A prospective study of serum metabolites and risk of ischemic stroke

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Study objective and summary result
This study explored relationships between serum metabolites and incident ischemic stroke (IS), and it found that elevated levels of 2 long-chain dicarboxylic acids, tetradecanedioate and hexadecanedioate, are associated with an increased risk of IS.

What is known and what this paper adds
Recent studies have identified serum and urine metabolic profiles that are associated with cerebral infarctions, but these studies were cross-sectional. This study identifies metabolites associated with IS in longitudinally collected data.

Participants and setting
This study analyzed data for 3,904 individuals (60% female; 61% African-American; 39% white) who participated in the Atherosclerosis Risk in Communities (ARIC) study, which recruited participants from Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. At baseline assessments in 1987–1989, these individuals were aged 45–64 years and were free of stroke and TIA.

Design, size, and duration
Fasting serum levels were collected at baseline, and metabolite levels were quantified with gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. The ARIC study collected hospitalization data through annual telephone contacts with participants. This study reviewed these data and hospital records to identify stroke-related hospitalizations that occurred in 2015 or earlier. Stroke subtypes were determined by reviewing neuroimaging and autopsy findings and medical records. Cox proportional hazards regression models were used to test associations between baseline metabolite levels and IS risks. The design included replication in an independent population of ischemic stroke cases and controls from Germany.

Main results and the role of chance
Elevated baseline serum levels of tetradecanedioate and hexadecanedioate were independently associated with increased risks of IS ($p < 0.0001$).

Bias, confounding, and other reasons for caution
Metabolic profiling was performed at only 1 timepoint, and this study could only analyze stroke events serious enough to warrant hospitalization.

Generalizability to other populations
This study’s relied on data from white and African-American residents of the US with independent replication in a patients with acute ischemic stroke and controls from Germany. The study may not generalize to other international or race groups.

Study funding/potential competing interests
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<table>
<thead>
<tr>
<th>Table</th>
<th>Associations between baseline serum metabolite levels and risks of incident IS</th>
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<tbody>
<tr>
<td>Metabolite</td>
<td>Hazard ratio (95% confidence interval) for IS per 1-SD increase in baseline serum level</td>
</tr>
<tr>
<td>Tetradecanedioate</td>
<td>1.11 (1.06–1.16)</td>
</tr>
<tr>
<td>Hexadecanedioate</td>
<td>1.12 (1.07–1.17)</td>
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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.
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