Reduced Risk of Intracerebral Hemorrhage With Dynamic Recreational Exercise but Not With Heavy Work Activity

Amanda G. Thrift, PhD; Geoffrey A. Donnan, MD; John J. McNeil, PhD

Background and Purpose—It is unclear whether intracerebral hemorrhage (ICH) is associated with dynamic or static exercise. Our aim was to assess whether such an association exists.

Methods—A case-control study was undertaken involving 331 consecutive cases of primary ICH and 331 age- and sex-matched community-based neighborhood controls. Cases, verified by CT or autopsy, were identified from 13 major hospitals in Melbourne, Australia. A questionnaire was used to elicit information about lifetime physical activity at leisure and work and other potentially confounding factors.

Results—Individuals undertaking recent regular dynamic exercise exhibited an odds ratio (OR) for ICH of 0.63 (95% CI 0.39 to 1.01) when adjustment was made for all potential confounding factors, except hypertension, cholesterol, and body mass index. Among men and women separately, the ORs were 0.51 (95% CI 0.27 to 0.97) and 1.22 (95% CI 0.52 to 2.87), respectively. When hypertension, cholesterol, and body mass index were also included in the multivariate model, the OR among men was 0.57 (95% CI 0.28 to 1.14). There was no association between physical activity at work and ICH (OR 1.14, 95% CI 0.58 to 2.25).

Conclusions—These results provide preliminary evidence for a role of exercise in reducing the likelihood of ICH among men. In women, the CI was wide, and the association was not statistically significant. There was further support that factors other than blood pressure status, cholesterol, and body mass index may play a role in the observed inverse association between dynamic exercise and ICH among men. (Stroke. 2002;33:559-564.)

Key Words: Australia ■ case-control studies ■ epidemiology ■ intracerebral hemorrhage ■ risk factors

Stroke is the third most common cause of death in most Western countries. Although intracerebral hemorrhage (ICH) constitutes only \(\approx 10\%\) to 15\% of all strokes,\(^1\)-\(^5\) it results in a higher mortality and greater morbidity than the more prevalent cerebral infarction. This particular form of stroke currently has limited potential for treatment. Consequently, prevention remains the most effective method of reducing the impact of this disease. Preventive methods must be focused on factors that have a strong reversible association with ICH and are modifiable.

There have been only a few epidemiological studies of the relationship between physical activity and ICH, largely because of the relative rarity of the condition and the consequent difficulty in accumulating sufficient cases. Earlier studies commonly involved only fatal ICH and were thus biased toward the more severe cases.\(^6\),\(^7\) In a recent study, subarachnoid hemorrhages were included with ICHs in a “hemorrhagic stroke” group and may have obscured an effect of exercise on ICH because of differences in the etiology of the 2 conditions.\(^8\) In this latter study,\(^8\) as well as in 2 other recent investigations,\(^9\),\(^10\) small numbers of cases were included, thus resulting in imprecise relative risks and wide CIs.

Hypertension is the dominant risk factor for ICH.\(^11\)-\(^13\) Therefore, the relationship between physical activity and ICH is likely to be influenced by the effects of exercise on blood pressure. This relationship is complicated by differences between the acute and chronic blood pressure response to different exercise patterns. In general, static exercise (typically encountered in occupational settings) causes an acute increase in systolic and diastolic blood pressure.\(^14\) In contrast, dynamic exercise (typical of leisure-time activity) produces an acute rise in systolic blood pressure and little change in diastolic blood pressure.\(^15\) Although regular static exercise produces little long-term change, regular dynamic exercise moderately reduces resting blood pressure levels.\(^15\)-\(^21\)

In view of the established hypotension effect of regular dynamic exercise, we examined the hypothesis that regular leisure time activity would reduce the risk of ICH. By examining odds ratios (ORs) before and after statistically controlling for a history of hypertension, hyperlipidemia, and body mass index, we investigated the likelihood of any such protective effect being mediated through an effect on these variables.
Subjects and Methods

The patients and methods have been described in detail elsewhere. Briefly, consecutive cases of primary ICH during the period 1990 through 1992 were identified from discharge records of 13 hospitals serving the Melbourne metropolitan area and by regular inspection of the Coroner’s records. The participating hospitals manage most such cases, except for the very old residents of nursing homes.

Inclusion and Exclusion Criteria

Patients, aged between 18 and 80 years, with primary ICH were included in the study when this was their first episode of stroke. Individuals with any prior stroke or in whom the event was a subarachnoid hemorrhage or secondary transformation of infarction to hemorrhage were not included. We also excluded those in whom the ICH was secondary to arteriovenous malformation, tumor, or clotting abnormalities (including those resulting from anticoagulants) or in whom the ICH occurred following the ingestion of sympathomimetic drugs. Case subjects residing in nursing homes at the time of stroke were also excluded from the case series.

Control Subjects

Controls were matched individually by age (±5 years) and sex and were chosen from neighbors of the case subject. The same nurse who interviewed the matching case recruited the control by visiting sequential houses in the same street in which the case lived at the time of the stroke. Usually, the first eligible control subject free of previous cerebrovascular disease was identified and interviewed. When the first eligible control refused to participate, the next eligible control subject identified was interviewed instead. When a targeted individual was absent at the time of the initial visit, repeated attempts at contact were made during the evening and weekends to ensure that there was not an overrepresentation of unemployed or disabled subjects.

Risk Factor Ascertainment

Person-to-person interviews were conducted by nurse interviewers who used a structured questionnaire. Information was obtained about personal characteristics and habits, such as cigarette smoking, alcohol consumption, past exercise and dietary practices, and medical history.

Patients who died or were mentally impaired were included in the study by interview of the closest available informant. To minimize information bias, participants acting as controls for these case subjects were asked to nominate a relative of the same relationship as that of the case’s proxy to the case subject. Proxy interviews were conducted on 43% of cases and 31% of controls.

Because of the nature of ICH, interviewers could not be blinded to the case-control status of the interviewee. However, participants were informed that the study was of lifestyle factors and stroke and were unaware of the specific hypotheses under investigation.

Adherence to study protocols was monitored at weekly quality control meetings. During these meetings, procedures for recently obtained interviews were discussed, and response rates were carefully scrutinized.

Definitions

The definitions used were as follows: ICH, a sudden onset of an acute focal neurological event with confirmation of intraparenchymal ICH provided by CT scanning, MRI, or autopsy; hypertension, diabetes, previous cardiovascular disease, and high cholesterol, a history of the condition as reported to the patient by a medical practitioner; never smoker, a person who had never smoked at least 1 cigarette, cigar, or pipe per day for at least 3 months at some period in his or her lifetime; current smoker, a person smoking at least 1 cigarette, cigar, or pipe per day for the preceding 3 months (this was further subcategorized into those who smoked <20 cigarettes per day on average and those who smoked ≥20 cigarettes per day); exsmoker, a person who did not meet the criteria for never or current smoking; sedentary, a person never exercising a minimum of once a week in the subject’s lifetime; ever exerciser, a person who ever engaged in active dynamic physical exercise (at least once a week) that caused perspiration and breathlessness, such as brisk walking, running, swimming, cycling, squash, and vigorous team sports; current exerciser, a person who reported participating in active dynamic physical exercise up until the time of their stroke (case) or interview (control) that caused perspiration and breathlessness (this category was further divided into those who exercised rarely and those who exercised monthly or more); never heavy physical exertion at work, a person who never engaged in heavy physical activity at work; ever heavy physical exertion at work, a person who ever engaged in heavy physical activity at work at some time in their lifetime; current heavy work activity, a person who reported currently undertaking heavy physical exertion at work; past heavy work activity, a person who reported that their current work activity involved mainly being on their feet; current sedentary work activity, a person who reported that their current work activity involved mainly being seated; current drinker, a person who drank alcohol in his or her lifetime; current drinker, a person who drank alcohol at the time of their stroke (cases) or interview (controls) (this was further subcategorized into 3 levels of alcohol consumption [moderate, intermediate, and heavy drinkers]); past drinker, a person who did not meet the criteria for a never or current drinker; and body mass index, self-reported weight (kilograms) divided by the square of height (meters).

Statistical Analysis

The OR of ICH was estimated for subjects in various categories of exercise status. Conditional logistic regression (using EGRET statistical software) was used to compute ORs approximating the relative risks of ICH for various exposures. Initially, univariate ORs were calculated for exercise and potentially confounding variables. We initially included all plausible potential confounding factors in the multivariate analyses. However, this resulted in substantially reduced numbers of matched sets with complete data. We then excluded those variables for which data were especially incomplete (aspirin and claudication). Analyses for women also included an(0,10),(995,995)
Leisure-Time Physical Activity

Compared with those who never engaged in physical activity during leisure time, for those performing such activity once or more per month at the time of the stroke (cases) or interview (controls) the crude OR of ICH was 0.51 (95% CI 0.33 to 0.78, Table 2). For the same time period, the OR of ICH among those exercising rarely was 0.68 (95% CI 0.40 to 1.15). The relationship was similar when those who had ever exercised once or more per week were compared with those who had either never exercised or exercised less than once a month (0.62, 95% CI 0.44 to 0.87).

Two types of multivariate analyses were performed for exercise variables. In the first of these, multiple logistic regression controlled for previous cardiovascular disease, smoking, alcohol, diabetes, and education level (Table 2). After controlling for these possible confounding factors, the OR for ICH among those currently exercising was 0.63 (95% CI 0.39 to 1.01), whereas among those who had ever exercised, it was 0.85 (95% CI 0.57 to 1.26). By use of a $\chi^2$ test for linear trend, there was an apparent dose-response association between the level of physical activity and reduced incidence of ICH among men ($P$ for trend = 0.035). When a history of hypertension, cholesterol, and body mass index were included in the multivariate model, the association between exercising at least once a month and ICH among men increased slightly and lost significance statistically (OR 0.57, 95% CI 0.28 to 1.14). None of these differences between men and women were statistically significant (see Table 3 legend).

Work-Place Physical Activity

The crude OR for ICH among those undertaking heavy physical exertion at work (static exercise) at the time of the stroke (cases) or interview (controls) or among those ever undertaking such an activity was 1.07 (95% CI 0.60 to 1.89) and 1.07 (95% CI 0.74 to 1.56), respectively (Table 2). Similar results were obtained when adjustment was made for potential confounding factors.

Discussion

These data provide evidence of an inverse association between regular dynamic exercise and ICH. This result is most evident among men who were currently undertaking such exercise and remained statistically significant after controlling for potential confounding factors (except for a history of hypertension, hyperlipidemia, and body mass index). There also appeared to be a dose-response relationship, with an increasing level of physical activity being associated with a reduced incidence of ICH. If we assume an absence of bias in information ascertainment, these results raise the possibility that physical exercise reduces the risk of ICH among men.

These results are largely supported by previous studies undertaken in men.6,8,9 In the earliest of these, participation in university athletics was associated with a reduced risk of death from hemorrhagic stroke.6 In addition to the fact that this report relied on university sporting activity undertaken in the distant past, no attempt was made to adjust for potential confounding factors, and so one cannot accurately assess the implications of this association. Investigators in the Honolulu Heart Program6 found that compared with the men who were active, inactive and partially active men had a 2- to 3-fold excess of ICH. Interestingly, the association was evident among men aged 55 to 68 years at study initiation but not among a younger cohort of men aged 45 to 54 years at study initiation. No adjustment was made for potentially confounding variables in this analysis of ICH alone (ie, without subarachnoid hemorrhages).

In a more recent cohort study involving 84 hemorrhagic strokes, there was a reduced relative risk of hemorrhagic
stroke among those who undertook regular physical activity. Analyzes were undertaken that both included and excluded adjustment for hypertension, high cholesterol, diabetes, and body mass index. Both analyses showed a trend toward an inverse association between physical activity and the risk of developing a hemorrhagic stroke (P=0.07 and P=0.10, respectively).

No association between physical inactivity and ICH was identified in females. Similar results were obtained by Hu et al in a previous investigation among a cohort of females. It is likely that the failure to identify a similar relationship among females is a direct result of the relatively small sample size among women in both of these studies (42 women with ICH in the previous study and 131 in the present study). Alternatively, the range of physical activity undertaken by women at the age groups involved may not be sufficiently variable to allow a relationship to be identified. Therefore, it is not possible to draw conclusions about putative sex differences in the risk for ICH from these results.

It is not possible to precisely quantify either the intensity or duration of exercise in an unsupervised setting; thus, the present results provide only a semiquantitative indication of the strength of association between various grades of exercise and the risk of ICH. The result may be confounded by the likelihood that those who do not undertake even occasional physical activity have other concomitant illnesses that predispose them to ICH. Alternatively, those who do undertake physical activity may engage in other “healthy lifestyle” practices, and one or more of these may be associated with a reduced risk of ICH. Because this was not an a priori hypothesis, this finding is more in the realm of hypothesis generating than hypothesis testing. However, it seems reasonable to conclude that the present observations demonstrate the need for this hypothesis to be rigorously tested.

The type of exercise typified by running or swimming involves the activity of large muscle groups, which is a result of changes in muscle length. During dynamic exercise, the systolic blood pressure commonly rises, but there is generally little change in diastolic blood pressure. People who undertake regular dynamic exercise have shown to have a lower resting blood pressure, a low serum cholesterol, and a lower body weight. Physical activity exerts its effect partly via these mechanisms. As previously discussed by the investigators of the US Physicians’ Health Study, these intermediate variables need to be taken into account when assessment is made of the association between physical activity and ICH.

To assess whether dynamic exercise had any effect on the occurrence of ICH over and above its beneficial influences on blood pressure, cholesterol, and body weight, we undertook a second multivariate analysis that included these variables. Compared with the OR obtained without adjustment for these intermediate variables among men, the OR in this second analysis changed by 12%. Although the association was no longer statistically significant, the point estimate was still low (0.57), and the CIs were wide. Thus, one cannot make any firm statements about the potential mechanism, except that it is possible that mechanisms other than those adjusted for may have a role.

An important finding in the present study was that regular work-related physical activity did not substantially increase the risk of ICH. It is likely that in most cases, exertion at work reflects static exercise. Static exercise refers to muscular activity involving extensive muscular force but with very little movement. The present data for static exercise rely on

### Table 2. Crude and Adjusted Relative Risks of Primary Intracerebral Hemorrhage for Various Exposures to Physical Activity Estimated by Multiple Logistic Regression

<table>
<thead>
<tr>
<th>Frequency of Vigorous Exercise</th>
<th>Cases, n (%)</th>
<th>Controls, n (%)</th>
<th>Crude OR (P)</th>
<th>Multivariate OR1*</th>
<th>Multivariate OR2†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Now exerciser</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Never</td>
<td>242 (73)</td>
<td>208 (63)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rarely</td>
<td>35 (11)</td>
<td>40 (12)</td>
<td>0.68 (0.152)</td>
<td>0.67 (0.37–1.22)</td>
<td>0.192</td>
</tr>
<tr>
<td>Once or more per month</td>
<td>54 (16)</td>
<td>83 (25)</td>
<td>0.51 (0.002)</td>
<td>0.63 (0.39–1.01)</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>Ever exerciser</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>136 (41)</td>
<td>104 (31)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Once or more a week</td>
<td>195 (59)</td>
<td>227 (69)</td>
<td>0.62 (0.007)</td>
<td>0.85 (0.57–1.26)</td>
<td>0.426</td>
</tr>
<tr>
<td><strong>Level of exercise at work</strong></td>
<td></td>
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</tr>
<tr>
<td>Sedentary</td>
<td>120 (36)</td>
<td>120 (36)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Current light to moderate</td>
<td>173 (52)</td>
<td>175 (53)</td>
<td>0.99 (0.945)</td>
<td>0.93 (0.61–1.40)</td>
<td>0.721</td>
</tr>
<tr>
<td>Current heavy work activity</td>
<td>38 (11)</td>
<td>36 (11)</td>
<td>1.07 (0.827)</td>
<td>1.14 (0.58–2.25)</td>
<td>0.705</td>
</tr>
<tr>
<td><strong>Heavy physical exertion at work</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>200 (60)</td>
<td>204 (62)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever</td>
<td>131 (40)</td>
<td>127 (38)</td>
<td>1.07 (0.706)</td>
<td>0.98 (0.64–1.51)</td>
<td>0.928</td>
</tr>
</tbody>
</table>

Crude OR indicates unadjusted OR.
*Multivariate analysis is adjusted for previous heart disease, smoking, alcohol consumption, diabetes, and education level.
†Adjustment for all of the variables above, plus history of hypertension, history of high cholesterol, and body mass index.
TABLE 3. Sex-Specific Adjusted Relative Risks of Primary Intracerebral Hemorrhage for Various Exposures to Physical Activity Estimated by Multiple Logistic Regression

<table>
<thead>
<tr>
<th>Frequency of Vigorous Exercise</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Multivariate OR1*</td>
<td>Multivariate OR2†</td>
<td>P</td>
<td>Multivariate OR1*</td>
<td>Multivariate OR2*</td>
<td>P</td>
<td>Multivariate OR1*</td>
<td>Multivariate OR2*</td>
<td>P</td>
<td>Multivariate OR1*</td>
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<tr>
<td>Now exerciser</td>
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<tr>
<td>Never</td>
<td>1.0</td>
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<td></td>
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</tr>
<tr>
<td>Rarely</td>
<td>0.61 (0.29–1.28)</td>
<td>0.191</td>
<td>0.57 (0.26–1.23)</td>
<td>0.149</td>
<td>0.54 (0.15–1.93)</td>
<td>0.342</td>
<td>0.57 (0.11–2.99)</td>
<td>0.507</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Once or more per month§</td>
<td>0.51 (0.27–0.97)</td>
<td>0.040</td>
<td>0.57 (0.29–1.14)</td>
<td>0.109</td>
<td>1.22 (0.52–2.87)</td>
<td>0.651</td>
<td>1.26 (0.43–3.70)</td>
<td>0.670</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>P for trend=0.035</td>
<td></td>
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<td>P for trend=0.086</td>
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<td></td>
<td>P for trend=0.800</td>
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<td></td>
<td>P for trend=0.704</td>
<td></td>
</tr>
<tr>
<td>Ever exerciser</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Sedentary</td>
<td>1.0</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Once or more a week</td>
<td>0.76 (0.43–1.34)</td>
<td>0.335</td>
<td>0.80 (0.43–1.48)</td>
<td>0.470</td>
<td>1.18 (0.58–2.41)</td>
<td>0.645</td>
<td>1.10 (0.46–2.66)</td>
<td>0.828</td>
<td>1.0</td>
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</tr>
</tbody>
</table>

*Multivariate analysis is adjusted for previous heart disease, smoking, alcohol consumption, diabetes, and education level.
†Adjustment for all of the variables above, plus history of hypertension, history of high cholesterol, and body mass index.
§Ratio of the 2 ORs between males and females was 0.42 (95% CI 0.14–1.22, P=0.110) for multivariate analysis 1 and 0.45 (95% CI 0.13–1.63, P=0.225) for multivariate analysis 2.

Analyzed for females also include adjustment for hormone replacement therapy.

the assumption that work activity is a surrogate for static exercise. It does not exclude a possible association with more extreme levels of static exercise, such as those of weightlifters, because this is likely to be uncommonly encountered in a typical working environment. Moreover, no information about other strenuous activity, such as weightlifting, was collected, thus limiting the interpretation of the present results. In a previous study in which the level of physical activity was undertaken at work was implied by the job status, the association between physical activity at work and hemorrhagic stroke among men was 1.73.7 Because the 95% CIs for the association between heavy work activity and ICH in the present study (0.58 to 2.25) overlap this point estimate, our findings are in keeping with those of the previous investigators.

There are many biases that could affect the findings of a study such as this. There may have been differential recall of information between cases and controls that may have arisen because of neurological impairment among cases or because of poorer recall among proxies. Even though more proxy interviews were conducted for cases than for controls, we have made every effort to minimize information bias. Previous reports of index-proxy agreement have provided evidence that agreement is highest when the proxy lives in the same household as the index subject4,26. In the present study, interviews were conducted with either the index subject or with a proxy living in the same household as the index subject in 82% of cases and 91% of controls, thus reducing the potential for bias introduced by proxy respondents not living in the same household.

The present study constitutes the largest number of intracerebral hemorrhage cases in which assessment has been made of the role of physical activity on the risk of ICH. The results provide support for an inverse association between dynamic physical activity and ICH. The dose-response relationship for the present level of physical activity provides further support for this finding. No similar association was seen with work-related activity. It is possible that this finding for leisure-time physical activity and ICH may be partly mediated by the beneficial effects of exercise on blood pressure levels, serum cholesterol levels, and body weight. Because of the difficulties involved in accurately assessing exercise activity in a nonsupervised setting, the present results, supporting a role of exercise in reducing the risk of ICH, should be regarded principally as hypothesis-generating. Although the results are biologically plausible, the results require confirmation in a larger study, preferably of cohort design.

Acknowledgments

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References


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