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Childhood stature and growth in relation to first ischemic stroke or intracerebral hemorrhage

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Abstract

Background and Purpose: Attained height, an indicator of genetic potential and childhood growth-environment, is inversely associated with stroke, but the mechanisms are poorly understood. We investigated whether childhood height and growth are associated with ischemic stroke (IS) and intracerebral hemorrhage (ICH).

Methods: In a cohort of Danish schoolchildren born 1930-1989, with measured height from 7-13 years, we investigated associations of childhood stature and growth with risks of adult IS and ICH. Cox proportional hazards regressions were performed to estimate hazard ratios (HRs) with confidence intervals (CIs) separately for women and men.

Results: Among 311,009 individuals, 10412 were diagnosed with IS and 2546 with ICH. Height at 7 years was inversely and significantly associated with IS in both sexes (per z-score, equivalent to approximately 5.2cm in women and 5.1cm in men, women: HR=0.89 [95%CI: 0.87-0.92], men: HR=0.90 [95%CI: 0.88-0.92]) and with ICH in men (HR=0.89 [95%CI: 0.84-0.94]), but not in women (HR=0.97 [95%CI: 0.91-1.04]). Associations were similar at older childhood ages and were stable throughout the study period. No statistically significant associations for growth from 7-13 years were observed for IS or ICH.

Conclusions: Short stature at 7-13 years is significantly associated with increased risks of IS in both sexes and with ICH in men. Growth during this period of childhood is not significantly associated with either of these stroke subtypes, suggesting that underlying mechanisms linking height with risks of stroke may exert their influence already by early childhood.
Introduction

The global burden of stroke will increase in the future, \textsuperscript{1, 2} and identifying disease mechanisms that improve possibilities of primary stroke prevention is essential. In most high income countries a decline in stroke incidence and mortality rates, which were mainly observed in women\textsuperscript{3}, occurred simultaneously with a general increase in attained adult height. Taken together, this suggests the involvement of shared underlying mechanisms for height growth and stroke disease development.\textsuperscript{4}

Adult stature is inversely associated with stroke\textsuperscript{5-7}, particularly intracerebral hemorrhage (ICH)\textsuperscript{6}; the Emerging Risk Factors Collaboration, including more than 1 million participants, found that per 6.5cm increase in adult height the risk of dying from ischemic stroke (IS) and ICH was reduced by 6\% and 10\%, respectively.\textsuperscript{7} Although short stature has associations with the risk of stroke that are nearly as strong as for body mass index (BMI), studies investigating growth, as opposed to weight gain, have been neglected.\textsuperscript{8, 9}

A potential explanation is that it is not possible to intervene on adult height and the effects of doing so in childhood are uncertain. However, in addition to being genetically determined, adult height is a marker of exposures affecting childhood growth (e.g. maternal diet during pregnancy, childhood diet, infection, and psychological stress), of which many are modifiable and all are thought to affect the risk of stroke.\textsuperscript{6} The decline in stroke incidence and mortality rates may thus not only be explained by enhanced management of stroke risk factors and stroke treatment, but also by improved growth-promoting childhood conditions.

Studies that investigated associations of childhood stature with later stroke are few and small in size (maximum of 507 total stroke cases)\textsuperscript{10-12} with one also investigating the effect of growth in infancy\textsuperscript{11}
and another also investigating growth later in childhood\textsuperscript{10}. None of these studies investigated men and women separately, and the youngest participants included in these studies were born in 1944, thus their results may not be generalizable to the children of today. Investigating height and especially growth during childhood, across a longer period of time in the 20\textsuperscript{th} Century where average height increased, may provide insights into the complex height-related mechanisms underlying stroke. We hypothesised that short stature and poor childhood growth are associated with increased risks of IS and potentially even stronger increased risks of ICH, and that the strength of the associations have attenuated over time due to the increase in average height. Therefore, in a cohort of children born from 1930-1989, we investigated associations of childhood stature and growth with first IS or ICH in women and men separately.
Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request and pending approval by the data steering committee.

We studied a cohort of 372,636 children from the Copenhagen School Health Records Register (CSHRR). The children were born from 1930-1989 and attended public or private schools in Copenhagen. Information from mandatory health examinations, which were performed annually until 1983 and thereafter at school entry and exit, has been computerized. In April 1968 all Danish residents were assigned a unique identification number, and it was recorded on every child’s health card from this date, or subsequently retrieved for children who left school before this time.

We used information on height from ages 7-13 years, which was measured without shoes at health examinations by trained school physicians and nurses using standardized procedures. Height was transformed into z-scores based on internal age-, sex- and birth cohort (5-year intervals) specific references to account for secular increases in height. Unless a measurement was taken at the exact age, the z-score was interpolated or extrapolated within a ±12 month period. Absolute height was based upon back-transformed z-scores to get a value as close to exact age as possible.

The identification number was used to link to the Danish National Hospital Register, which was established in 1977, and the Danish Cause of Death Register (computerized since 1970) for data on first IS or ICH. Stroke was defined by the 8th revision of the International Classification of Diseases (ICD) codes until 1994 and the 10th revision thereafter: IS (ICD-8, 433, 434; ICD-10, I63), ICH (ICD-8, 431; ICD-10, I61) and unspecified stroke (ICD-8, 436; ICD-10, I64). Information on vital status was obtained from the computerized Danish Civil Registration System.
Our starting population consisted of individuals with an identification number and who were at least 25 years of age upon study-entry. Follow up began in 1977, when the Danish National Hospital Register was established, and ended on the date of first-ever stroke diagnosis, of death, of emigration, of loss to follow-up or December 31, 2013, whichever came first. We excluded individuals if they had an outlying measurement of height and/or BMI (as a quality control) or lacked data on height and/or BMI at all childhood ages, or if they had a stroke diagnosis before 25 years (Figure I in the online-only Data Supplement).

The study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for purely register-based research.

**Statistical analysis**

We calculated the change in average height between 7 and 13 years during the study period by subtracting the mean height of individuals from the oldest birth cohort (born 1930-1934) from the mean height of individuals from the youngest birth cohort (born 1980-1988). Thereafter, we investigated the association of height, using z-scores and absolute height, at ages 7-13 years with IS and ICH, respectively, using Cox proportional hazards regression with age as the underlying time axis separately for each sex. Statistical significance was set at a p-value <0.05 and all tests were two-sided.

The linearity of the associations was tested against a restricted cubic spline with 5 knots, and we found no deviations from linearity (all p-values >0.10) for IS. For associations with ICH in men, but not in women, we found limited indications of deviations from linearity (all p-values >0.06, except for height at 8, 9, and 12 years, with p-values of 0.03, 0.03, and 0.04, respectively). Therefore we also conducted
a categorical analysis using quintiles of height as exposure. The assumption of proportional hazards
was tested by stratifying the analyses into quartiles of age at diagnosis and using time varying
coefficients. Furthermore, we used the Nelson-Aalen estimator to investigate if an inflection point (a
change in the association) occurred at a specific age. We tested if the height-stroke associations
differed by birth cohort using the likelihood-ratio test (all p-values >0.05 for interactions between
childhood height and birth cohort in a model stratified by age at diagnosis for IS and a non-stratified
model for ICH). All analyses were conducted separately for women and men, although we only found
limited indications of interactions by sex (all p-values using the likelihood ratio test >0.08, except
height at 7 years and ICH [p=0.03]).

In a subsample of individuals with height measurements at 7 and 13 years, we conducted growth
analyses which were adjusted for baseline height at 7 years. Assumptions of proportional hazards were
investigated as were birth cohort effects.

In a sensitivity analysis of the associations between height and IS, unclassified stroke was included in
the outcome, as more than 60% of the unclassified strokes in Denmark are ischemic.¹⁶
Results

Study population

The study included 311,009 individuals (49% women). Girls were an average of 1 cm shorter than boys until 11 years at which point the height difference disappeared (Table 1). By 12-13 years the girls were an average of 1.5 cm taller than boys. During the study period, average height increased by 4.1 cm and 4.2 cm at 7 years and by 7.3 cm and 8.8 cm at 13 years, in girls and boys, respectively. The average growth (standard deviation [SD]) between 7-13 years was lower among individuals from the oldest birth cohort (women: 32.0 [3.7] cm; men: 29.8 [3.6] cm) compared with the most recent birth cohort (women: 35.5 [3.9] cm; men: 34.4 [5.1] cm). Follow-up was from 25 years through 83 years with a median duration of 31.1 years. During this period 5313 women and 7645 men were diagnosed with a first-ever IS (80.4%) or ICH (19.6%). Incidence rates for IS and ICH increased with age in both sexes. For IS, the rate was higher in men than women until 75 years, after which the rate rapidly increased in women (Figure 1). The incidence rate for ICH was higher in men at all ages. The majority of IS events were diagnosed at 55-75 years. For ICH the proportion of cases were more evenly distributed at ages younger than 75 years (Table I in the online-only Data Supplement).

Childhood height and IS

In both sexes we found inverse linear associations between childhood height and IS. Since the pattern of the associations was similar across all childhood ages, we present results for 7, 10 and 13 years (Figure 2, see other ages in Table II in the online-only Data Supplement). Already at 7 years a 1 z-score increase in height was associated with an 11% (HR=0.89, 95%CI [0.87-0.92]) reduced risk of IS in
women and a 10% (HR=0.90, 95%CI [0.88-0.92]) reduced risk in men. To put this into perspective, a 1
z-score difference, despite being birth cohort specific, corresponds to approximately 5.2cm in girls and
5.1cm in boys at 7 years (10 years: 6.3cm in girls and 6.1cm in boys, 13 years: 7.0cm in girls and
8.1cm in boys). When examining the risk of IS within quintiles of absolute height at 7 years, it seemed
to be the increased risk among shortest individuals that was responsible for the inverse association as
opposed to a lower risk among tallest individuals (Table 2). The associations did not differ between the
sexes and were consistent across all childhood ages and birth cohorts both when using z-scores and
absolute height. There were some indications of an attenuation of the inverse associations with age at
diagnosis, but there was not a distinct age at which the associations changed. We therefore present the
overall inverse association (see age-specific estimates in Table III in the online-only Data Supplement).

In the sensitivity analysis including 7286 IS (41% women) and 8159 unclassified (41% women) strokes
combined, we found inverse associations of childhood height with IS plus unclassified stroke in both
sexes (Table IV and Table V in the online-only Data Supplement). The patterns of the associations
were similar to those when only IS was used as the outcome.

**Childhood height and ICH**

As with IS, the pattern of associations between height and ICH was similar across childhood ages
(Figure 2, Table I in the online-only Data Supplement). Among women, childhood height was weakly
and inversely associated with ICH, whereas in men, the association was inverse. Additionally,
individuals in the lowest height quintiles appeared to have a higher risk of ICH compared with risk of
IS (Table 2). Moreover, the inverse association between childhood height and ICH was stable across
birth cohorts and did not change with age at diagnosis (all p-values >0.07 for an interaction between age at diagnosis and childhood height).

Growth in relation to IS and ICH

In the 252,146 women and men with height available at 7 and 13 years, we investigated if growth was associated with either IS or ICH. In both sexes, we found limited evidence for associations between growth from 7-13 years (expressed per 0.5 z-score change) and IS (women: HR= 1.03 95%CI [1.00-1.06]; men: HR=1.0295% CI [0.99-1.50]) or ICH (women: HR=0.98 95%CI [0.92-1.04]; men: HR=0.99 95%CI [0.94-1.05]).
Discussion

In this large population-based cohort study we found that height at 7 through 13 years was inversely associated with IS in both sexes, and with ICH in men. Growth was not significantly associated with either stroke subtype. Moreover, the inverse associations remained stable throughout the study period even though the average height among the children increased substantially.

Short childhood stature was also associated with increased risk of stroke in two smaller Finnish studies\textsuperscript{10, 11} investigating this relationship as well as in the Boyd Orr cohort\textsuperscript{12} from the UK where inverse associations between childhood height and leg length, which is a measure of pre-pubertal growth, were observed. However, these studies were limited by a small number of cases (507, 331 and 92 cases of total stroke, respectively), impeding their possibilities of making sex- and stroke subtype-specific analysis.

Our results primarily have implications for understanding disease aetiology rather than for clinical risk prediction. Attained adult height is an indicator of growth conditions during childhood, timing of puberty and genetic height potential.\textsuperscript{17-19} Although we found strong inverse associations between height already at 7 years and IS in both sexes, as well as with ICH in men, we observed limited indications of childhood growth being associated with these two stroke subtypes. This suggests that the main effects of height on stroke are initiated before 7 years, already well before entering puberty. In contrast with our findings, the earlier mentioned two Finnish studies reported a positive trend for change in height from 7-15 years among men who developed any kind of stroke\textsuperscript{10}, whereas growth from 2-11 years was not associated with total stroke among women and men.\textsuperscript{11} If accelerated growth in mid-childhood is associated with stroke, it is expected that the strength of the inverse association between height and
stroke would be weaker for adult height. This was investigated in the Boyd-Orr cohort, where indications of a weaker inverse association with self-reported adult height, compared with childhood height, was observed. We did not have information on adult height to investigate this hypothesis or to perform mediation analyses for the inverse childhood height-stroke association. It thus remains a possibility that a factor, such as pubertal timing, which affects mid-childhood growth in a more complex way than what we were able to investigate in our study, could influence the associations between short childhood stature and risk of stroke.

It is well known that height is positively associated with socioeconomic status (SES).\(^6\) SES, which represents exposures to risk factors, health behaviours of the mother and access to resources, has been found to be associated with stroke, especially low SES during childhood.\(^{20-22}\) The inverse association between adult height and stroke has, however, generally been robust to adjustments for SES.\(^6\)

Although we found equally strong overall inverse associations of childhood stature with both IS and ICH among men, the categorical analysis indicated that the risk of ICH was higher among the shortest quintiles of childhood height compared with the risk of IS. This is in line with the hypothesis of ICH having stronger links to poor nutrition and/or lower SES in childhood than IS which has been put forward in some previous studies on adult height.\(^{7, 23-25}\) However, the sex differences in the associations of childhood stature with ICH argues against confounding by SES as SES in our population-based cohort is expected to be equally distributed among women and men (unless SES affects men and women differently in regards to this stroke subtype).

Unlike the three previous studies which investigated associations of childhood height with stroke in individuals born within a maximum of a 10-year period during the first half of the 20\(^{th}\) century, we studied a more recent population born from 1930-1988, during which living circumstances, smoking
patterns, alcohol consumption, preventive treatment and stroke care markedly changed. During the study period, we observed a significant increase in average childhood height, which is in line with what has been observed for average adult height in the general population⁴, and thought to be a result of overall improved early life growth conditions, such as access to food, dietary diversification, sanitation, living standards and reductions in childhood infections.⁴,⁶ Both poor nutrition²⁷ and infectious burden²⁸ have been found to be associated with risk of stroke. If it was these factors that were driving the inverse associations between childhood height and later stroke, we would expect the inverse associations to be weaker in the most recent birth cohorts, where nutrition conceivably was better and chronic childhood infections were less frequent. This is, however, not what we observed as we did not detect birth cohort effects, nor was it observed in the Emerging Risk Factor Collaboration study⁷, where stronger inverse associations between adult height and risk of stroke were reported in more recent birth cohorts. Even though the relation between SES and adult height may have changed little in recent decades,²⁹,³⁰ the stable inverse associations for both relative height (z-scores) and absolute height across birth cohorts, despite an increase in average height, point towards a causal (i.e. genetically determined) relationship between height and stroke because the pace of change in average height cannot be attributable to changes in the gene pool. The potential causal effect of adult height on stroke was investigated in a Mendelian Randomization study, where an allele score based on 69 single nucleotide polymorphisms associated with adult height, was used in an instrumental variable analysis applied in 17 prospective studies, including 43790 participants with 4878 stroke events.³¹ The study reported a null-effect for stroke, which remained unchanged after adjustment for cardiovascular traits (BMI, blood pressure, lung function, lipids and CRP) that showed an association with the gene score for height, but the authors emphasized that the estimate from the analysis was imprecise and that a causal effect of height on stroke cannot be excluded by their findings.
It thus remains a possibility that childhood height is an indicator of other factors experienced during early life, maybe already in utero, expressing their effects on growth as well as stroke risk in adulthood which have not changed during our long study period. As some strokes occur relatively early in adult life, it is plausible that early-life exposures have a greater influence on stroke early in adulthood compared with stroke diagnosed later in life. We found some support for this hypothesis in the current study, in which we observed stronger inverse associations of childhood height with IS diagnosed at earlier versus older ages. Moreover in the Emerging Risk Factor Collaboration study, the inverse associations of height with stroke were not appreciably altered after adjustment long-term smoking, adiposity, inflammation biomarkers, blood pressure, lipids and diabetes, thus reducing the likelihood that these well-known adult risk factors are mediators of the inverse associations.

The major strengths of this study include the prospective study design with a long study period, mandatory height exams, multiple measures of height, among a large group of schoolchildren, thus minimizing the possibility of reverse causality. Moreover, we followed the children for an extensive period of time with minimal loss to follow-up through the national registers. The coverage of each register is very high, with virtually every event recorded. IS is recorded with a high degree of validity in the National Hospital Discharge Register (positive predictive value of > 97%), whereas the diagnoses of ICH may be less accurate (positive predictive value of 74%)\(^1\). In the National Cause of Death Register cardiovascular disease diagnoses are less precise.\(^1\) However, <5% of the cases in this study came only from that register. Moreover, the analyses of the combined end-points of IS and unspecified stroke were in accordance with the results for IS only. However, there were some limitations as well. As previously mentioned we were unable to compare the magnitude of the inverse associations for childhood height with corresponding measurements in adulthood, or to attempt to
disentangle the independent effects of childhood measures versus adult measures on stroke risk.

Finally, although height may be a proxy for SES, and thus a greater access to care and preventive treatment, this explanation is less plausible in a setting, such as Denmark, in which participants have had universal access to tax paid medical care and thus no direct payments for services.

Conclusions

In this large prospective study shorter stature during childhood was associated with increased risks of IS in women and men, and with ICH in men. In both sexes growth during mid-childhood was not associated with any of these stroke subtypes. The inverse associations were stable during the study period, in which average childhood height increased significantly. Our results support the potential role of early-life exposures associated with growth before mid-childhood, in stroke-genesis. Future studies should focus on the mechanisms underlying the relation between childhood height and later stroke.
Acknowledgements

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Disclosures

None
References


Figure 1: Incidence rate of adult stroke (cases per 1000 person years) for each stroke subtype according to age at diagnosis.
**Figure 2:** Childhood height and risk of ischemic stroke and intracerebral hemorrhage.

*Hazard ratios and 95% confidence intervals are given for a 1-unit increase in height z-score.

†Abbreviations: CI, confidence interval.

‡All analyses were stratified by birth cohort.
Table 1: Height in cm of the 311,009 women and men by stroke subtypes†.

<table>
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<th>Intracerebral hemorrhage cases</th>
<th></th>
</tr>
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<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
</tr>
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<td>BMI</td>
<td>Mean (SD)</td>
<td>WC</td>
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Growth from 7-13

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<th>Mean (SD)</th>
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<td>5330</td>
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<td>1253</td>
<td>30.7 (3.8)</td>
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*Abbreviations: N, number; SD, standard deviation; y, years

†Cases were defined as first-ever ischemic stroke or intracerebral hemorrhage and were mutually exclusive
Table 2: Quintiles of height at age 7 years and risks of ischemic stroke and intracerebral hemorrhage.

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<th>Height quintile</th>
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<th>Intracerebral hemorrhage</th>
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<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
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<td>1.22 (1.11-1.33)</td>
<td>1.05 (0.87-1.33)</td>
</tr>
<tr>
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<td>2</td>
<td>1.03 (0.94-1.14)</td>
<td>1.03 (0.85-1.25)</td>
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<td></td>
<td>3</td>
<td>1 [ref]</td>
<td>1 [ref]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.89 (0.80-0.99)</td>
<td>1.02 (0.83-1.25)</td>
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<td>5</td>
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<td>0.97 (0.79-1.21)</td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1.24 (1.14-1.34)</td>
<td>1.35 (1.15-1.59)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.15 (1.06-1.25)</td>
<td>1.19 (1.01-1.42)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 [ref]</td>
<td>1 [ref]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.00 (0.91-1.09)</td>
<td>1.04 (0.87-1.25)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.93 (0.85-1.02)</td>
<td>1.02 (0.84-1.23)</td>
</tr>
</tbody>
</table>

*Abbreviations: HR, hazard ratio; CI, confidence interval;
†All analyses are stratified by birth cohort