Influence of Cardiovascular Fitness and Muscle Strength in Early Adulthood on Long-Term Risk of Stroke in Swedish Men

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Background and Purpose—Low cardiovascular fitness (fitness) in mid- and late life is a risk factor for stroke. However, the respective effects on long-term stroke risk of fitness and muscle strength in early adulthood are unknown. Therefore, we analyzed these in a large cohort of young men.

Method—We performed a population-based longitudinal cohort study of Swedish male conscripts registered in 1968 to 2005. Data on fitness (by the cycle ergometric test; n=1166035) and muscle strength (n=1563750) were trichotomized (low, medium, and high). During a 42-year follow-up, risk of stroke (subarachnoidal hemorrhage, intracerebral hemorrhage, and ischemic stroke) and fatality were calculated with Cox proportional hazards models. To identify cases, we used the International Classification of Diseases-Eighth to Tenth Revision in the Hospital Discharge Register and the Cause of Death Register.

Results—First-time stroke events were identified (subarachnoidal hemorrhage, n=895; intracerebral hemorrhage, n=2904; ischemic stroke, n=7767). For all stroke and fatality analysis any type of first-time stroke was recorded (n=10197). There were inverse relationships in a dose–response fashion between fitness and muscle strength with any stroke (adjusted hazard ratios for the lowest, compared with the highest, tertile of each 1.70 [1.50–1.93] and 1.39 [1.27–1.53], respectively). There were stronger associations for fatal stroke. All 3 stroke types displayed similar associations. Associations between fitness and stroke remained when adjusted for muscle strength, whereas associations between muscle strength and stroke weakened/disappeared when adjusted for fitness.

Conclusions—At the age of 18 years, low fitness and to a lesser degree low muscle strength were independently associated with an increased future stroke risk. (Stroke. 2015;46:00–00. DOI: 10.1161/STROKEAHA.115.009008.)

Key Words: epidemiology ■ exercise ■ incidence ■ muscles ■ stroke

Stroke afflicts 1 in 6 people in their lifetime,1 causing 6.2 million deaths worldwide.2 To improve stroke prevention, knowledge of key risk factors, especially those that are modifiable such as physical activity, is essential. In middle-aged men3 and women,4 it has been shown that higher levels of physical activity are associated with reduced risk of future ischemic stroke (IS). Specifically, in 2 meta-analyses on 16 original studies of middle-aged men and women undertaking more intensive versus lower levels of physical activity, the overall risk reduction was 19% to 27%.5,6 However, in these and most other such studies, physical activity is assessed by self-report in questionnaires and interviews in large numbers of subjects, yet it has been shown that self-report leaves the true degree of physical activity vulnerable to bias.7

Aerobic or cardiovascular fitness (henceforth fitness), however, can be measured objectively. Although measurement requires relatively time-consuming ergometric tests, and so has generated fewer observations and studies, it has been shown to be a more accurate predictor of cardiovascular risk.
than has self-reported physical activity. To our knowledge, there has been only 1 large long-term follow-up study assessing the correlation between objectively measured fitness and stroke incidence. In that study, low fitness was associated with a 2-fold increase in stroke incidence. However, most subjects were middle-aged (45–60 years), and it remains unclear whether fitness at younger ages may affect long-term stroke incidence.

Aerobic exercise, furthermore, can increase muscle strength, and it has been shown that muscle strength at the age of 18 years has a modest correlation with future cardiovascular events. The study by Timpka et al showed that high muscle strength was independently associated with a 12% risk reduction in the combined outcome of coronary heart disease and stroke incidence, whereas low muscle strength showed no significant associations. However, no independent analysis of stroke incidence was presented.

The aim of our study was therefore to determine whether, independently and in combination, fitness and muscle strength at a young age are associated with long-term risk of stroke. In Sweden, where the study was undertaken, stroke affects 1.2% of the population each year. About 85% of these strokes are IS, the remainder are mostly hemorrhagic and include intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). We performed a prospective cohort study of all Swedish men born between 1950 and 1987 who were enlisted for mandatory military service at the age of 18 years, and followed them for at least 5 and ≤42 years. We also assessed incidence of the major stroke types (IS, ICH, and SAH) and stroke fatality.

Methods

Study Design, Setting, and Participants

A cohort of 18-year-old Swedish men (n=1 694 179) who enlisted for compulsory military service in 1968 to 2005 (ie, born between 1950 and 1987; Figure 1) was compiled from the Swedish Military Service Conscription Register. Exemptions were granted only for incarceration or for severe chronic medical or mental conditions (+2%–3% each year). At conscription, conscripts whose test data were incomplete were excluded from the analysis (Figure 1). Linkage to other registers was performed via personal identification numbers of all Swedes. Further details, which have been published previously, are also given in the online-only Data Supplement.

Ethical Approval

The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved the study.

Tests of Fitness and Muscle Strength

Fitness was assessed using the cycle ergometric test. The final work level (Wmax) after exhaustion was divided by body weight (Wmax/kg), which was further transformed into stanine (1–9) scores. Isometric muscle strength was measured by a combination of knee extension, elbow flexion, and hand grip. These 3 measures were weighted and divided into stanines (1–9). Further details, published previously, are given in the online-only Data Supplement.

Classification of Stroke

Stroke cases were classified according to the International Classification of Diseases (ICD) codes used in the Hospital Discharge and Cause of Death registers from which diagnoses were retrieved: ICD-Eighth Revision (1968–1986); ICD-Ninth Revision (1987–1996); and ICD-Tenth Revision (1997 until present). The use of these codes for highly sensitive discrimination between the major stroke types (SAH, ICH, and IS) has been validated previously (ICD-9 and ICD-10) in Sweden. We have not found any specific validation of ICD-8 on stroke in a Swedish setting, but as ICD-8 is similar to ICD-9 (as compared with ICD-10, see below), we believe there is good reason to extrapolate the validation of ICD-9 to ICD-8. In our study, all cases of stroke were categorized as IS, ICH, or SAH, as follows. IS: 433 and 434 (ICD-8 and ICD-9) and I63 (ICD-10). ICH: 431 (ICD-9) and 161 (ICD-10). SAH: 430 (ICD-8 and ICD-9) and I60 (ICD-10). In addition, acute cerebrovascular disease-unspecified (436 in ICD-8 and ICD-9 and I64 in ICD-10) increased the number of cases (6.3% of all stroke diagnoses). This category was more commonly used before more stringent reporting requirements were introduced in the 1990s. For the purpose of this study, these unspecified cases were included in the IS group in subsequent analyses. First stroke event was censored by any type of stroke for all stroke analysis (fatal or nonfatal), excluding duplicates. In the analyses of stroke types, the first event was censored by each stroke type, thereby capturing multiple first-stroke events for the same patient and resulting in a somewhat larger sum of events than for all strokes (Figure 1). Fatal strokes were defined as patients who were hospitalized for stroke and died from any cause within 28 days. All other cases were classified as nonfatal strokes.

Covariates From the LISA Database

As an easily retrieved factor indicative of socioeconomic background, information on parental education was obtained from the longitudinal integration database for health insurance and labor market studies (in Swedish: longitudinal integrationsdatabas för sjukförsäkrings- och arbetsmarknadstudier; LISA) at Statistics Sweden (>80% coverage), as described previously and given in the online-only Data Supplement.

Statistical Analysis

All statistical calculations were performed with SAS version 8.1 (SAS Institute, NC). The follow-up period began at the date of
conscription (baseline) and subjects were censored at time of (1) first stroke event, (2) death from other causes, (3) emigration, or (4) at the end of follow-up (ie, December 31, 2010). This provided a minimum of 5 years and a maximum of 42 years of follow-up.

We used Cox proportional hazards models to assess the influence of fitness and muscle strength at the age of 18 years and potential confounders on the occurrence of first onset of fatal or nonfatal stroke during the observation period. Before 1996, original data (ie, actual scores of tests) were not electronically recorded and only stanine scores were available for assessment in our analyses. Fitness and muscle strength stanines were trichotomized as low (stanine score, 1–3), medium (stanine score, 4–6), and high (stanine score, 7–9); the high group was used as the reference category.

To assess effects of secular variation in rates of strokes and differences in conscription procedures over time, we adjusted for calendar years by stratifying the Cox model by conscription decade (1960s, 1970s, etc). As differences among regions and test centers could introduce bias, conscription test centers were adjusted for. Adjustments for the continuous variables body mass index, systolic and diastolic blood pressure, and education levels for each parent were also included as confounders.

Population-attributable risk (PAR), the association of a specific risk factor with a specific disease as a proportion of all risk factors for that disease, was calculated by the method of Natarajan et al,18 using the hazard ratios (HRs) from the Cox proportional hazard regression models.

Because of the large number of observations, the P values were small; in all analyses when the 95% confidence interval was separated from 1, the P values were <0.0001. Therefore, P values are not reported and the risk for type I errors is considered low. Variation is presented as confidence interval or in some cases SDs, as indicated. In Table 1, differences in the tertiles of fitness and muscle strength were assessed by the Student–Newman–Keuls test (all parameters P<0.05, not shown). BMI indicates body mass index; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

### Table 1. Population Characteristics by Category of Fitness and Muscle Strength

<table>
<thead>
<tr>
<th>Fitness</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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<tbody>
<tr>
<td>Total, n (%)</td>
<td>45,908 (3.9)</td>
<td>625,439 (53.7)</td>
<td>494,011 (42.4)</td>
</tr>
<tr>
<td>Age at conscription, y, mean (SD)</td>
<td>18.6 (1.3)</td>
<td>18.4 (0.9)</td>
<td>18.3 (0.7)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>66.6 (17.2)</td>
<td>67.9 (10.0)</td>
<td>72.1 (8.4)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>176.5 (7.1)</td>
<td>178.3 (6.5)</td>
<td>180.6 (6.2)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>21.4 (4.8)</td>
<td>21.5 (2.9)</td>
<td>22.1 (2.3)</td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>126.9 (11.0)</td>
<td>127.5 (10.7)</td>
<td>129.2 (10.8)</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>68.0 (9.7)</td>
<td>67.1 (9.7)</td>
<td>67.6 (9.8)</td>
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<tr>
<td>Parental education</td>
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<tr>
<td>Elementary school only, father (%)</td>
<td>55.0</td>
<td>43.5</td>
<td>37.5</td>
</tr>
<tr>
<td>University, father (%)</td>
<td>10.5</td>
<td>17.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Elementary school only, mother (%)</td>
<td>54.7</td>
<td>41.0</td>
<td>37.1</td>
</tr>
<tr>
<td>University, mother (%)</td>
<td>9.7</td>
<td>17.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Muscle strength, stanine, mean (SD)</td>
<td>4.6 (1.8)</td>
<td>5.3 (1.8)</td>
<td>6.2 (1.8)</td>
</tr>
<tr>
<td>Total no. of strokes (%)</td>
<td>535 (1.17)</td>
<td>4268 (0.68)</td>
<td>3011 (0.61)</td>
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<tr>
<td>No. of strokes with missing fitness data: 3103</td>
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</tbody>
</table>

Muscle strength

| Total, n (%) | 216,482 (13.9) | 884,369 (56.6) | 462,080 (29.6) |
| Age at conscription, y, mean (SD) | 18.3 (0.8) | 18.3 (0.8) | 18.4 (0.8) |
| Weight, kg, mean (SD) | 62.0 (9.0) | 68.1 (8.9) | 76.0 (10.6) |
| Height, cm, mean (SD) | 176.2 (6.8) | 178.7 (6.4) | 181.0 (6.3) |
| BMI, mean (SD) | 20.2 (2.8) | 21.5 (2.7) | 23.3 (3.0) |
| SBP, mean (SD) | 126.4 (11.1) | 128.2 (10.9) | 130.1 (10.9) |
| DBP, mean (SD) | 67.8 (9.5) | 67.6 (9.8) | 67.7 (10.0) |
| Parental education | | | |
| Elementary school only, father (%) | 37.2 | 40.7 | 38.8 |
| University, father (%) | 22.9 | 20.4 | 21.3 |
| Elementary school only, mother (%) | 35.3 | 39.1 | 34.9 |
| University, mother (%) | 23.0 | 20.3 | 22.7 |
| Physical fitness, stanine, mean (SD) | 5.5 (1.6) | 6.3 (1.7) | 6.9 (1.7) |
| Total no. of strokes (%) | 1340 (0.62) | 5769 (0.65) | 2422 (0.52) |
| No. of strokes with missing muscle strength: 1386 |

Numbers of any type of first stroke (see Methods). Differences between low, medium, and high assessed by Student–Newman–Keuls test (all parameters P<0.05, not shown). BMI indicates body mass index; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Results

Data on primary exclusions, average observation time, and total number of person-years are found in Figure 1. From
Table 2.  All Strokes, Fatal, and Nonfatal, With Respect to Fitness and Muscle Strength

<table>
<thead>
<tr>
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<th>Hazard Ratio (95% CI)</th>
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<tr>
<td></td>
<td>All stroke, n=10917 (1517)</td>
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<tr>
<td>Low*</td>
<td>1.58 (1.44–1.73)</td>
</tr>
<tr>
<td>Medium*</td>
<td>1.30 (1.24–1.36)</td>
</tr>
<tr>
<td>Muscle strength Model A (n=9531)</td>
<td>Model C (n=5843)</td>
</tr>
<tr>
<td>Low*</td>
<td>1.11 (1.03–1.18)</td>
</tr>
<tr>
<td>Medium*</td>
<td>0.96 (0.91–1.01)</td>
</tr>
</tbody>
</table>

|                      | Fatal stroke, n=1652 (1517) | Fitness | Model A (n=1114) | Model B (n=1109) | Model C (n=590) | Model D (n=589) | PAR | Model M (n=589) |
| Low*                 | 2.20 (1.75–2.76) | 2.58 (2.04–3.26) | 2.50 (1.81–3.47) | 2.52 (1.82–3.50) | 0.05 (0.03–0.07) | 2.20 (1.57–3.08) |
| Medium*              | 1.56 (1.38–1.78) | 1.71 (1.50–1.95) | 1.61 (1.35–1.93) | 1.62 (1.35–1.93) | 0.22 (0.13–0.3) | 1.54 (1.28–1.84) |
| Muscle strength Model A (n=1386) | Model B (n=1378) | Model C (n=746) | Model D (n=738) | PAR | Model F (n=589) |
| Low*                 | 1.54 (1.30–1.82) | 2.07 (1.73–2.48) | 2.16 (1.69–2.75) | 2.16 (1.69–2.77) | 0.09 (0.06–0.13) | 1.66 (1.24–2.23) |
| Medium*              | 1.10 (0.97–1.26) | 1.30 (1.13–1.49) | 1.26 (1.05–1.51) | 1.27 (1.06–1.53) | 0.13 (0.02–0.23) | 1.17 (0.95–1.44) |

|                      | Nonfatal stroke, n=9265 (0) | Fitness | Model A (n=6700) | Model B (n=6676) | Model C (n=4170) | Model D (n=4166) | PAR | Model M (n=4165) |
| Low*                 | 1.48 (1.34–1.63) | 1.75 (1.58–1.94) | 1.60 (1.39–1.83) | 1.60 (1.40–1.84) | 0.02 (0.02–0.03) | 1.56 (1.35–1.79) |
| Medium*              | 1.25 (1.19–1.32) | 1.36 (1.30–1.44) | 1.29 (1.21–1.37) | 1.29 (1.21–1.37) | 0.12 (0.09–0.15) | 1.28 (1.20–1.36) |
| Muscle strength Model A (n=8145) | Model B (n=8117) | Model C (n=5097) | Model D (n=5057) | PAR | Model F (n=4165) |
| Low*                 | 1.04 (0.97–1.12) | 1.35 (1.25–1.46) | 1.29 (1.17–1.43) | 1.30 (1.18–1.44) | 0.03 (0.02–0.05) | 1.11 (0.99–1.25) |
| Medium*              | 0.94 (0.89–0.99) | 1.09 (1.04–1.15) | 1.05 (0.99–1.13) | 1.06 (0.99–1.13) | N/A | 1.01 (0.94–1.08) |

Model A, unadjusted crude; model B, adjusted for decade, body mass index, conscription test center; model C, adjusted for B and parental education; model D, adjusted for C and systolic and diastolic blood pressure; model F adjusted for D and fitness; and model M adjusted for D and muscle strength. PAR estimates are given for the last adjustment in the case of a significant association. For each model and analysis the numbers of included subjects are shown (n). Numbers in parentheses are the number of cases identified by the Cause of Death Register. CI indicates confidence interval; and PAR, population-attributable risk.

*Reference category: high.
Table 3 shows age-adjusted and fully adjusted HRs and PAR estimates by stroke type in relation to fitness and muscle strength. Figure 2B to 2D shows type-specific cumulative stroke incidence.

In fully adjusted models, low fitness was associated with an increased risk for inpatient care for SAH, ICH, and IS, with the greatest HR found for ICH (HR, 2.10; Table 3). Exclusion of the unspecified cases in the IS group (6%) changed HR little (range, 0%–6%), with no change in overlap of confidence intervals (not shown). The strength of the associations changed little in the different models of adjustment. The associations remained essentially unchanged when muscle strength was added as a covariate (Table 3, model M).

Low muscle strength showed weaker associations compared with fitness for SAH, ICH, and IS incidence (fully

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**Stroke Types**

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Low muscle strength showed weaker associations compared with fitness for SAH, ICH, and IS incidence (fully
incidence, including for the type-specific strokes, withstood
harms is further supported by the fact that the HRs for stroke
 fissility is more critical than
low and medium muscle strength, regardless of stroke fatality and
ichotomy (HR, 1.60) and for subsequent ICH (HR, 2.10) com-
risk was slightly stronger for fatal (HR, 2.52) than for nonfatal
age of 18 years had an increased risk of stroke (HR, 1.70). This
In this large national cohort study, men with low fitness at the
levels except in the case of ICH (Table 3, model F).
adjusted HRs, 1.33–1.62). For SAH incidence, the combined
PAR for low and medium fitness was 20%, compared with 5% for
low and medium muscle strength. For ICH incidence, the
combined PAR for low and medium fitness was 22%, com-
pared with 16% for low and medium muscle strength. For IS
incidence, the PAR estimates showed the largest differences
between low fitness and low muscle strength (14% and 3%,
respectively). When fitness was added as a covariate, the HRs
adjusted for muscle strength, whereas estimates for muscle
strength became nonsignificant after adjustment for fitness,
except for all stroke, fatal stroke, and ICH.

Fitness and muscle strength have previously been shown
to have no or minor association (r=0.05–0.2). In contrast,
we found a moderate association (r=0.25), although it should
be noted that our analysis is based on correlating stanines and
not raw data. Although muscle strength seems to be associ-
ated with measures of combined cardiovascular disease risk
independently of aerobic fitness, only high muscle strength
showed a protective effect, although a relatively weak one
(relative risk reduction, 12%). Compared with the study
by Timpka et al, our data show a higher HR of low muscle
strength for all stroke incidence (HR, 1.39 and HR, 1.17 after
adjustment for fitness). Apart from the fact that our study
focuses on stroke rather than coronary heart disease, the dif-
ferent magnitudes of the HRs may partly be because of dif-
ferences in the selection of reference groups. Importantly,
our study shows that although muscle strength is associated
with stroke incidence, it is mostly via low fitness, as shown
by comparisons of HRs, PAR estimates, and crosswise adjust-
ments (Table 3, models M and F).

The associations between low fitness and subsequent risk of
stroke differed between stroke types. The weaker associ-
ations with SAH and IS (both HR, 1.60) and the stronger
association with ICH (HR, 2.10) were within the outer ranges

### Table 3. Major Types of Strokes With Respect to the Various Independent Variables

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Hazard Ratio (95% CI)</th>
<th>Model A (n=648)</th>
<th>Model B (n=645)</th>
<th>Model C (n=374)</th>
<th>Model D (n=373)</th>
<th>PAR</th>
<th>Model M (n=373)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subarachnoid hemorrhage</strong></td>
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<td></td>
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<tr>
<td>Low*</td>
<td>1.74 (1.25–2.43)</td>
<td>1.86 (1.32–2.63)</td>
<td>1.57 (0.99–2.51)</td>
<td>1.60 (1.00–2.55)</td>
<td>0.02 (0.0–0.05)</td>
<td>1.55 (0.96–2.50)</td>
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<tr>
<td>Medium*</td>
<td>1.68 (1.42–1.99)</td>
<td>1.76 (1.48–2.09)</td>
<td>1.42 (1.14–1.77)</td>
<td>1.43 (1.15–1.78)</td>
<td>0.18 (0.06–0.30)</td>
<td>1.40 (1.12–1.75)</td>
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<tr>
<td><strong>Muscle strength</strong></td>
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<tr>
<td>Age, model A (n=798)</td>
<td>1.45 (1.15–1.83)</td>
<td>1.68 (1.31–2.15)</td>
<td>1.46 (1.05–2.01)</td>
<td>1.51 (1.09–2.09)</td>
<td>0.05 (0.0–0.10)</td>
<td>1.15 (0.78–1.72)</td>
<td></td>
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<tr>
<td>Low*</td>
<td>1.17 (0.98–1.39)</td>
<td>1.26 (1.05-1.51)</td>
<td>1.14 (0.91–1.43)</td>
<td>1.15 (0.92–1.44)</td>
<td>N/A</td>
<td>1.14 (0.89–1.47)</td>
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<tr>
<td><strong>Intracerebral hemorrhage</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Fitness</td>
<td></td>
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<tr>
<td>Low*</td>
<td>1.74 (1.46–2.07)</td>
<td>2.04 (1.70–2.44)</td>
<td>2.09 (1.66–2.64)</td>
<td>2.10 (1.67–2.65)</td>
<td>0.04 (0.02–0.05)</td>
<td>1.94 (1.53–2.46)</td>
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<tr>
<td>Medium*</td>
<td>1.36 (1.24–1.49)</td>
<td>1.47 (1.34–1.62)</td>
<td>1.47 (1.30–1.65)</td>
<td>1.47 (1.31–1.66)</td>
<td>0.18 (0.12–0.24)</td>
<td>1.42 (1.26–1.61)</td>
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<tr>
<td><strong>Muscle strength</strong></td>
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</tr>
<tr>
<td>Low*</td>
<td>1.18 (1.04–1.34)</td>
<td>1.62 (1.41–1.86)</td>
<td>1.60 (1.35–1.90)</td>
<td>1.62 (1.36–1.92)</td>
<td>0.06 (0.03–0.08)</td>
<td>1.37 (1.12–1.68)</td>
<td></td>
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<tr>
<td>Medium*</td>
<td>0.98 (0.90–1.08)</td>
<td>1.18 (1.07–1.30)</td>
<td>1.18 (1.05–1.33)</td>
<td>1.19 (1.06–1.35)</td>
<td>0.10 (0.02–0.17)</td>
<td>1.12 (0.98–1.28)</td>
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<tr>
<td><strong>Ischemic stroke</strong></td>
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<td>Fitness</td>
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<tr>
<td>Low*</td>
<td>1.53 (1.38–1.71)</td>
<td>1.84 (1.65–2.06)</td>
<td>1.60 (1.37–1.86)</td>
<td>1.60 (1.38–1.86)</td>
<td>0.03 (0.02–0.04)</td>
<td>1.55 (1.32–1.81)</td>
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<tr>
<td>Medium*</td>
<td>1.26 (1.19–1.33)</td>
<td>1.38 (1.30–1.46)</td>
<td>1.28 (1.19–1.37)</td>
<td>1.27 (1.19–1.37)</td>
<td>0.11 (0.08–0.15)</td>
<td>1.26 (1.17–1.36)</td>
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<tr>
<td><strong>Muscle strength</strong></td>
<td></td>
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<tr>
<td>Low*</td>
<td>1.08 (1.00–1.17)</td>
<td>1.40 (1.29–1.53)</td>
<td>1.33 (1.19–1.48)</td>
<td>1.33 (1.19–1.48)</td>
<td>0.03 (0.02–0.05)</td>
<td>1.13 (0.99–1.29)</td>
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<tr>
<td>Medium*</td>
<td>0.94 (0.89–1.00)</td>
<td>1.10 (1.03–1.16)</td>
<td>1.04 (0.97–1.12)</td>
<td>1.05 (0.97–1.13)</td>
<td>N/A</td>
<td>1.00 (0.92–1.08)</td>
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</table>

*Reference category: high.

Discussion

In this large national cohort study, men with low fitness at the
age of 18 years had an increased risk of stroke (HR, 1.70). This
risk was slightly stronger for fatal (HR, 2.52) than for nonfatal
stroke (HR, 1.60) and for subsequent ICH (HR, 2.10) com-
pared with SAH and IS (both HR, 1.60). Low muscle strength
was also associated with subsequent stroke (HR, 1.39),
including fatal (HR, 2.16) and nonfatal (HR, 1.30) strokes,
but with lower magnitude than fitness. The PAR estimates for
low and medium fitness were consistently higher than for low
and medium muscle strength, regardless of stroke fatality and
stroke type, which indicates that fitness is more critical than
muscle strength for stroke risk. The greater importance of fit-
ess is further supported by the fact that the HRs for stroke
incidence, including for the type-specific strokes, withstood
of each other’s 95% confidence intervals. This indicates that the effects of low fitness on different stroke types differed only modestly. Nevertheless, these differences are indicative of the fact that stroke is a heterogenic disease with different risk factors for different types of stroke. As SAH risk derives largely from arterial wall malformations, such as aneurysms, risk factor associations with fitness could be different than for ICH and IS. Nevertheless, fitness was also independently associated with SAH, and it is known that aneurysm growth and rupture can be provoked by high blood pressure.21 High blood pressure is a strong risk factor for ICH, but also for other types of IS.21 As increasing physical activity lowers blood pressure (meta-analysis on middle-aged subjects22), achieving a higher degree of fitness could be efficient in lowering the risk of ICH and IS. In our study of young adults, the blood pressures differed only marginally between the fitness groups (Table 1), and inclusion of blood pressures in the models of regression changed HRs little (comparing models C and D). However, physical activity also improves metabolic status, as for example, by lowering serum lipids and blood glucose,22 which may affect stroke incidence. As physical activity and changes in fitness may affect blood pressure to a larger degree in middle-aged subjects,22 it would have been preferable to have been able to obtain follow-up blood pressures, but these were not available.

It is known that high levels of physical activity are associated with decreased risk of stroke in middle-aged men and women (meta-analysis of 13 and 8 studies, respectively, with partial overlap-generating meta-analysis of original studies28) and that actual fitness levels in a wide age span of chiefly middle-aged subjects are protective against stroke with an odds ratio of 1.5 to 2.9 What is new in our study is the finding that fitness, independently of muscle strength, at a young age is associated with stroke risk later in life. Several potential mechanisms exist through which fitness could affect the brain later in life. For example, previous studies have shown that fitness could favor activation of neuroprotective factors and neuroplasticity in the brain,23 which in turn may contribute to resilience against vascular risk factors.22 Several of these vascular biomarkers have been found to be increased in the circulation as well as locally in the brain. For example, cardiovascular exercise increases the expression of brain-derived neurotrophic factor and insulin-like growth factor 1,23 the latter known to negatively associate with blood pressure.24 The fact that low fitness at the age of 18 years is associated with a HR for all stroke of 1.70, compared with the lower risk reductions of high versus low physical activity in middle-aged subjects,7,16 suggests that achieving a good level of fitness in early adulthood may provide an additional degree of protection to that provided by exercise programs begun in middle age.

The strengths of this study are that it was a prospective study with a large national population-based cohort of more than a million individuals, that it used objective measures of fitness and muscle strength, and that it achieved a virtually complete follow-up (5–42 years). About stroke incidence, the Swedish National Hospital Discharge Register and the Cause of Death Register have been shown to have high reliability and few missed cases with regard to ICD-10,17 which constituted 85% of all stroke cases, but slightly lower quality with regard to the remaining cases retrieved from ICD-9.16 To our knowledge, there are no validation studies available with regard to ICD-8 and stroke in a Swedish setting, but as ICD-8 is similar to ICD-9, we think this should not affect our results to a large degree.

The study also has some limitations. First, data on fitness are available at baseline only. Even with several sampling points, regression analysis on observational data cannot draw causal conclusions. The associations may be reflective of other behaviors of which we have no record (smoking, future physical activity, etc). With only 1 sampling point, no causal relationships can be proven, rather the HRs suggest the relations that may be most important. Although the use of PARs is advantageous in indicating the magnitude of the risk factor, it nevertheless has the same shortcoming in describing causality. For example, it cannot be presumed that the PAR of 16% for all strokes attributable to low and medium fitness could be alleviated by increasing fitness to the high fitness level. Instead, in our study, the strongest indicator of the relative importance of fitness and muscle strengths is found in the cross-wise inclusion of these factors in the regression models (models F and M). However, even with these models, causality cannot be proven. Nevertheless, the pattern of HRs and PARs suggests where future intervention studies could be undertaken.

Second, the Hospital Discharge Register, although starting in 1970, did not have national coverage until 1987. However, as the absolute majority of cases occurred after 1987,25 this will not likely have affected results, nor will the potential but probably negligible exclusion of nonhospitalized cases.

Third, the results cannot be directly extrapolated to women, especially as stroke incidence in women occurs later in life.42 Fourth, a considerable number of subjects were not included because of missing data on fitness (Figure 1). A more complete record of individuals could have been generated if individuals with estimations of stanines had been included, but we chose not to do this. Even so, our criterion of including measured and excluding estimated data did not select certain types of individuals and so would not greatly affect the associations. Rather, the selection bias affected mostly missing data for certain years (especially 1968–1972, 1978, and 1985), which would not affect the general associations to a large degree.

Finally, although the study controls for an important socioeconomic factor (parental education), we did not have access to data for either baseline or subsequent smoking, but because only small differences in fitness of 7% have been observed in adolescents who smoke,26 this factor could not explain more than a small part of the difference in stroke risk that we found. Although genetic and nutritional factors are also important determinants of fitness, it is encouraging that fitness can be improved comparatively easily by exercise, typically by ≈25%.27

Conclusions

Low fitness and muscle strength at the age of 18 years were both independently associated with an increased stroke risk in adulthood, although low fitness showed a stronger association
than muscle strength, as estimated by both HRs and PAR. The data also indicate that the HR for low muscle strength to stroke incidence most likely reflected the stronger association with low fitness. Furthermore, long-term intervention studies with several points of sampling fitness are needed to elucidate the relative importance of time, changes in fitness, and relation to physical activities.

Acknowledgments

We wish to thank Tommy Johnsson (University of Gothenburg, Sweden) for statistical advice and analysis and Tim Haydon (Sydney, Australia) for proof-reading.

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Disclosures

None.

References


Influence of Cardiovascular Fitness and Muscle Strength in Early Adulthood on Long-Term Risk of Stroke in Swedish Men

N. David Åberg, H. Georg Kuhn, Jenny Nyberg, Margda Waern, Peter Friberg, Johan Svensson, Kjell Torén, Annika Rosengren, Maria A.I. Åberg and Michael Nilsson

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Influence of cardiovascular fitness and muscle strength in early adulthood on long-term risk of stroke in Swedish men

David Åberg, H. Georg Kuhn, Jenny Nyberg, Margda Waern, Peter Friberg, Johan Svensson, Kjell Torén, Annika Rosengren, Maria A.I. Åberg and Michael Nilsson

SUPPLEMENTAL MATERIAL
Method

Swedish military service conscription register data

During a two-day baseline examination, all conscripts underwent standardized physical examinations at the six different conscription centres in Sweden before being assigned to service in the Swedish armed forces. All conscripts were examined by a physician who diagnosed any medical disorder. Weight, height and blood pressure were measured. Men with incomplete data on fitness and muscle strength were initially excluded (Figure 1). Subsequently, in the adjusted models with Cox proportional hazards (see below), extreme values (probably due to data errors) were also excluded, resulting in fewer n (Tables 1-2). These extreme values were systolic blood pressure above 220 or below 80, diastolic above 150 or 30, and height below 140 cm or above 215 cm.

Fitness test

Cardiovascular fitness was assessed using the cycle ergometric test, as previously described\(^1,2\). The procedure, including elements of validity and reliability, has been described in detail previously\(^3\). Briefly, after a normal resting electrocardiogram (ECG), 5 min of submaximal exercise was performed at work rates of 75–175 W, depending on body weight. Under heart rate registration, the work rate was continuously increased by 25 W/min (with pedal cadence maintained between 60–70 rpm) until exhaustion. The final work level (Wmax) was divided by body weight. This measure was employed because it yielded a better correlation with maximum oxygen consumption (VO\(_{2}\text{max}\)) (correlation coefficient \(-0.9\)) than predicted VO\(_{2}\text{max}\) (correlation coefficient \(-0.6-0.7\))\(^4,5\). The resulting values (Wmax/kg) were transformed into stanine (1-9) scores that served as a measure of fitness.

Muscular strength test

Isometric muscle strength was measured by knee extension (weighted 1.3x), elbow flexion (weighted 0.8x), and hand grip (tested with a tensiometer; weighted 1.7x)\(^3\). These three measures were weighted and integrated into one estimate (kilopond before 1979 or Newton after 1979), and divided into stanines (1-9).

Secular trends for fitness and muscle strength

We found some secular trends but believe their effect on our analysis was minor, for the following reasons. Over the different years of conscription, there was an approximately 20% increase in maximum load (from 250 to 300 W) and an approximately 12% increase in body mass (from 66 to 74kg), which actually increased the values (maximum load/kg) by 14%. However, as the limits for fitness were adjusted in 1980, the average stanine scores remained very stable (<1% change). A similar pattern was found for muscle strength, with an approximately 15% increase over the years but with very stable stanine values. Again, the reason for stable stanine values was that they were adjusted for body mass. Additionally, the algorithms of the transition of original data for muscle strength into stanines were somewhat changed in 1979 (kilopond or Newton, see above).
Covariates from the LISA database

Information on parental education was obtained from the longitudinal integration database for health insurance and labour market studies (Swedish acronym LISA). The LISA database (http://www.scb.se/sv_/Hitta-statistik/Publiceringskalender/Visa-detaljerad-information/?PublObjId=16129) at Statistics Sweden was initiated in 1990 and includes all registered residents aged 16 years and older, with an approximate 80% coverage. The database integrates data from the labour market, as well as educational and socioeconomic factors. Parental education was rated in 7 levels: (1) pre high school education for less than 9 years, (2) pre high school education for 9 years, (3) high school education, (4) college education for less than 2 years, (5) college education for 2 years, (6) college education for more than 2 years, and (7) postgraduate education. These registers have been used in exactly the same way previously1, 2.

References in supplemental material:

Influence of Cardiovascular Fitness and Muscle Strength in Early Adulthood on Long-Term Risk of Stroke in Swedish Men

N. David Åberg, PhD, MD; H. Georg Kuhn, PhD, MSc; Jenny Nyberg, PhD, MSc; Margda Waern, PhD, MD; Peter Friberg, PhD, MD; Johan Svensson, PhD, MD; Kjell Torén, PhD, MD; Annika Rosengren, PhD, MD; Maria Å. Åberg, PhD, MD; Michael Nilsson, PhD, MD

(Stroke. 2015;46:1769-1776.)

Key Words: epidemiology ■ exercise ■ incidence ■ muscles ■ stroke

Abstract 1

Background and Objectives

Young and middle-aged cardiovascular fitness (fitness) is a stroke risk factor. However, the effects of fitness and muscle strength on long-term stroke risk in early adulthood are not well known. Therefore, this study analyzed these in a large cohort of young men.

Methods

An epidemiological cohort study of Swedish conscripts (n=1166035) was conducted from 1968 to 2005. Cardiovascular fitness (cycle ergometric test: n=1166035) and muscle strength (n=1563750) were divided into tertiles (low, middle, high). During 42 years of follow-up, incidence and case-fatality of stroke (intracerebral hemorrhage, cerebral hemorrhage, ischemic stroke) were calculated using a Cox proportional hazards model. Case ascertainment was from the Hospital Discharge Register (International Classification of Diseases, 8-10th editions) and the Cause of Death Register.

Results

One first stroke was identified (intracerebral hemorrhage, n=895; cerebral hemorrhage, n=2904; ischemic stroke, n=7767). For incidence and case-fatality analysis, the first stroke regardless of type was considered (n=10917). Fitness and muscle strength showed a dose-response relationship in all types of stroke. The lowest tertile had a risk increase of 1.70 (1.50–1.93) and 1.39 (1.27–1.53) compared to the highest tertile. Muscle strength showed a stronger association in case-fatality. All three types of stroke showed a similar association. After adjusting for fitness, muscle strength was not associated with stroke. When adjusting for fitness, the association of muscle strength with stroke was attenuated/lost.

Conclusions

Fitness and muscle strength were independent risk factors for stroke in young men.
급성혈혈뇌졸중 후 일별 혈압 변동성과 기능적 결과
후쿠오카 뇌졸중 등록체계

Day-by-Day Blood Pressure Variability and Functional Outcome After Acute Ischemic Stroke
Fukuoka Stroke Registry

Kenji Fukuda, MD, PhD; Hisashi Kai, MD, PhD; Masahiro Kamouchi, MD, PhD; Jun Hata, MD, PhD; Tetsuro Ago, MD, PhD; Hiroshi Nakane, MD, PhD; Tsutomu Imaizumi, MD, PhD; Takanari Kitazono, MD, PhD; on behalf of the FSR Investigators* (Stroke. 2015;46:1832-1839.)

Key Words: blood pressure ■ cerebral infarction ■ prognosis ■ risk factors ■ stroke

배경과 목적
급성혈혈뇌졸중 환자에서 혈압 변동성과 기능적 결과 사이의 연관성은 아직 불명확하다. 이 연구는 병원내 일별 혈압 변동성이 급성혈혈뇌졸중 후 기능적 결과와 연관성이 있는지를 규명하고자 하였다.

방법
본 연구는 후쿠오카 뇌졸중 등록체계를 이용하여 발생 전에 기능적으로 독립된 생활이 가능했고 증상 발생 24시간 이내에 입원이 가능했던 처음 혈혈뇌졸중을 가진 2566명의 환자를 포함한 환자를 포함하였다. 혈압이 매일 측정되었고, 변동성은 표준편차, 변동계수