Rate of Stroke Death after Depression: A 40-year Longitudinal Study Extension of Chichester/Salisbury Catchment Area Study

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Background: This study examined clinically diagnosed depression as a risk factor for incidence of death by stroke in a prospective clinically based design study. Risk for stroke was examined separately by sex in a long-term follow-up study spanning 40 years. *Methods:* Patients who were diagnosed with depression in the Chichester (population 100,000)/Salisbury (population 85,000) Catchment Area Study were followed up for 40 years. Death certificates were used to determine the cause of death in the cohort. Death rates in the general population, adjusted for age, gender, and year, were used as a control. *Results:* Clinical depression was found to be a risk factor for subsequent death from stroke in men but not in women. Death by stroke was a statistically significant cause of death in the men with diagnoses of endogenous depression but not in those men diagnosed with reactive depression. The strength of the relationship of depression with stroke increased over time. *Conclusions:* These findings suggest that the identification of depressive symptoms at younger ages may have an impact on the primary prevention of stroke in later life. The notion that depression has stronger effects over a long period is consistent with a view that severe clinical depression and physical illness occur concurrently, one exacerbating the other, and health is degraded through slow-acting, cumulative processes. Data were unavailable for the type of stroke or the health-risk behaviors (smoking, diet, and so forth) in the cohort which constituted a limitation of the study. Neither is it known what proportion of the cohort suffered a nonlethal stroke nor to what extent the treatment of clinical depression militates against suffering a lethal stroke. **Key Words:** Mortality—depression—stroke—sex differences—prevention.

Severe Depressive Illness Preceding Death by Stroke

The World Health Organization (WHO) reports[1] that "globally; cerebrovascular disease (stroke) is the second leading cause of death. It is a disease that predominantly occurs in mid-age and older adults. WHO estimated that in 2005, stroke accounted for 5.7 million deaths worldwide, equivalent to 9.9 % of all deaths. Over 85% of these deaths will have occurred in people living in low and middle income countries and one third will be in people aged less than 70 years." In response to the need for improvements in stroke data collection, prevention, and treatment, WHO has developed an international stroke surveillance system.[1]

Numerous studies suggest that individuals suffering from severe depression are at increased risk for death from natural causes.[2-9] Particular attention has been given to the relationship of clinical depression with death from stroke. Long-term follow-up studies suggest that the onset of major depression is followed by an increased probability of having a stroke[10] and death from stroke.[6,11,12] The association between depression and increased risk of death from stroke persists even when other cardiovascular risk factors and sociodemographic variables are controlled statistically.[2,13-18] The present

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Received October 29, 2013; revision received January 22, 2014; accepted March 13, 2014.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.03.013

study will seek to increase our understanding of the association between major depression and premature death from stroke by considering the degree to which the strength of this relationship may differ by sex and by using a long-term follow-up period spanning 40 years.

In the broader literature on depression and premature mortality, attention has been given to sex differences in the strength of the relationship between major depression and premature mortality. For example, Thomson[7] found that the association between major depression and premature mortality from natural causes was statistically significant for men and women, yet was also significantly stronger for women compared with men. By contrast, relatively little attention has been given to potential sex differences in the size of the association between depression and risk for death from stroke. The results of long-term follow-up studies of depression and death from stroke have yielded inconsistent findings concerning possible sex differences. Angst et al[19] found a significant association between depression and death from stroke among males but not females. By contrast, Osby et al[20] found that depression was associated with increased risk of death from stroke for males and females. Shah et al[12] found increased risk of early stroke mortality for both sexes, although the effects of depression were stronger for women.

The present study will examine the association between depression and stroke mortality over a long follow-up time frame (40 years). With few exceptions, studies of depression and risk of death from stroke have followed patients for less than 10 years. Notable exceptions to this general trend have followed study participants for 14 to 38 years.[12-15,19,20] To the extent that depression has very long-term effects on stroke mortality that emerge over decades, such effects may be overlooked when follow-up assessments end after 10 to 15 years. The present work will follow a cohort of patients who have been diagnosed with major depression and will use a follow-up interval that is rarely found in the literature on depression and mortality.

Methods

Participants and Procedures

The sample for the present study is a longitudinal extension of the one that was used in the Thomson[7] follow-up study of depression and premature mortality. In the present work, the time frame for the investigation was extended from 24 to 40 years using procedures described in a broader study of depression and premature mortality from all natural causes.[8] Permission was granted to use the data collected by Sainsbury et al[21] to evaluate community care in 2 distinct health authorities in Southern England. The present study uses data from subjects who were formally diagnosed with depression of clinical severity in 1960 by senior psychiatrists under the strict criteria of the Medical Research Council.[22] The particular strength of this study is the diagnostic rigor used to include patients in the study cohort. Senior psychiatrists collected standardized data from all referrals from a total population of 2 census areas in the United Kingdom. The 2 areas selected were Chichester and Salisbury, clearly defined areas in the South of England with responsibility for the provision of all medical and health-related services. The services were selected for study because they had similar demographic population structures. A strength of the research design was that it was a total sample of patients diagnosed as depressed by senior psychiatrists. To this extent, the cohort was representative of the large majority of English regional senior psychiatrist-diagnosed cases of depression. A reliability study was conducted, which showed an acceptable level of concordance between the psychiatrists making the diagnosis.[23]

The total population of patients referred to the 2 catchment areas was 1413, of whom 685 were diagnosed as depressed: 480 were diagnosed as having endogenous depression, and 205 were diagnosed as having neurotic reactive depression. The mean age of patients with reactive depression was 44 compared with 58 years for the patients with endogenous depression. Males formed 33.3% of the total cohort, with a mean age at referral of 58.1 years. Females formed 67.7% of the total population, with a mean age at referral of 51.2 years. Because the present study used actuarial information about age-adjusted death rates, cases were included only if the date of birth and death could be ascertained. In addition, cases younger than 16.5 years of age at the start of the study were not included. Of the 685 cases that formed the original cohort, 566 were used for the present study based on the availability of birth and death dates, as well as meeting the age criterion for inclusion. The data obtained from the 2 catchment areas were pooled for purposes of analysis.

Measures and Procedures

Four senior psychiatrists made diagnoses of reactive and endogenous depression at the time of referral to either Chichester or Salisbury psychiatric service areas; information concerning the diagnostic procedures has been reported earlier.[21] The resulting diagnoses have been found to be reliable and to possess high levels of diagnostic convergence concerning depression.[23] Illustratively, diagnosticians exhibited 85% agreement concerning the severity of symptoms of depression. The Chichester and Salisbury samples focused on patients with a primary diagnosis of depression, not depression secondary to physical illnesses such as stroke. A strength of the research design was that it involved a total sample of patients referred to the services at that time. There is no reason to believe that the criteria for diagnosing