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 A.I. Åberg, PhD, MD; Michael Nilsson, PhD, MD

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=10917). 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.

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 to be a more accurate predictor of cardiovascular risk compared 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 ≈0.25% to 0.3% 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 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 ≈0.25% to 0.3% 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.

![Flow chart of included and excluded subjects according to Strengthening the Reporting of Observational Studies in Epidemiology.](image)

**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 Clearances 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 stani (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 stani (1–9). Further details, published previously, are also 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 high sensitivity discrimination between the major stroke types (SAH, ICH, and IS) has been validated previously (ICD-9th and ICD-10th 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 and ICD-8; ICH: 431 (ICD-9) and 161 (ICD-10); SAH: 430 (ICD-8) and 160 (ICD-10). In addition, acute cerebrovascular disease-unspecified (436 in ICD-8 and ICD-9 and 164 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: Longitudinell 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...
Aberg et al. Fitness and Stroke Incidence

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, 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.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>45908 (3.9)</td>
<td>625439 (53.7)</td>
<td>494011 (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>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>No. of strokes with missing fitness data:</td>
<td>3103</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Muscle strength

<table>
<thead>
<tr>
<th>Category</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>216482 (13.9)</td>
<td>884369 (56.6)</td>
<td>462080 (29.6)</td>
</tr>
<tr>
<td>Age at conscription, y, mean (SD)</td>
<td>18.3 (0.8)</td>
<td>18.3 (0.8)</td>
<td>18.4 (0.8)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>62.0 (9.0)</td>
<td>68.1 (8.9)</td>
<td>76.0 (10.6)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>176.2 (6.8)</td>
<td>178.7 (6.4)</td>
<td>181.0 (6.3)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>20.2 (2.8)</td>
<td>21.5 (2.7)</td>
<td>23.3 (3.0)</td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>126.4 (11.1)</td>
<td>128.2 (10.9)</td>
<td>130.1 (10.9)</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>67.8 (9.5)</td>
<td>67.6 (9.8)</td>
<td>67.7 (10.0)</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school only, father (%)</td>
<td>37.2</td>
<td>40.7</td>
<td>38.8</td>
</tr>
<tr>
<td>University, father (%)</td>
<td>22.9</td>
<td>20.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Elementary school only, mother (%)</td>
<td>35.3</td>
<td>39.1</td>
<td>34.9</td>
</tr>
<tr>
<td>University, mother (%)</td>
<td>23.0</td>
<td>20.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Physical fitness, stanine, mean (SD)</td>
<td>5.5 (1.6)</td>
<td>6.3 (1.7)</td>
<td>6.9 (1.7)</td>
</tr>
<tr>
<td>Total no. of strokes (%)</td>
<td>1340 (0.62)</td>
<td>5769 (0.65)</td>
<td>2422 (0.52)</td>
</tr>
<tr>
<td>No. of strokes with missing muscle strength:</td>
<td>1386</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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...
was correlation in terms of fitness and muscle strength stanines vice versa, albeit with relatively large SD. The Pearson muscle strength was higher in the high fitness group, and lower in the low and medium fitness groups, the form of the response relation, with the highest HRs for stroke in the low fitness group (HR, 1.70). Although stroke incidence was increased risk for future stroke (Table 2). In fully adjusted models, low fitness was associated with an HR, 1.39), showing higher HRs for fatal stroke (HR, 2.52) than with regard to nonfatal stroke (HR, 1.60). In addition, low muscle strength was associated with increased risk of future stroke (HR, 1.39), showing higher HRs for fatal stroke than for nonfatal stroke.

The magnitudes of HR for stroke incidence were somewhat higher for low fitness than for low muscle strength (Table 2). However, PAR estimates, with some limitations (see Discussion), are a better tool to evaluate the relative magnitudes of different factors. Of note, low and medium fitness were related to 16% of all stroke incidence as compared with 8% for low and medium muscle strength. The HRs for associations between low fitness and stroke were higher with regard to fatal stroke (HR, 2.52) than with regard to nonfatal stroke (HR, 1.60). In addition, low muscle strength was associated with increased risk of future stroke (HR, 1.39), showing higher HRs for fatal stroke than for nonfatal stroke.

Table 2. All Strokes, Fatal, and Nonfatal, With Respect to Fitness and Muscle Strength

<table>
<thead>
<tr>
<th>All stroke, n=10917 (1517)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitness</td>
<td>Model A (n=7814)</td>
</tr>
<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</td>
<td>Model C (n=9531)</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>
<tr>
<td>Nonfatal stroke, n=9265 (0)</td>
<td>Model A (n=1114)</td>
</tr>
<tr>
<td>Fitness</td>
<td>Model A (n=6700)</td>
</tr>
<tr>
<td>Low*</td>
<td>2.20 (1.75–2.76)</td>
</tr>
<tr>
<td>Medium*</td>
<td>1.56 (1.38–1.78)</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Model A (n=1386)</td>
</tr>
<tr>
<td>Low*</td>
<td>1.54 (1.30–1.82)</td>
</tr>
<tr>
<td>Medium*</td>
<td>1.10 (0.97–1.26)</td>
</tr>
</tbody>
</table>

The magnitudes of HR for stroke incidence were somewhat higher for low fitness than for low muscle strength (Table 2). However, PAR estimates, with some limitations (see Discussion), are a better tool to evaluate the relative magnitudes of different factors. Of note, low and medium fitness were related to 16% of all stroke incidence as compared with 8% for low and medium muscle strength. The HRs for associations between low fitness and stroke were higher with regard to fatal stroke (HR, 2.52) than with regard to nonfatal stroke (HR, 1.60). In addition, low muscle strength was associated with increased risk of future stroke (HR, 1.39), showing higher HRs for fatal stroke than for nonfatal stroke.

The magnitudes of HR for stroke incidence were somewhat higher for low fitness than for low muscle strength (Table 2). However, PAR estimates, with some limitations (see Discussion), are a better tool to evaluate the relative magnitudes of different factors. Of note, low and medium fitness were related to 16% of all stroke incidence as compared with 8% for low and medium muscle strength. The same pattern, showing dominance of fitness over muscle strength, was found for fatal and nonfatal strokes. In addition, when muscle strength was added as a covariate in the fitness analysis (Table 2, model M), the associations decreased only slightly but remained significant. When fitness was added as a covariate in the muscle strength analysis, the associations with stroke incidence decreased, and only low muscle strength remained significantly associated with all stroke and fatal stroke incidence (Table 2, model F).

the included subjects, descriptive information on the distribution of stroke diagnoses among the different conscription variables stratified for low–medium–high fitness and muscle strength is shown in Table 1. All variables differed significantly in the stratified groups, and we included all the variables that differed by ≥2% (high versus low) as covariates; these were all the variables except age. Thus, height and weight were included in the concept of body mass index, parental education and blood pressures were included as covariates below. Furthermore, although secular trends in stanine values of fitness and muscle strength were minimal (online-only Data Supplement), decade of testing was included as a covariate. Of note, muscle strength was higher in the high fitness group, and vice versa, albeit with relatively large SD. The Pearson correlation in terms of fitness and muscle strength stanines was r=0.25 (P<0.0001).

All Stroke, Fatal Stroke, and Nonfatal Stroke Incidences as Outcomes

In fully adjusted models, low fitness was associated with an increased risk for future stroke (Table 2). There was a dose–response relation, with the highest HRs for stroke in the low fitness group (HR, 1.70). Although stroke incidence was higher in the low and medium fitness groups, the form of the curve indicated that the increase was relatively uniform across the years (Figure 2). The magnitude of associations changed little in models that controlled for decade, body mass index, conscription test center, parental education, and systolic and diastolic blood pressure. The HRs for associations between low fitness and stroke were higher with regard to fatal stroke (HR, 2.52) than with regard to nonfatal stroke (HR, 1.60). In addition, low muscle strength was associated with increased risk of future stroke (HR, 1.39), showing higher HRs for fatal stroke than for nonfatal stroke.
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

**Stroke Types**

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
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) compared 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 fitness is further supported by the fact that the HRs for stroke incidence, including for the type-specific strokes, withstood adjustment 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 associated 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 different magnitudes of the HRs may partly be because of differences 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 adjustments (Table 3, models M and F).

The associations between low fitness and subsequent risk of stroke differed between stroke types. The weaker associations with SAH and IS (both HR, 1.60) and the stronger association with ICH (HR, 2.10) were within the outer ranges 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%, compared 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 between low fitness and low muscle strength (14% and 3%, respectively). When fitness was added as a covariate, the HRs were reduced to nonsignificant for low and medium fitness, whereas estimates for muscle strength became nonsignificant after adjustment for fitness, except for all stroke, fatal stroke, and ICH.
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 low-
ering the risk of ICH and IS. In our study of young adults,
the blood pressures differed only marginally between the fit-
ness 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 meta-
bolic status, as for example, by lowering serum lipids and
blood glucose,22 which may affect stroke incidence. As physi-
cal 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 associ-
ated 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 16 original
studies46) 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,
already at a young age is associated with stroke risk later in
life. Several potential mechanisms exist through which fit-
ness could affect the brain later in life. For example, previ-
ous 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 associ-
ate 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, com-
pared with the lower risk reductions of high versus low physi-
cal activity in middle-aged subjects,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 rela-
tions that may be most important. Although the use of PARs
is advantageous in indicating the magnitude of the risk fac-
tor, 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 fit-
ness could be alleviated by increasing fitness to the high fit-
ness 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
on average.22

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 staminas had been included,
but we chose not to do this. Even so, our criterion of includ-
ing measured and excluding estimated data did not select cer-
tain types of individuals and so would not greatly affect the
associations. Rather, the selection bias affected mostly miss-
ing 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 socio-
economic 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 mostly 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.

Sources of Funding

This study was supported by grants from the Märtha Lundqvists Stiftelse, the Swedish Research Council for Worklife and Social Science (FAS, Swedish acronym for förnyelse, arbetsmiljö, samverkan), the Swedish Research Council, the Swedish government under the ALF (Swedish acronym for Avtal om Läkarutbildning och Forskning) agreement for biomedical research, Hjärnfonden, Sten A. Olsson Foundation, Stroke Riksförbundet (all of these in Sweden), and The Brawn Bequest (University of Newcastle, England).

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

Stroke. published online June 9, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2015/06/09/STROKEAHA.115.009008

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/06/22/STROKEAHA.115.009008.DC1
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.115.009008.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
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 (\(\text{VO}_2\text{max}\)) \((\text{correlation coefficient } \sim 0.9)\) than predicted \(\text{VO}_2\text{max}\) \((\text{correlation coefficient } \sim 0.6-0.7)\)\(^4\)-\(^5\). 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 A.I. Åberg, PhD, MD; Michael Nilsson, PhD, MD

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

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

Abstract

Background and Objective
Middle-aged and older men with low cardiovascular fitness (cardiorespiratory fitness) have an increased risk of stroke. However, the influence of fitness and muscle strength on long-term risk of stroke in early adulthood is not known. Therefore, this study analyzed a large cohort of young men.

Methods
A 1968-2005 register-based cohort study of Swedish men was performed. Fitness data (cycle ergometric test; n=1166035) and muscle strength (n=1563750) were divided into tertiles (low, middle, high). Over a 42-year follow-up period, incidence of stroke (intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke) and mortality was calculated using Cox regression models. Confirmation of cases was obtained from the Hospital Discharge Register and the Cause of Death Register using International Classification of Diseases (ICD) 8-10.

Results
The first stroke event was identified (intracerebral hemorrhage, n=895; subarachnoid hemorrhage, n=2904; ischemic stroke, n=7767). For all strokes and deaths, first strokes were included (n=10917). Fitness and muscle strength had a dose-response relationship with stroke risk (lowest tertile [1.70 [1.50–1.93] vs highest tertile [1.39 [1.27–1.53]) in a model that adjusted for other factors. Muscle strength was also highly correlated with stroke risk. Tertile analysis of the relationship between fitness and stroke was consistent with the analysis of muscle strength. After adjusting for fitness, muscle strength was correlated with stroke risk, but the correlation between muscle strength and stroke was smaller and statistically significant.

Conclusion
Low fitness and muscle strength in early adulthood are independently associated with increased stroke risk.
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