Depressive Symptoms, a Time-Dependent Risk Factor for Coronary Heart Disease and Stroke in Middle-Aged Men
The PRIME Study

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Background and Purpose—To date, the association between depressive symptoms and the risk of cardiovascular diseases remains controversial. We investigated prospectively, within the same population, the time course of the association between baseline depressive symptoms and first stroke or coronary heart disease event.

Methods—In the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study, a multicenter, observational, prospective cohort, 9601 men from France and Northern Ireland were surveyed for the occurrence of first coronary heart disease (n=647) and stroke events (n=136) over 10 years. At baseline, the fourth quartile of a 13-item modified Center for Epidemiological Studies questionnaire was used to define the presence of depressive symptoms. We sought the best time-dependent function to assess the association between depressive symptoms and outcomes. Thus, the hazard ratios were estimated by a Cox proportional hazard model after splitting the follow-up before and after 5 years of follow-up time periods.

Results—Depressive symptoms at baseline were associated with coronary heart disease in the first 5 years of follow-up (hazard ratio, 1.43; 1.10–1.87) and with stroke in the second 5 years of follow up (hazard ratio, 1.96; 1.21–3.19) after adjustment for age, study centers, baseline socioeconomic factors, traditional vascular risk factors, and antidepressant treatment. The association was even stronger for ischemic stroke (n=108; hazard ratio, 2.48; 1.45–4.25).

Conclusions—The current study suggests that in healthy, European, middle-aged men, baseline depressive symptoms are associated with an increased risk of coronary heart disease in the short-term, and for stroke in the long-term. (Stroke. 2012;43:1761-1767.)

Key Words: coronary heart disease ■ depressive symptoms ■ risk factors ■ time-dependent association

Psychosocial factors are being explored increasingly as potential risk factors for the onset of cardiovascular diseases.¹ For instance, depressive symptoms have been shown to be associated with incident coronary heart disease (CHD) in several large prospective studies.² Conversely, their association with stroke has been studied less extensively, and mixed conclusions have emerged.³–¹⁰ Few studies investigated and compared the association between depressive symptoms and CHD or stroke events within the same population.¹¹ A recent meta-analysis has shown a stronger association between depressive symptoms and CHD in studies with shorter follow-up, suggesting reverse causality as a possible explanation.²,¹² The reverse causality hypothesis might also apply to the association with stroke risk, given that depressive symptoms might be the expression of preexisting cerebrovascular disease; this is the so-called vascular depression hypothesis.¹³ Alternatively, the association of depressive symptoms with stroke might only become apparent in the long-term, given that stroke hazard increases with aging.⁷

Using data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study, our aim was to investigate prospectively the associations of depressive
symptoms with first CHD and stroke events, exploring in particular whether these associations were time-dependent.

Methods

Study Population
Details regarding recruitment and baseline examination of the PRIME Study cohort have been previously described. Overall, 10,602 men age 50 to 59 years were recruited between 1991 and 1993 by 4 collaborating World Health Organization Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) centers in Belfast, Northern Ireland, and in Lille, Strasbourg, and Toulouse, France. Among these, 891 men had a history of CHD or a history of stroke at baseline examination; an additional group of 110 men had several missing covariates (Figure 1). The study protocol was approved by the Institutional Review Board of the Broussais Hospital in Paris, France. Written informed consent was obtained for each subject who agreed to participate in the PRIME Study.

Baseline Characteristics
A full description of the clinical and laboratory measurements that were carried out has been published elsewhere. Briefly, a self-administered health questionnaire was completed by subjects at their homes and was subsequently checked by trained interviewers at the clinic. It covered a broad range of clinical information, smoking habits, and use of medications. A subset of biological measurements was carried out using fresh plasma for the entire cohort.

Assessment of Baseline Depressive Symptoms
The Center for Epidemiological Studies Depression Scale is a 20-item, self-report rating scale (each item can be scored 0–3) that is widely used in epidemiological studies designed to evaluate the frequency and severity of depressive symptoms. In our study, we used a modified Center for Epidemiological Studies Depression Scale with 13 binary items to assess depressive symptoms. Based on our previous work, the last quartile of the depressive symptoms score was used to define the presence of depressive symptoms. A depressive symptoms score could not be computed in 11.2% of the study population (n=1,107) because of missing data in some items. Those men were characterized by less favorable socioeconomic features compared with men without missing data on the depressive symptoms score. Missing depressive symptoms scores were imputed in the analysis (see Statistical Analysis).

Follow-Up and Verification of Cases
During the 10-year follow-up period, subjects were contacted annually by letter and were asked to complete a clinical event questionnaire. For all subjects reporting a possible event, clinical information was sought directly from hospital or general practitioner records. CHD and stroke events were validated by 2 independent medical committees. CHD events (stable and unstable angina, myocardial infarction, and coronary death) were defined as previously described using clinical, biological, stress-test, scintigraphic, or angiographic criteria. Stroke was defined, according to World Health Organization MONICA criteria, as a new focal or global neurological deficit with a rapid onset and of vascular origin, persisting for more than 24 hours (except if the symptoms were interrupted by surgical intervention or death). Transient ischemic attacks and strokes caused by a blood disease, cerebral tumor or metastasis, or secondary to a trauma, were not considered by the stroke medical committee. Follow-up was 100%.

Statistical Analysis
The baseline characteristics were compared by quartiles of the depressive symptoms score using Chi-square tests and by analysis of variance for categorical and continuous variables, respectively. Men from the first 3 quartiles of the depressive symptoms score served as the reference category for the estimation of the hazard ratios because their CHD and stroke event rates did not differ. The time-dependent association hypothesis between depressive symptoms and each outcome was first explored by plotting annual incidence rates (actuarial method) and by estimating the regression coefficients over time using smooth spline functions. To assess the best time-dependent function, an interaction term between baseline depressive symptoms and several functions of time, including log of time, 1/time, time, squared time, and time interval (before and after 5 years of follow-up), were alternatively employed in an unadjusted Cox model. Splitting the follow-up into 2 periods of before and after 5 years provided the most statistically significant interaction term with probability values of 0.004 and of 0.041 for CHD and stroke events, respectively. Thereafter, Cox proportional hazards models by 5 year-time intervals (in the first 5 years and thereafter) were used. Analyses were adjusted for confounding factors, including age; study centers; education level (college, high school, junior school); employment status (employed, unemployed, retired, disability); marital status; physical activity; smoking status (current/past or never); daily alcohol intake; and possible mediating factors, including systolic blood pressure, use of antihypertensive drugs, body mass index, total and high-density lipoprotein cholesterol, treatment for diabetes, and use of antidepressant treatment. A dummy variable indicator of missing value for the depressive symptoms score was included in the models. In sensitivity analysis, missing values for the depressive symptoms score were imputed using multiple imputations by chain equations. All tests were 2-sided, and the alpha error probability was set to 5%. The software R (R Foundation for Statistical Computing, http://www.R-project.org) was used for statistical analysis.

Results

Baseline Characteristics
The flow chart of the study is reported in Figure 1. The mean age of the 9,601 men was 55 years (range, 48–64 years). The mean depressive symptoms score was 2.03 (range, 0–13), and 1.8% of men used antidepressant treatment.

The baseline characteristics by quartile of the depressive symptoms score are reported in Table 1. Subjects from the fourth quartile of the depressive symptoms score were more often from the north of France, and were current smokers, less likely to be physically active, and more often under treatments for hypertension, diabetes, and depression. They were more often single, unemployed, or in work disability. They also had a higher average of daily alcohol intake and a lower education level compared with those in the bottom quartiles (first, second and third quartiles).
Depressive Symptoms, CHD, and Stroke Hazards

Over a median follow-up of 10 years, 647 first CHD and 136 first stroke events occurred, yielding a mean annual incidence rate of 7.2 (95% CI, 6.7–7.8) and 1.5 (1.2–1.7) per 1000 person-years, respectively. Figure 2 shows that annual incidence rates of CHD were higher in men from the fourth quartile of the depressive symptoms score compared with men from the bottom quartiles during the first 5 years of follow-up, and especially between 3 and 5 years. This difference was observed in the second 5 years of follow-up for stroke. Smooth spline functions of time-dependent regression coefficients showed the same trends (Figure 3). The hazard ratios (HR) for each outcome by 5-year time intervals are reported in Table 2. After adjustment for confounding and mediating factors, men from the fourth quartile of the depressive symptoms score had a 43% increased risk of CHD (HR, 1.43; 95% CI, 1.10–1.87) in the first 5 years of follow-up, and an almost 2-fold increased risk of stroke in the late 5 years of follow-up (HR, 1.96; 95% CI, 1.21–3.19) compared with men from the bottom quartiles. The association with depressive symptoms was even stronger for ischemic stroke events (n=108; HR, 2.47; 95% CI, 1.45–4.25).

In sensitivity analysis, imputing missing depressive symptoms score yielded very similar results as shown by adjusted HRs of 1.42 (1.15–1.92) and 2.00 (1.22–3.28), respectively, for CHD in the first 5 years and stroke in the late 5 years (online-only Supplemental Table). During follow-up, 23 men experienced both stroke and CHD events, and censoring time to the first event provided similar results.

Discussion

In this prospective observational study of healthy, white, middle-aged men, baseline depressive symptoms were independently and significantly associated with CHD in the first 5 years of follow-up and with stroke in the second 5 years. The risk associated with depressive symptoms was stronger for ischemic stroke than for CHD events.

Comparison With Other Studies

The current study confirms that depressive symptoms are independently associated with CHD events. Despite the variety of tools used to assess depressive symptoms in published studies, the magnitude of the HR in the current study (1.43) is in the range of previously published risk estimates in the primary prevention setting (from 1.5–2.0).\(^1\)\(^2\)

Whereas the association of depressive symptoms with stroke events has been less extensively studied and with the report of mixed results,\(^5\)\(^–\)\(^\text{8}\)\(^,\)\(^24\)\(^–\)\(^26\) a recent meta-analysis\(^27\) found a significant association between depression (including depressive symptoms, CHD, and Stroke Hazards

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symptoms) and stroke risk. The described association in our article is in line with results reported in 3 previous large, population-based studies, and with results of the large case-control study, the Interstroke Study phase 1. The lack of association between depressive symptoms and stroke in some previous studies may lie in differences in the studied populations (age range, follow-up duration) or in statistical issues, including the assessment of a possible time-dependent association.

Interpretation and Possible Explanation of Study Results
A noteworthy point is that no significant association would have been observed either with CHD (HR, 1.12; 95% CI, 0.91–1.36) or with stroke events (HR, 1.41; 95% CI, 0.95–2.11) if CHD and stroke hazards had been estimated over 10 years without considering time-dependent effects. The present study suggests a time-dependent association of depressive symptoms with CHD and stroke events, and some hypotheses can be suggested. The short-term association with CHD could reflect reverse causality if men had depressive symptoms in response to a silent coronary artery disease. This is supported by a recent meta-analysis by Nicholson et al., showing that the highest risk estimates between depressive symptoms and CHD events were found in studies with shorter follow-up periods. In support of the reverse causality hypothesis, depression had no significant association with incident CHD.

Figure 2. Annual incidence rates (for 1000 person-years) of coronary heart disease (CHD) and stroke over 10 years for men from the fourth quartile (Q4) compared with men from the bottom quartiles of the baseline depressive symptoms score (Q1–Q3) with 95% Confidence Intervals.

Figure 3. Estimates of time-varying coefficients from survival models comparing men from the fourth quartile with men from the bottom quartiles of the baseline depressive symptoms score with 95% Confidence Intervals. CHD indicates coronary heart disease.
Table 2. Unadjusted and Multivariate-Adjusted Hazard Ratios for Coronary Heart Disease and Stroke by 5-Year Time Intervals in Men From the Last Compared With Men From the Bottom Quartiles of the Baseline Depressive Symptoms Score

<table>
<thead>
<tr>
<th>CHD</th>
<th>Events</th>
<th>Incidence</th>
<th>HR Unadjusted</th>
<th>HR Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 10 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>647</td>
<td>7.23 (6.67–7.79)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>444</td>
<td>6.97 (6.32–7.62)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q4</td>
<td>132</td>
<td>8.24 (6.83–9.64)</td>
<td>1.18 (0.97–1.44)</td>
<td>1.12 (0.92–1.37)</td>
</tr>
<tr>
<td>0 to 5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>321</td>
<td>6.86 (6.11–7.61)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>210</td>
<td>6.34 (5.49–7.20)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q4</td>
<td>81</td>
<td>9.53 (7.46–11.61)</td>
<td>1.51 (1.17–1.95)</td>
<td>1.43 (1.10–1.87)</td>
</tr>
<tr>
<td>5 to 10 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>326</td>
<td>7.63 (6.80–8.46)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>234</td>
<td>7.65 (6.67–8.63)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q4</td>
<td>51</td>
<td>6.77 (4.91–8.63)</td>
<td>0.89 (0.65–1.20)</td>
<td>0.83 (0.61–1.13)</td>
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<table>
<thead>
<tr>
<th>Stroke</th>
<th>Events</th>
<th>Incidence</th>
<th>HR Unadjusted</th>
<th>HR Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 10 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>1.48 (1.23–1.73)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>89</td>
<td>1.36 (1.08–1.65)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q4</td>
<td>36</td>
<td>2.18 (1.47–2.89)</td>
<td>1.60 (1.09–2.36)</td>
<td>1.41 (0.95–2.11)</td>
</tr>
<tr>
<td>0 to 5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>1.12 (0.82–1.42)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>39</td>
<td>1.16 (0.8–1.53)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q4</td>
<td>9</td>
<td>1.04 (0.36–1.72)</td>
<td>0.90 (0.43–1.85)</td>
<td>0.70 (0.33–1.47)</td>
</tr>
<tr>
<td>5 to 10 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>1.87 (1.47–2.27)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q1-Q3</td>
<td>50</td>
<td>1.57 (1.14–2.01)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q4</td>
<td>27</td>
<td>3.42 (2.13–4.71)</td>
<td>2.17 (1.36–3.47)</td>
<td>1.96 (1.21–3.19)</td>
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</table>

<table>
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<tr>
<th>Ischemic Stroke</th>
<th>Events</th>
<th>Incidence</th>
<th>HR Unadjusted</th>
<th>HR Adjusted</th>
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<td>0 to 10 y</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
<td>1.18 (0.95–1.40)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q1-Q3</td>
<td>66</td>
<td>1.01 (0.77–1.25)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q4</td>
<td>32</td>
<td>1.94 (1.26–2.61)</td>
<td>1.92 (1.26–2.93)</td>
<td>1.65 (1.07–2.55)</td>
</tr>
<tr>
<td>0 to 5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>0.91 (0.64–1.18)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q1-Q3</td>
<td>31</td>
<td>0.93 (0.60–1.25)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Q4</td>
<td>8</td>
<td>0.93 (0.28–1.57)</td>
<td>1.00 (0.46–2.18)</td>
<td>0.75 (0.33–1.62)</td>
</tr>
<tr>
<td>5 to 10 y</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>1.46 (1.11–1.82)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q1-Q3</td>
<td>35</td>
<td>1.10 (0.74–1.47)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Q4</td>
<td>24</td>
<td>3.04 (1.82–4.25)</td>
<td>2.76 (1.64–4.63)</td>
<td>2.48 (1.45–4.23)</td>
</tr>
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</table>

Incidence is computed for 1000 person-years with 95% CI. Hazard Ratios and 95% CI were estimated by Cox proportional hazard model. Events count, incidence, and HR in individuals with missing depressive symptoms score are not shown. HR indicates hazard ratio; CHD, coronary heart disease; Q1, first quartile; Q3, third quartile; Q4, fourth quartile. *Adjusted for age; study centers; and socioeconomic factors, including marital status, education level, employment status, physical activity, smoking status, daily alcohol intake, systolic blood pressure, use of anti-hypertensive drugs, body mass index, total and high-density lipoprotein cholesterol, treatment for diabetes, and use of antidepressant treatment.
in a long-term follow-up survey of very young men, ie, when silent coronary artery disease is not likely and therefore reverse causation not feasible.\textsuperscript{12} Conversely, depressive symptoms may trigger CHD events through biological mechanisms, including imbalanced sympathetic-parasympathetic activity, disturbances in blood-clotting mechanisms, coronary artery endothelial dysfunctions, and activation of immune and inflammatory systems.\textsuperscript{1,18,32}

The current apparent lack of association between baseline depressive symptoms and stroke in the short-term may be caused by the limited number of events, given that 53 stroke events occurred in that period compared with 83 events in the second period. Thus, the current results regarding the short-term association between depressive symptoms and stroke need to be confirmed in higher-powered studies. The reverse causality hypothesis might apply to the association with stroke as well, because depressive symptoms might be markers for preexisting cerebrovascular disease, the vascular depression hypothesis.\textsuperscript{13} Of note, the results of 2 recent observational studies from the Rotterdam Study\textsuperscript{33} and the Health and Retirement Study\textsuperscript{34} do not support this hypothesis. The increase of stroke incidence with age\textsuperscript{24,26,35} may partly explain why the association with depressive symptoms becomes statistically significant in the long-term. Moreover, in our study, CHD events were 5 times more common than were stroke events, and the onset of CHD is known to be earlier than for stroke.\textsuperscript{36} Therefore, a competing risk phenomenon between CHD and stroke may also contribute to the time-dependent association between depressive symptoms and stroke.

Strengths and Limitations of Study

The prospective design, the survey of CHD and stroke events by the same teams within the same cohort, and the use of stringent diagnostic criteria to adjudicate CHD and stroke events, represent major strengths of the current study. Several limitations need to be acknowledged, however. Residual confounding cannot be excluded. In particular, atrial fibrillation was not investigated in the current study, precluding us to estimate its possible confounding effect on the association between depressive symptoms and stroke.\textsuperscript{26,36} Random effects attributable to small numbers could also be an explanation for the observed data, especially regarding the association between depressive symptoms and stroke.\textsuperscript{26,36} Change in and duration of depressive symptoms was also not available in the present study.\textsuperscript{37} Finally, the current results were obtained in middle-aged white men, and their reproducibility in other populations should be evaluated.

Conclusions

To conclude, the current data in apparently CHD- and stroke-free, middle-aged European men suggests an association of depressive symptoms with CHD in the short-term and with stroke in the long-term. The mechanisms underlying this heterogeneity, if confirmed in other studies, remain to be studied.

Acknowledgments

B.M.: statistical analysis, interpretation, and writing of the manuscript. J.-P.E.: supervision of statistical analysis, and interpretation of data and of writing of the manuscript. D.A., J.-B.R., M.M., B.H.: substantial contributions to acquisition of data and critical revision of the manuscript for important intellectual content. J.F., F.K., K.A., P.A., P.D.: substantial contributions to conception and design of the PRIME Study and critical revision of the manuscript for important intellectual content. P.D. and A.B.: coordination of the PRIME Study and critical revision of the manuscript for important intellectual content.

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Disclosures

None.

References


Depressive Symptoms, a Time-Dependent Risk Factor for Coronary Heart Disease and Stroke in Middle-Aged Men: The PRIME Study
Bilal Majed, Dominique Arveiler, Annie Bingham, Jean Ferrieres, Jean-Bernard Ruidavets, Michèle Montanye, Katherine Appleton, Bernadette Haas, Frank Kee, Philippe Amouyel, Pierre Ducimetiere and Jean-Philippe Empana

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Supplemental table
### Supplemental Table:

Hazard Ratios of men from the fourth quartile of the depressive symptoms score compared to those from the bottom quartiles. Missing values for the depressive symptoms score were imputed when performing these analyzes.

<table>
<thead>
<tr>
<th></th>
<th>0 to 10 Years</th>
<th>0 to 5 Years</th>
<th>5 to 10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>univariate</td>
<td>multivariate</td>
<td>univariate</td>
</tr>
<tr>
<td>CHD</td>
<td>1.17 (0.97,1.41)</td>
<td>1.10 (0.91,1.34)</td>
<td>1.48 (1.15,1.92)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.62 (1.12,2.38)</td>
<td>1.44 (0.97,2.15)</td>
<td>1.03 (0.49,2.17)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.92 (1.27,2.91)</td>
<td>1.67 (1.09,2.56)</td>
<td>1.16 (0.53,2.54)</td>
</tr>
</tbody>
</table>