The underestimated stroke risk factors

Hakan Sarikaya
Universitätsklinik für Neurologie
Classical risk factors

- Arterial hypertension
- Hyperlipidemia
- Diabetes mellitus
- Smoking
- Obesity
Classical risk factors

• Arterial hypertension
• Hyperlipidemia
• Diabetes mellitus
• Smoking
• Obesity

Non-modifiable risk factors

• Age
• Genetics

• Low birth weight
• Ethnics
Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study

Lancet 2016; 388: 761–75
(Old) new risk factors

Migraine with Aura

Migraine and risk of stroke

OSAS

Does Treatment of Obstructive Sleep Apnea Decrease Risk of Ischemic Stroke?
Curr Treat Options Neurol (2019) 21:29

Depression

(New) new risk factors?

- Air pollution
- Sleep duration
- Psychological Stress
- Working hours
- Drugs
- Passive smoking
### Air pollution

<table>
<thead>
<tr>
<th>Air pollution component</th>
<th>Cardiovascular effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozone</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Out-of-hospital cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Thrombosis</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Particulate matter</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Out of hospital cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Increased myocardial infarction risk</td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Transient ischaemic attack and stroke</td>
</tr>
<tr>
<td></td>
<td>Increased myocardial infarction risk</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Increased myocardial infarction risk</td>
</tr>
<tr>
<td>Lead</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

![Diagram of inhaled toxicant effects](image)

- Pulmonary inflammation
- Pulmonary oxidative stress
- Activation of pulmonary autonomic nervous system
- Entry of toxicant into circulation
- Systemic inflammation
- Systemic oxidative stress
- Autonomic nervous system imbalance
- Vasculature
- Heart
- Blood
- Vasoconstriction
- Hypertension
- Atherosclerosis
- Myocardial infarction
- Fibrosis
- Heart failure
- Heart rate variability
- Arrhythmia
- Thrombosis
- Coagulation
- Leukocyte epigenetic changes
Air pollution

stroke burden attributable to air pollution high (34%) in low and middle income-countries (10% in high income countries)

emerging global risk factor for stroke

Ambient Air Pollution and the Risk of Atrial Fibrillation and Stroke. https://doi.org/10.1289/EHP4883
Air pollution

Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

- 65’893 postmenopausal women without previous cardiovascular disease
- 36 U.S. metropolitan areas from 1994 to 1998
- median follow-up of 6 years
- the women’s exposure to air pollutants were assessed
- 1816 women suffered from cardiovascular events

PM$_{2.5}$: each increase of 10 μg per m$^3$ associated with a 35% increase in stroke risk
HR 1.35 (95% CI 1.08 - 1.68)

Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project

- 117 575 Chinese men and women without stroke at baseline

PM$_{2.5}$: participants in highest quarter (>80 ug/m3) had a 80% increase in stroke risk
HR 1.82 (95% CI 1.55 – 2.14)
Sleep duration

Short and long sleep durations are both associated with increased risk of stroke: a meta-analysis of observational studies

Beihai Ge, Xiaomei Guo
Figure 1. *Pathways associating sleep duration with the risk of stroke.*

**Sleep duration**

- Sleep loss/deprivation
  - Inhibition of post-stroke axonal sprouting
    - ↑ Inflammatory mediators (IL-6, CRP, TNF-α)
    - ↑ Classical stress responses
    - ↑ Oxidative stress
  - ↓ Leptin
  - ↑ Ghrelin
  - ↓ Insulin sensitivity
    - ↑ Hunger and food intake
    - Impaired glucose tolerance
    - Attenuation of post-stroke brain repair
    - ↓ Functional recovery after stroke
    - Diabetes
      - ↓ Risk of stroke

- Sleep disordered breathing
  - Sleep apnoea
  - Cyclical hypoxia
    - Sympathetic stimulation
      - Cyclic hypertension
      - Stress hormones
        - Catecholamine
        - Cortisol release
      - Metabolic errors
        - Insulin resistance
      - Hypertension, ischemic heart diseases
      - ↑ Thrombosis

- Prolonged sleep duration
  - Variations in the sympathetic and parasympathetic system activity

*Journal of Stroke and Cerebrovascular Diseases, Vol. 24, No. 5 (May), 2015: pp 905-911*
Working hours

The effect of exposure to long working hours on stroke: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury

Alexis Descatha 1, Grace Sembajwe 2, Frank Pega 3, Yuka Ujita 4, Michael Baer 5, Fabio Boccuni 6, Cristina Di Tecco 7, Clement Duret 8, Bradley A Evanoff 9, Diana Gagliardi 10, Lode Godderis 11, Seong-Kyu Kang 12, Beon Joon Kim 13, Jian Li 14, Linda L Magnusson Hanson 15, Alessandro Marinaccio 16, Anna Ozguler 17, Daniela Pachito 18, John Pell 19, Fernando Pico 20, Matteo Ronchetti 21, Yves Roquelaure 22, Reiner Rugulies 23, Martijn Schouteden 24, Johannes Siegrist 25, Akizumi Tsutsumi 26, Sergio Iavicoli 27

Cumulative Exposure to Long Working Hours and Occurrence of Ischemic Heart Disease: Evidence From the CONSTANCES Cohort at Inception

Marc Fadel 1, 2, Jian Li 3, Grace Sembajwe 4, Diana Gagliardi 5, Fernando Pico 6, 7, Anna Ozguler 1, 2, Bradley A Evanoff 8, Michel Baer 9, Akizumi Tsutsumi 9, Sergio Iavicoli 5, Annette Leclerc 4, Yves Roquelaure 10, Johannes Siegrist 11, Alexis Descatha 1, 10, 2

working >55 h/week is harmful for stroke incidence!

increased risk of IHD in men, but not in women!
Outbursts of anger as a trigger of acute cardiovascular events: a systematic review and meta-analysis


<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence Rate Ratio and 95% Confidence Interval (Log Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI/ACS</td>
<td></td>
</tr>
<tr>
<td>Mostofsky</td>
<td>2.43 (2.02, 2.92)</td>
</tr>
<tr>
<td>Möller</td>
<td>5.70 (3.03, 10.71)</td>
</tr>
<tr>
<td>Strike</td>
<td>7.30 (5.22, 10.20)</td>
</tr>
<tr>
<td>Lipovetsky</td>
<td>5.36 (3.49, 8.24)</td>
</tr>
<tr>
<td>Combined ($I^2=92.5%, P&lt;0.001$)</td>
<td>4.74 (2.50, 8.99)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Koton</td>
<td>7.60 (4.26, 13.57)</td>
</tr>
<tr>
<td>Stroke Onset Study</td>
<td>1.66 (0.78, 3.53)</td>
</tr>
<tr>
<td>Combined ($I^2=89.8%, P=0.002$)</td>
<td>3.62 (0.82, 16.08)</td>
</tr>
<tr>
<td>Intracranial aneurysm</td>
<td></td>
</tr>
<tr>
<td>Viak</td>
<td>6.30 (1.59, 24.90)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Lampert</td>
<td>1.83 (1.05, 3.19)</td>
</tr>
<tr>
<td>Albert</td>
<td>3.20 (1.80, 5.69)</td>
</tr>
</tbody>
</table>

Excess cases of coronary heart disease per 10,000 individuals per year

Frequency of anger outbursts

1 per month  | 2 per day  | 5 per day
Low          | Medium     | High       | Low          | Medium     | High       | Low          | Medium     | High       |
63           | 129        | 268        | 657          | 320        | 657        | 158          | 320        | 657        |
Other triggers?

Trigger factors present in 44.2% of acute stroke patients (n=290)
- psychological stress (17.6%)
- acute alcohol abuse (10.7%)
- clinical infections (8.3%)

Trigger factors present in 38% of acute stroke patients (n=200)
- negative emotions (OR 14.0, 95% CI 4-90)
- anger (OR 14.0, 95% CI 3-253)
- sudden changes in body posture (OR 24.0, 95% CI 5-428)
### Table: Triggering factors and stroke risk

<table>
<thead>
<tr>
<th>Triggering factor</th>
<th>The day of the stroke only</th>
<th>The day before only</th>
<th>Both periods</th>
<th>No exposure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one of seven potential triggers*</td>
<td>76</td>
<td>9</td>
<td>13</td>
<td>102</td>
<td>8.4 (4.5–18.1)</td>
</tr>
<tr>
<td>At least one of three potential triggers†</td>
<td>57</td>
<td>4</td>
<td>2</td>
<td>137</td>
<td>14.3 (5.3–54.2)</td>
</tr>
<tr>
<td>Negative emotions</td>
<td>29</td>
<td>2</td>
<td>2</td>
<td>167</td>
<td>14 (4.4–89.7)</td>
</tr>
<tr>
<td>Anger</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>184</td>
<td>14 (2.8–253.6)</td>
</tr>
<tr>
<td>Sudden posture change in response to a startling event</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>174</td>
<td>24 (5.1–428.9)</td>
</tr>
<tr>
<td>Sudden temperature change</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>194</td>
<td>5 (0.8–95.8)</td>
</tr>
<tr>
<td>Positive emotions</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>188</td>
<td>4 (1.0–26.5)</td>
</tr>
<tr>
<td>Heavy eating</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>189</td>
<td>4 (1.0–26.5)</td>
</tr>
<tr>
<td>Heavy physical exertion</td>
<td>15</td>
<td>7</td>
<td>0</td>
<td>178</td>
<td>2.1 (0.9–5.6)</td>
</tr>
</tbody>
</table>

### Table: Time of day of stroke

<table>
<thead>
<tr>
<th>At least one of seven potential triggers*</th>
<th>The day of the stroke only</th>
<th>The day before only</th>
<th>Both periods</th>
<th>No exposure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hour</td>
<td>71</td>
<td>10</td>
<td>7</td>
<td>112</td>
<td>7.1 (3.8–14.7)</td>
</tr>
<tr>
<td>2nd hour</td>
<td>31</td>
<td>4</td>
<td>5</td>
<td>160</td>
<td>7.8 (3.1–26.1)</td>
</tr>
<tr>
<td>3rd hour</td>
<td>22</td>
<td>3</td>
<td>2</td>
<td>173</td>
<td>7.3 (2.5–30.9)</td>
</tr>
<tr>
<td>4th hour</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td>178</td>
<td>5.7 (1.9–24.3)</td>
</tr>
<tr>
<td>5th hour</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>187</td>
<td>5.5 (1.5–35.5)</td>
</tr>
</tbody>
</table>
Summary

- avoid air pollution √
- sleep 6-8h √
- work < 55h/w √
- avoid stress √
  take it easy √
- be happy (≠ depressive)