Letters to the Editor

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Meta-Analysis Reported Incompatible Statistics and Omitted Pertinent Studies

To the Editor:

The evidence that higher levels of physical activity and cardiorespiratory fitness confer protection against ischemic heart disease (IHD) is persuasive, particularly in middle- and older-aged men. With the most common type of stroke, ischemic stroke, and ischemic heart disease sharing similar pathophysiological traits, a sedentary existence has been advanced as a lifestyle risk factor for stroke. As the cohorts on which the observations of a physical activity–IHD association are based mature, a growing number of publications examining the link between physical exertion and stroke have appeared. The aggregation of results from these studies in the meta-analysis of Lee and others is therefore timely. However, in our view, the authors reported confusing statistics and omitted some relevant studies.

In Table 3 of their report, the relative risk (95% CI) of ischemic stroke in the moderate compared with the low active groups is 0.91 (0.80 to 1.05), but this seems incompatible with the reported probability value ($P<0.001$). Similar observations are made for the hemorrhagic stroke result (RRmoderate versus low active; 95% CI: 0.85; 0.64 to 1.13), which has a probability value of 0.001, and for total stroke in a pooling of findings from case-control studies (RRhigh versus low active: 0.36; 0.25 to 0.52), which has a probability value of 0.04.

Additionally, although the authors’ search strategy was clearly reported, it was not comprehensive. In addition to an electronic search of several medical databases (the authors searched only MEDLINE), scrutiny of the reference sections of relevant articles, contacting experts in the field, and reviewing one’s own files have all been recommended to bolster the number of identified studies. We were aware of 2 additional reports that appear to meet Lee and others’ inclusion criteria but were omitted from their meta-analysis. In these prospective cohort studies of European populations from the United Kingdom (362 stroke deaths in 12 552 London-based male civil servants) and Sweden (111 stroke deaths in 7142 Göteborg men), physical activity was essentially unrelated to total stroke risk at conventional levels of statistical significance.

In the former report from the Whitehall study, we described the relation of physical activity to stroke risk based on a question administered to the first 12 552 study participants in the late 1960s about how much time, if any, they spent walking or cycling to work.

Hazard Ratios (95% CIs) for Leisure Time Physical Activities in Relation to Stroke Mortality in the Original Whitehall Study

<table>
<thead>
<tr>
<th>Classification of Activity</th>
<th>No. of Deaths</th>
<th>No. of Subjects</th>
<th>Age-Adjusted</th>
<th>Multiply-Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>47</td>
<td>1532</td>
<td>0.85</td>
<td>0.95</td>
</tr>
<tr>
<td>Moderate</td>
<td>92</td>
<td>2665</td>
<td>0.91</td>
<td>1.01</td>
</tr>
<tr>
<td>Inactive</td>
<td>77</td>
<td>2253</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Multiply-adjusted hazards ratios are adjusted for: age, employment grade, cholesterol, systolic blood pressure, smoking, body mass index, forced expiratory volume in 1 second, glucose intolerance, diabetes, and disease at entry (ischemia, intermittent claudication, dyspnea, unexplained weight loss in the preceding year, and physician-diagnosed heart problems or high blood pressure).

Following modification of the study questionnaire during baseline data collection, different inquiries regarding leisure-time physical activity were made to the final 6702 men recruited into the cohort. Although we have previously reported on the relation of IHD and cancer subtypes to this index of physical exertion, we have yet to examine its predictive capacity for stroke. In new analyses presented here (Table), there were 216 deaths attributed to stroke during 25 years’ surveillance in these men. There was little evidence of an activity-stroke relation, however. We were unable to examine the relation of this index of physical exertion with stroke subtypes because the majority of stroke fatalities were ill-defined on death certificates, a problem across all UK cohort studies which hold outcome data on deaths.

The omission of these reports notwithstanding, given that inclusion of the total number of stroke deaths from them and the present analyses (n=689) increases the total number of incident stroke reported in Table 1 of the meta-analysis by around only 14%, the magnitude of the pooled effect estimate for cohort studies with its tight CIs (RRhigh versus low active: 0.75; 0.69 to 0.82) is unlikely to be markedly attenuated. Therefore, the conclusion of Lee and others that physical activity is inversely related to total stroke risk is likely to be unaffected.

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Response

We thank Dr Batty and colleagues for their careful review and comments on our meta-analysis of physical activity and...
Indeed, as they pointed out, we unfortunately transcribed 3 probability values incorrectly. The correct probability values for Table 3, testing the null hypothesis of ln(RR) = 0, are as follows: ischemic stroke (low versus moderate), P = 0.09; hemorrhagic stroke (low versus moderate), P = 0.13; and total stroke (case-control) (low versus high), P < 0.001. We regret our error but have verified that all other RRs and probability values presented in the article are correct.

Batty and colleagues also pointed out that we omitted 2 cohort studies (the Whitehall study and the multifactor primary prevention study in Göteborg) from the analysis. In fact, we had identified but did not include the Whitehall study, because as we described in our Methods, we included only studies of leisure-time physical activity. The Whitehall study assessed physical activity as the time spent commuting to work by bicycle or on foot, which we judged not to be leisure-time activity. We somehow did not find the Swedish men’s data, and when we added it to the meta-analysis, the results were identical to those in Table 3: RRs (low versus high, cohort) 95% CI: 0.75, 0.69, 0.82, P < 0.001; and RRs (low versus moderate, cohort) 95% CI: 0.83, 0.76, 0.89, P < 0.001.

The overall conclusion of our article was unchanged by correcting the 3 probability values. However, we must correct the conclusion about stroke subtypes to say that moderate levels of physical activity are not clearly associated with reduced risk of ischemic or hemorrhagic strokes, individually, even though high levels of physical activity are.

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