Sex Hormones and Ischemic Stroke: A Prospective Cohort Study and Meta-Analyses

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Context and Objective: Whether endogenous sex hormones are associated with ischemic stroke (IS) is unclear. We tested the hypothesis that extreme concentrations of endogenous sex hormones are associated with risk of IS in the general population.

Design, Setting, and Participants: Adult men (n = 4615) and women (n = 4724) with measurements of endogenous sex hormones during the 1981–1983 examination of the Copenhagen City Heart Study, Denmark, were followed for up to 29 years for incident IS, with no loss to follow-up. Mediation analyses assessed whether risk of IS was mediated through potential mediators. Present and previous findings were summarized in meta-analyses.

Main Outcome Measures: Plasma total testosterone and total estradiol were measured by competitive immunoassays. Diagnosis of IS was ascertained from the national Danish Patient Registry and the national Danish Causes of Death Registry and verified by experienced neurologists.

Results: During follow-up, 524 men and 563 women developed IS. Men with testosterone concentrations ≤10th percentile compared to the 11th–90th percentiles had a hazard ratio for IS of 1.34 (95% confidence interval, 1.05–1.72); 21% of this risk was mediated by body mass index (P = .002) and 14% by hypertension (P = .02). In accordance with this, the corresponding hazard ratio was 1.46 (1.09–1.95) in overweight/obese and hypertensive

men. The corresponding hazard ratio in the meta-analysis was 1.43 (1.21–1.70). Other extreme concentrations of testosterone or estradiol were not associated with risk of IS in men or women.

Conclusions: Extremely low endogenous testosterone concentrations were associated with high risk of IS in men, a risk mediated in part by body mass index and hypertension. Whether or not low testosterone is a causal factor for IS or merely a biomarker of poor metabolic health is still not known.

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DOI: http://dx.doi.org/10.1210/jc.2015-2687
Received: June 26, 2015
Accepted: October 22, 2015

First Published Online: October 28, 2015