Depression and Risk of Stroke
A Meta-Analysis of Prospective Studies

Jia-Yi Dong, BSc; Yong-Hong Zhang, MD, PhD; Jian Tong, MD, PhD; Li-Qiang Qin, MD, PhD

Background and Purpose—A history of depression may be associated with an increased risk of stroke. We aimed to determine the association between depression and risk of stroke by performing a meta-analysis of prospective studies.

Methods—Relevant studies were identified by a PubMed database search through May 2011 without restrictions and by reviewing reference lists of obtained articles. Community-based or population-based prospective studies that reported relative risk estimates with 95% confidence intervals for the association between depression and stroke were selected. Studies that enrolled participants with preexisting stroke at baseline were excluded. A random-effects model was used to compute the pooled risk estimate.

Results—Random-effects meta-analysis of 17 prospective studies involving 206,641 participants and 6086 cases demonstrated a significant positive association between depression and subsequent risk of stroke (pooled relative risk, 1.34; 95% confidence interval, 1.17–1.54) after adjustment for potential confounding factors. The associations were similar between men and women. Potential publication bias may exist, but correction for this bias using a formal statistical method did not materially alter the combined risk estimate.

Conclusions—Depression significantly increased the risk of development of stroke, and this increase was probably independent of other risk factors, including hypertension and diabetes. (Stroke. 2012;43:00-00.)

Key Words: cohort studies ■ depression ■ meta-analysis ■ risk factors ■ stroke

Depression is highly prevalent in the United States1 and worldwide,2 imposing a large burden on public health. A large body of evidence suggests that depression is associated with an increased risk of many chronic diseases, including hypertension,3,4 diabetes,5 and particularly coronary heart disease.6 The fact that coronary heart disease and stroke share many common risk factors, such as hypertension and diabetes, indicates a potential link between depression and stroke.

During the past decades, a number of prospective studies7-23 have assessed the association of depression with stroke risk; however, the results were inconsistent. A 2007 meta-analysis24 reported a pooled risk estimate of 1.43 (95% confidence interval [CI], 1.17–1.75) for total stroke, but with significant unexplained heterogeneity across studies and a lack of data by gender. Because women have higher rates of depression,25 investigating the sex differences in the depression–stroke association is of interest. Moreover, the potential bias of reverse causality (depression could be the consequence, rather than the cause, of stroke) was not well-addressed, which may pose a threat to the validity of previous findings. Clarifying this issue has important implications; if depression were the consequence of stroke, then treating depression might have little effect on stroke prevention. To fill these gaps, we systematically evaluated the association between depression and incidence of first stroke by conducting an updated meta-analysis.

Materials and Methods

Literature Search
We searched the PubMed database for relevant studies through May 2011 using the search terms “depression,” “depressive symptoms,” and “stroke” combined with “cohort studies,” “follow-up studies,” and “prospective studies” without restrictions. In addition, we reviewed the reference lists of obtained articles.

Study Selection
Studies were included for analysis if they met the following criteria: (1) the study had a community-based or population-based, prospective design; (2) the exposure was depression or depressive symptoms; (3) the end point was stroke incidence (fatal or nonfatal or both); (4) participants were free of stroke at study entry; and (5) risk estimate and the corresponding 95% CI for the depression–stroke association were reported.

Data Extraction
We used a standardized data collection form to extract the following information: last name of the first author; publication year; study population; location; follow-up time; number of cases and size of the cohort; assessment of depression and stroke; most fully adjusted risk

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The online-only Data Supplement is available at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.630871/-/DC1.
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estimate with the corresponding 95% CI; and statistical adjustment for the main confounding or mediating factors. Two authors (J.Y.D., L.Q.Q.) independently performed the literature search, studies selection, and data extraction, with disagreements resolved by discussion.

Statistical Analysis
The relative risk (RR) was used as the common measure of association between depression and stroke. One study\textsuperscript{17} reported stratified risk estimates by age and another study\textsuperscript{15} reported stratified risk estimates by cardiac disease status, and we combined these estimates using a random-effects model and then used the pooled estimates for the meta-analysis. For 2 studies\textsuperscript{9,15} that presented estimates using a random-effects model and then used the pooled risk estimates by cardiac disease status, and we combined these stratified risk estimates by age and another study\textsuperscript{21} reported stratified correlation test\textsuperscript{28} and Egger linear regression test\textsuperscript{29} at against their standard errors. We also performed the Begg rank Begg funnel plots in which the natural logarithms of RR were plotted association by stroke subtypes, but the sparse data precluded such combining the remainders in each turn. We planned to examine the single study on the overall risk estimate by omitting one study and tion, and incident case number. We also examined the influence of a sion criteria regarding depression assessment method, study duration, and incident case number. We also examined the influence of a single study on the overall risk estimate by omitting one study and combining the remainders in each turn. We planned to examine the association by stroke subtypes, but the sparse data precluded such analysis.

We assessed potential publication bias by visual inspection of Begg funnel plots in which the natural logarithms of RR were plotted against their standard errors. We also performed the Begg rank correlation test\textsuperscript{28} and Egger linear regression test\textsuperscript{29} at P<0.10 level of significance. We also computed the $I^2$ statistic, which is a quantitative measure of inconsistency across studies.\textsuperscript{26} Because there was considerable heterogeneity among included studies, a random-effects model, which considered both within-study and between-study variation,\textsuperscript{27} was used to calculate the combined risk estimate.

To explore possible explanations for heterogeneity and to test the robustness of the association, we conducted stratified analyses by sex and study location and sensitivity analyses based on various exclusion criteria regarding depression assessment method, study duration, and incident case number. We also examined the influence of a single study on the overall risk estimate by omitting one study and combining the remainders in each turn. We planned to examine the association by stroke subtypes, but the sparse data precluded such analysis.

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Results

Literature Search
We initially identified 1050 unique citations from the PubMed database. Of these, the majority were excluded after the first screening of abstracts or titles, mainly because they were reviews, case-control studies, cross-sectional studies, or not relevant to our analysis. After assessing full text of the 25 potentially relevant articles, we yielded 17 eligible articles\textsuperscript{7–23} for final analysis. Reasons for exclusion of the other 8 studies are present in Supplemental Table I (http://stroke.ahajournals.org).

Study Characteristics
The characteristics of the 17 prospective studies linking depression to stroke risk are presented in the Table. These studies were published between 1994 and 2010. Of them, 10 studies were conducted in the United States, 6 were conducted in European countries, and 1 was conducted in Japan. The mean length of follow-up ranged from 3 to 29 years, with a median of 8 years. Fourteen studies enrolled both men and women, with 6 reporting results by sex, 2 studies included men only, and 1 study included women only. The number of stroke cases diagnosed in the primary studies ranged from 56 to 1864, with a total of 6086; the size of the cohorts ranged from 494 to 93 676, with a total of 206 641. The assessment of depression varied across studies, with nearly half of them using the Center for Epidemiological Studies Depression scale. Among the selected studies, 14 reported results of total stroke (fatal or nonfatal or both) and the remaining 3 reported results of fatal stroke. Stroke case ascertainment was from a variety of sources, including clinical diagnoses, medical records, death certificates, and self-reports. The major adjusted confounding or mediating factors included age, sex, body mass index, smoking, educational level, hypertension, diabetes, and history of cardiac disease.

Depression and Risk of Stroke
The multivariable adjusted RR of stroke in relation to depression from individual studies and the combined RR are presented in Figure. Among the 17 selected studies, 14 detected a positive association between depression and stroke incidence, with 8 reaching statistical significance. Participants with depression, compared with those free of it, experienced a significant increased risk for development of stroke (combined RR, 1.34; 95% CI, 1.17–1.54). Substantial heterogeneity was observed (P=0.003; $I^2=55.1%$).

The associations between depression and stroke were similar between men (RR, 1.49; 95% CI, 1.28–1.74; n=8) and women (RR, 1.35; 95% CI, 1.05–1.72; n=7). No heterogeneity was observed in men (P=0.24; $I^2=23.4%$). The pooled RR of stroke were 1.28 (95% CI, 1.12–1.47; n=10) for studies conducted in the United States and 1.47 (95% CI, 0.97–2.24; n=6) in Europe. Exclusion of studies that had a follow-up time <5 years yielded a pooled RR of 1.33 (95% CI, 1.16–1.53; n=15). Restricting analysis to studies that had >100 stroke cases yielded a pooled RR of 1.25 (95% CI, 1.16–1.35; n=12), without evidence of heterogeneity (P=0.31; $I^2=13.3%$). Restricting analysis to studies that used the Center for Epidemiological Studies Depression scale for depression assessment yielded a pooled RR of 1.23 (95% CI, 1.13–1.34; n=8), with no evidence of heterogeneity either (P=0.86; $I^2=0%$). Further analyses examining the influence of a single study on the results by omitting a study at each turn yielded a range of RR from 1.29 to 1.38.

Publication Bias
Visual inspection of the Begg funnel plot showed some asymmetry: The Begg test suggested borderline evidence of publication bias, whereas the Egger test did not (Begg P=0.09; Egger P=0.19). Random-effects RR corrected for publication bias using the trim and fill method was 1.22 (95% CI, 1.05–1.42) for all studies combined. Correction for potential publication bias therefore did not materially alter the combined risk estimate.

Discussion
Our updated meta-analysis of 17 prospective studies involving 206 641 participants and 6086 cases confirmed a significant positive association between depression and subsequent risk of stroke; people with a history of depression experienced 34% (95% CI, 17%–54%) higher risk for development of stroke after adjustment for potential confounding factors. In addition, the associations were similar between men and women.

Despite extensive research, it remains unclear whether the association between depression and subsequent stroke inci-
Table. Characteristics of Prospective Studies of Depression and Stroke

<table>
<thead>
<tr>
<th>Sources</th>
<th>Study Participants</th>
<th>Duration, y</th>
<th>Depression Assessment</th>
<th>Stroke Ascertainment</th>
<th>No. of Stroke Cases</th>
<th>Adjustment for Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogt et al,1994</td>
<td>2573 men and women aged 18 y or older in the United States</td>
<td>15</td>
<td>Depressive Index</td>
<td>Death index or vital records</td>
<td>NA</td>
<td>Age, sex, socioeconomic status, length of health plan membership, subjective health status, and smoking</td>
</tr>
<tr>
<td>Everson et al,1998</td>
<td>6676 men and women aged 17–94 y in the United States</td>
<td>29</td>
<td>HPL Depression Scale</td>
<td>Death certificates</td>
<td>169*</td>
<td>Age, sex, race, education, alcohol use, smoking, BMI, hypertension, and diabetes</td>
</tr>
<tr>
<td>Jonas et al,2000</td>
<td>6095 men and women aged 25–74 y in the United States</td>
<td>16</td>
<td>GWS</td>
<td>Hospital records and death certificates</td>
<td>483</td>
<td>Age, race, sex, blood pressure, education, smoking, BMI, alcohol, physical activity, cholesterol, diabetes, and history of cardiac disease</td>
</tr>
<tr>
<td>Larson et al,2001</td>
<td>1703 men and women aged 18 y or older in the United States</td>
<td>13</td>
<td>DIS</td>
<td>Self-reports or death certificate</td>
<td>95</td>
<td>Age, sex, education, diabetes, blood pressure, smoking, and history of cardiac disease</td>
</tr>
<tr>
<td>Ohira et al,2001</td>
<td>901 men and women aged 40–78 y in Japan</td>
<td>10.3</td>
<td>SDS</td>
<td>Death certificate, medical records, or clinical diagnosis</td>
<td>69</td>
<td>Age, sex, BMI, blood pressure, cholesterol, alcohol use, smoking, antidepressive use, and diabetes</td>
</tr>
<tr>
<td>Ostir et al,2001</td>
<td>2478 men and women aged 65 y or older in the United States</td>
<td>6</td>
<td>CES-D</td>
<td>Clinical diagnosis or death certificate</td>
<td>340</td>
<td>Age, sex, race, marital status, education, BMI, smoking, diabetes, hypertension, and history of cardiac disease</td>
</tr>
<tr>
<td>Wassertheil-Smoller et al,2004</td>
<td>93 676 women aged 50–79 y in the United States</td>
<td>4.1</td>
<td>CES-D and DIS</td>
<td>Self-reports or proxy-reports</td>
<td>751</td>
<td>Age, race, education, income, BMI, cholesterol, diabetes, smoking, hormone therapy, physical activity, and hypertension</td>
</tr>
<tr>
<td>Gump et al,2005</td>
<td>11 216 men aged 35–57 y in the United States</td>
<td>18.4</td>
<td>CES-D</td>
<td>Death certificate</td>
<td>167*</td>
<td>Age, intervention group, race, education, smoking, blood pressure, alcohol use, cholesterol, and history of cardiac disease</td>
</tr>
<tr>
<td>Kamphuis et al,2006</td>
<td>799 men aged 70–90 y in Finland, Italy, and the Netherlands</td>
<td>7.4</td>
<td>SDS</td>
<td>Death certificates</td>
<td>66*</td>
<td>Age, country, education, BMI, smoking, smoking intake, blood pressure, cholesterol, and physical activity</td>
</tr>
<tr>
<td>Arbelaez et al,2007</td>
<td>5525 men and women aged 65 y or older in the United States</td>
<td>11</td>
<td>CES-D</td>
<td>Medical records and death certificates</td>
<td>807</td>
<td>Age, sex, race, occupation, income, education, marital status, hypertension, diabetes, smoking, history of cardiac disease, cholesterol, triglycerides, and BMI</td>
</tr>
<tr>
<td>Salaycik et al,2007</td>
<td>4120 men and women aged 29–100 y in the United States</td>
<td>8</td>
<td>CES-D</td>
<td>Clinical diagnosis</td>
<td>228</td>
<td>Age, sex, blood pressure, diabetes, atrial fibrillation, history of cardiac disease, left ventricular hypertrophy, and smoking</td>
</tr>
<tr>
<td>Bos et al,2008</td>
<td>4424 men and women aged 61 y or older in the Netherlands</td>
<td>5.6</td>
<td>CES-D</td>
<td>Self-reports, clinical diagnosis, computed tomographic scan, or hospital records</td>
<td>291</td>
<td>Age, sex, blood pressure, diabetes, smoking, intima-media thickness, history of cardiac disease, history of transient ischemic attack, and medication use</td>
</tr>
<tr>
<td>Liebetrout et al,2008</td>
<td>494 men and women aged 85 y in Sweden</td>
<td>3</td>
<td>DSMMD-III</td>
<td>Hospital discharge register, death certificates, self-reports, and key informants</td>
<td>56</td>
<td>Sex, depression at baseline, and blood pressure</td>
</tr>
<tr>
<td>Surtees et al,2008</td>
<td>20 627 men and women aged 41–80 y in the United Kingdom</td>
<td>8.5</td>
<td>MHI-5</td>
<td>Clinical diagnosis or death certificate</td>
<td>595</td>
<td>Age, sex, smoking, blood pressure, cholesterol, obesity, history of cardiac disease, diabetes, social class, education, antihypertensive use, family history of stroke, and antidepressant use</td>
</tr>
<tr>
<td>Wouts et al,2008</td>
<td>2965 men and women aged 55 y or older in the Netherlands</td>
<td>7.7</td>
<td>CES-D</td>
<td>Self-reports or general practitioners diagnosis</td>
<td>176</td>
<td>Age, sex, Mini-Mental State Examination score, smoking, functional limitations, hypertension, diabetes, and obesity</td>
</tr>
<tr>
<td>Glymour et al,2010</td>
<td>19 087 men and women aged 50 y or older in the United States</td>
<td>8.1</td>
<td>CES-D</td>
<td>Self-reports or proxy-reports</td>
<td>1 864</td>
<td>Age, race, education, income, wealth, marital status, overweight, obese, alcohol use, smoking, hypertension, diabetes, and history of cardiac disease</td>
</tr>
<tr>
<td>Nabi et al,2010</td>
<td>23 282 men and women aged 20–54 y in Finland</td>
<td>7</td>
<td>BDI</td>
<td>Hospital discharge register or mortality records</td>
<td>129</td>
<td>Age, sex, education, alcohol use, sedentary lifestyle, smoking, obesity, hypertension, diabetes, and incident cardiac disease</td>
</tr>
</tbody>
</table>

BDI indicates Beck Depression Inventory; BMI, body mass index; CES-D, Center for Epidemiological Studies Depression; DIS, diagnostic interview schedule; DSMMD, Diagnostic and Statistical Manual of Mental Disorders; GWS, General Well-Being Schedule; HPL, Human Population Laboratory; MHI, Mental Health Inventory; NA, not available; SDS, self-rating depression scale.

*Fatal stroke.
Evidence is causal. Several points that may help further our understanding of this association merit considerations. Importantly, the possibility of reverse causality should be addressed. There is compelling evidence that a history of stroke increases depression incidence.31 Our meta-analysis addressed the temporal relationship between depression and stroke by including only first-time stroke events that occurred after baseline assessments of depression. However, the possibility that undiagnosed stroke may have caused depression remained despite our efforts to exclude studies that enrolled participants with preexisting stroke at study entry. To minimize this influence, studies with a long period of follow-up that enables exclusion of stroke occurred within the initial period of follow-up are required. In fact, primary studies8,9,13,15,20,23 that used this approach have yielded virtually unchanged results.

As with any observational studies, a causal relationship could not be established and confounding factors remain an alternative explanation for the observed positive relationship between depression and stroke risk. Major known risk factors for stroke, such as age, body mass index, hypertension, diabetes, smoking, education, and history of cardiac disease, were widely considered and adjusted for in primary studies. However, measurement errors of these variables could not be ruled out. In addition, dietary factors, physical activity, alcohol consumption, and socioeconomic status were not adequately adjusted for in individual studies, which raised the possibility that residual confounders may be partially responsible for our findings.

Further, possible effect modifiers on the depression–stroke association are of additional interest, including age and cardiac disease status. In one study, depression was associated with a significant increased risk of stroke only in those aged 65 years or younger.17 One explanation may be that older individuals are more likely to have occult stroke, which could weaken any true association in the elderly. In another study, a significant positive association between depression and stroke was observed in patients with preexisting cardiac disease but not in those without it.21 Presumably, cardiac disease is an important predictor of stroke, and depression in cardiac patients could aggravate the underlying atherosclerotic disease and eventually lead to stroke.21 Alternatively, these findings may be simply attributable to chance.

The underlying mechanisms linking depression to stroke are likely to be multifactorial. There is evidence that depression is related to unhealthy lifestyle, such as smoking32 and low physical activity,31 which in themselves increase the risk of stroke. Mounting evidence suggests depression is associated with increased risk of hypertension and diabetes, probably through increased adrenergic activity and poor health behaviors.3–5 It is therefore possible that depression increases stroke risk through the development of hypertension or diabetes or both. Moreover, patients with depression may have reduced medication compliance for these conditions. Other possible mechanisms include inflammation,34 atherosclerosis,35 cerebral white matter lesions,36 cardiac arrhythmia,37 and increased platelet reactivity.38

On the basis of our findings, it is expected that depression treatment would reduce the risk of development of stroke. Conversely, evidence from observational studies suggested an increased risk of stroke in relation to treatment with antidepressants.39,40 However, these findings should be treated with cautions because of the possible confounding by indication (depression severity). In other words, patients treated with antidepressants are more likely to have severe depressive symptoms, and the observed increased risk of stroke may be attributable to depression severity rather than the antidepressant use. It is also possible that the side effects of certain antidepressants have contributed to the unexpected increased risk for stroke.41

A major strength of our meta-analysis is that all included primary studies used a community-based or population-based and prospective design, which enhanced the generalizability of the findings and reduced the likelihood of selection bias.
and reverse causality. However, several limitations should be acknowledged. First, it would be interesting to determine whether the depression–stroke association differed by stroke subtypes, but few data were available for a stratified analysis. Among the 17 included studies, 3 studies\textsuperscript{11,16,18} reported results of ischemic stroke, with 2 studies\textsuperscript{11,16} showing a significant increased risk, and only 1 study\textsuperscript{11} reporting on hemorrhagic stroke showing a null association. Second, there was significant heterogeneity among included studies, which was not surprising given the differences in sample sizes, population characteristics, depression assessments, stroke ascertainment, and statistical adjustments for potential confounders. Our stratified analyses and sensitivity analyses indicated that studies conducted in men, with a larger number of cases, and using the Center for Epidemiological Studies Depression scale for depression assessments provided homogenous results. Third, a potential publication bias may exist, as shown by the funnel plot and the Begg test. Nevertheless, correction for this bias using the formal statistical method\textsuperscript{60} did not materially alter the combined risk estimate. Finally, because depression assessments were mainly based on self-reported questionnaires but not clinical diagnosis, and because computed tomographic scans and other imaging techniques were not always available for stroke diagnosis, some misclassification of both exposure and outcome was inevitable and likely to bias any true association between depression and stroke.

In summary, our meta-analysis demonstrated that depression significantly increased the risk of development of stroke, and this increase was probably independent of other risk factors, including hypertension and diabetes. To establish a potential causal relation between depression and stroke, further large-scale long-term studies need to adequately control for confounding factors and overcome the influence of reserve causality by targeting the young or middle-aged population. The underlying mechanisms that link depression to stroke and whether this association differs by stroke subtypes also deserve further investigations.

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**Disclosures**

None.

**References**

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SUPPLEMENTAL MATERIAL

Supplemental Table. Reasons for exclusion of 8 studies of depression and stroke

<table>
<thead>
<tr>
<th>Author</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherr</td>
<td>retrospective design</td>
</tr>
<tr>
<td>Lee</td>
<td>hospital-based design</td>
</tr>
<tr>
<td>Colantonio</td>
<td>depression analyzed as a continuous variable</td>
</tr>
<tr>
<td>Wassertheil-Smoller</td>
<td>depression analyzed as a continuous variable</td>
</tr>
<tr>
<td>Krishnan</td>
<td>depression analyzed as a continuous variable</td>
</tr>
<tr>
<td>Simons</td>
<td>subjects with stroke at study baseline not excluded</td>
</tr>
<tr>
<td>Whooley</td>
<td>subjects with stroke at study baseline not excluded</td>
</tr>
<tr>
<td>Peters</td>
<td>subjects with stroke at study baseline not excluded</td>
</tr>
</tbody>
</table>

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2. Lee HC, Lin HC, Tsai SY. Severely depressed young patients have over five times increased risk for stroke: A 5-year follow-up study. *Biol Psychiatry*. 2008;64:912-915
**Abstract**

**うつ病と脳卒中リスク — 前向き研究のメタアナリシス**

*Depression and Risk of Stroke — A Meta-Analysis of Prospective Studies*

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1Department of Nutrition and Food Hygiene, 1Department of Epidemiology, and 3Department of Toxicology, School of Public Health, Soochow University, Suzhou, China.

**背景および目的:** うつ病の既往と脳卒中リスク上昇の間に関連があると考えられる。本研究の目的は、前向き研究のメタアナリシスによって、うつ病と脳卒中リスクの関連を明らかにすることであった。

**方法:** 特に制限事項を設けずに2011年5月までのPubMedデータベースを検索し、得られた論文の参考文献リストを検討することによって関連の研究を収集した。地域住民または一般住民を対象に、うつ病と脳卒中の関連について、相対リスク推定値とその95%信頼区間が報告されている前向き研究を選択した。ベースライン時にすでに脳卒中のある被験者を組み入れた研究は除外した。変量効果モデルを用いて、プールしたリスク推定値を算出した。

**結果:** 被験者206,641例、症例6,086例を含む17件の前向き研究について、潜在的交絡因子に関する補正を行い、変量効果メタアナリシスを行った結果、うつ病とその後の脳卒中リスクの間には有意な正の関連が認められた（統合相対リスク = 1.34, 95%信頼区間: 1.17 ~ 1.54）。男性と女性の間で関連に違いはみられなかった。出版バイアスが存在する可能性はあるものの、正規の統計的手法によって出版バイアスの補正を行っても、総合的なリスク推定値に実質的な違いはみられなかった。

**結論:** うつ病があると脳卒中発症リスクは有意に上昇する。このリスク上昇は、高血圧や糖尿病といった他の危険因子とはおそらく無関係である。

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