroke risk in this study. However, further adjusting for prior history of psychiatric disorders or neurasthenia at baseline did not obviously change the hazard of incident stroke with adjusted HR of 1.14 (0.99-1.32). Finally, we assessed MDE only at the time of the baseline survey and did not track the progression of the disorder, which might also affect the association of MDE with stroke risk.

## Conclusions

In summary, our study showed a marginally positive association between past year MDE and stroke incidence, which could be modified by smoking status. Besides, there was a significant dose-response relationship between the number of depression symptoms and increased stroke risk. Further prospective studies in diverse populations are warranted to validate the results and enhance the generalizability of these findings.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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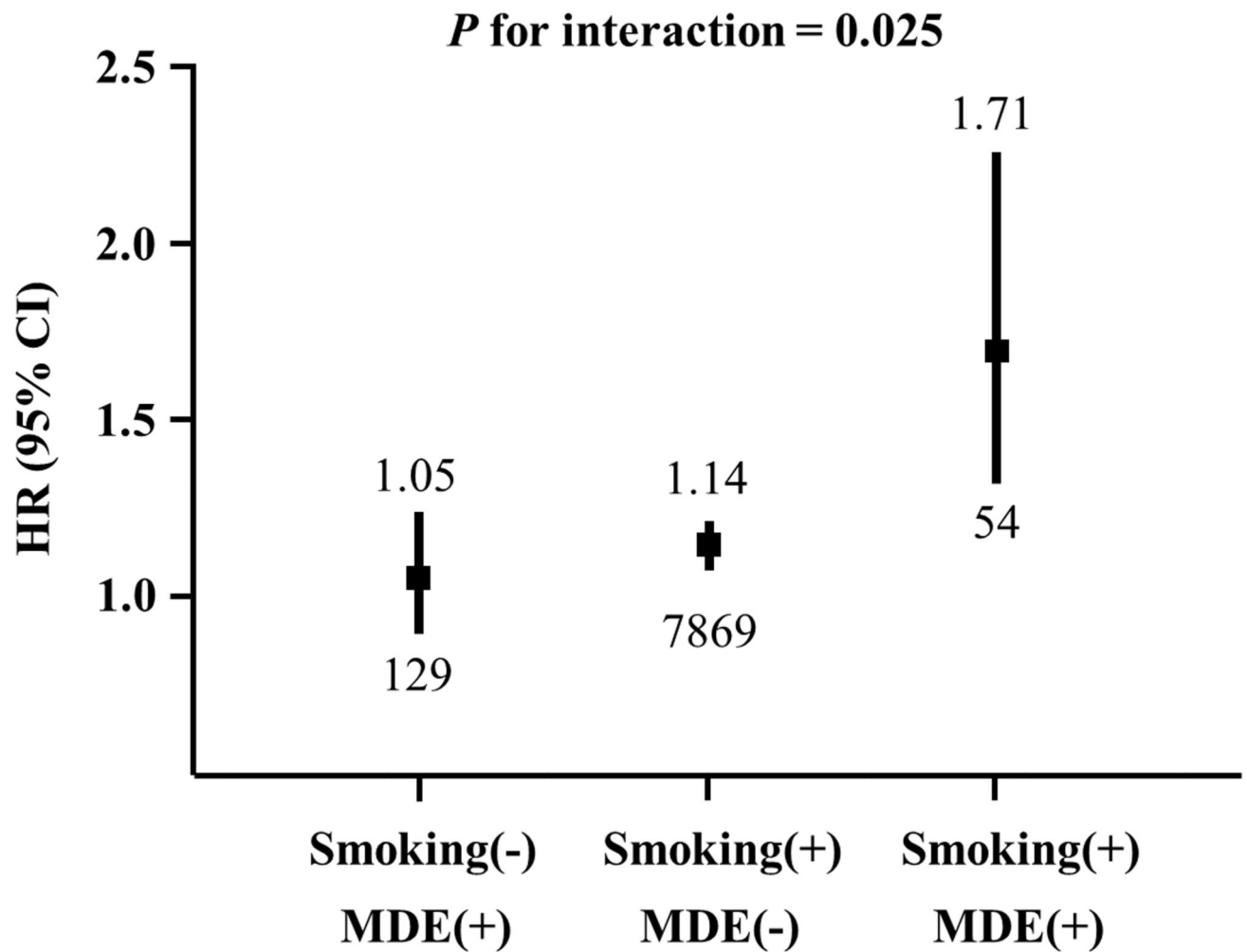
**Figure 1. Interaction analysis between smoking status and baseline depression status.**
Adjusted for age, sex, marital status, household income, education, region, alcohol consumption, physical activity, BMI, history of hypertension and history of diabetes. MDE, major depressive episodes. "Smoking(-) & MDE(-)" was used as the reference group. Squares represent the hazard ratios (HR) and vertical lines represent the corresponding 95% confidence intervals (95% CI). Numbers above the CIs are the HRs and numbers below the CIs represent participants with stroke events.

**Table 1**

**Baseline characteristics of the study population according to baseline depression status**

| Characteristic | All subjects | MDE | | P |
|---|---|---|---|---|
| | | No | Yes | |
| No. of participants (%) | 487 377 (100.0) | 484 389 (99.4) | 2988 (0.6) | |
| Mean age (yr) | 51.0 | 51.1 | 50.4 | <0.001 |
| Male, n (%) | 199 294 (40.9) | 198 456 (41.0) | 838 (28.1) | <0.001 |
| Rural area, n (%) | 277 236 (56.9) | 275 254 (56.8) | 1982 (66.3) | <0.001 |
| Currently married, n (%) | 442 943 (90.9) | 440 714 (91.0) | 2229 (74.6) | <0.001 |
| Middle school and above, n (%) | 239 676 (49.2) | 238 401 (49.2) | 1275 (42.7) | <0.001 |
| Household income 20 000 Yuan/year, n (%) | 208 490 (42.8) | 207 569 (42.9) | 921 (30.8) | <0.001 |
| Mean BMI (kg/m$^2$) | 23.6 | 23.6 | 23.1 | <0.001 |
| Diabetes, n (%) | 26 162 (5.4) | 25 975 (5.4) | 187 (6.3) | 0.030 |
| Hypertension, n (%) | 240 201 (49.3) | 238 845 (49.3) | 1356 (45.4) | <0.001 |
| Current regular smoker, n (%) | 130 371 (26.8) | 129 731 (26.8) | 640 (21.4) | <0.001 |
| Current regular drinker, n (%) | 73 644 (15.1) | 73 344 (15.1) | 300 (10.0) | <0.001 |
| Mean physical activity (MET-hr/day) | 21.6 | 21.6 | 20.7 | 0.002 |

MDE indicates major depressive episodes; BMI, body mass index; and MET, metabolic equivalent of task.

**Table 2**

**Hazard ratio (95% confidence intervals) of incident stroke according to baseline depression status and numbers of depression symptoms**

| Variables | No. of subjects | PYs of follow-up | Incident strokes | Incidence rate (per 1000 PYs) | Model 1 | Model 2 |
|---|---|---|---|---|---|---|
| MDE | | | | | | |
| No | 484 389 | 3 407 861 | 27 440 | 8.05 | 1.00 | 1.00 |
| Yes | 2988 | 21 947 | 183 | 8.34 | 1.14 (0.98-1.31) | 1.15 (0.99-1.33) |
| No. of depression symptoms | | | | | | |
| 0-2 | 484 389 | 3 407 861 | 27 440 | 8.05 | 1.00 | 1.00 |
| 3 | 475 | 3471 | 25 | 7.20 | 0.92 (0.62-1.36) | 0.99 (0.67-1.47) |
| 4 | 603 | 4424 | 32 | 7.23 | 0.97 (0.69-1.38) | 1.01 (0.71-1.43) |
| 5 | 741 | 5490 | 41 | 7.47 | 1.01 (0.75-1.37) | 1.01 (0.74-1.37) |
| 6 | 719 | 5251 | 53 | 10.09 | 1.37 (1.05-1.79) | 1.33 (1.01-1.74) |
| 7 | 450 | 3311 | 32 | 9.66 | 1.47 (1.04-2.08) | 1.47 (1.04-2.08) |
| *P* for trend | | | | | 0.010 | 0.011 |

Model 1: Adjusted for age and sex.

Model 2: Model 1 plus adjustment for marital status, household income, education, region, smoking status, alcohol consumption, physical activity, BMI, history of hypertension and history of diabetes.

MDE indicates major depressive episodes; and PYs indicates person-years.