Nature vs nurture in AAA pathophysiology

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Heredity versus environment

• Convincing data on environmental factors, in particular smoking
• Convincing data on the importance of heredity, increased risk among first degree relatives, and twins with AAA
• But which is most important, and how does the interaction take place?
• We hope to learn more during this session
Pathophysiology of AAA
Twin population, Sweden

- 24% probability that a monozygotic twin of a person with an AAA had the disease, a risk 71 times higher than for a monozygotic twin of a person without an AAA
- The heritability of the total trait variance was estimated to be 70%
Epidemiology and Prevention

Low Prevalence of Abdominal Aortic Aneurysm Among 65-Year-Old Swedish Men Indicates a Change in the Epidemiology of the Disease

Sverker Svensjö, MD; Martin Björck, MD, PhD; Mikael Gürtelschmid, MD; Khatereh Djavani Gidlund, MD; Anders Hellberg, MD, PhD; Anders Wanhainen, MD, PhD

Conclusions—On the basis of the observed reduced exposure to risk factors, lower-than-expected prevalence of AAA among 65-year-old men, unchanged AAA repair rate, and significantly improved longevity of the elderly population, the current generally agreed-on AAA screening model can be questioned. Important issues to address are the threshold diameter for follow-up, the possible need for rescreening at a higher age, and selective screening among smokers. (Circulation. 2011;124:1118-1123.)
Contemporary data suggests that smoking is a decisive factor

- In the first larger population-based AAA study on 65-year-old men in Sweden, prevalence of screening detected AAA was 1.7%, 0.5% had known AAA, total 2.2%
- Smoking rate among 65-year-old men decreased from 32% in 1980 to 11% in 2007
- 33% of the 373 with screening detected AAA were smokers, compared to 11% among those with normal aorta
Contemporary data suggests that smoking is a decisive factor

- We calculated the etiological fraction of smoking to be 71% in this investigation
- But genetic factors were not included in that equation
- But only 3/233 (1.3%) who were found to have an AAA on US screening had a first degree relative with AAA
- (26,256 were invited, 22,187 (85%) accepted)
The Rise and Fall of Abdominal Aortic Aneurysm
Frank A. Lederle, MD

Figure. US annual adult per capita cigarette consumption
and US age-adjusted AAA mortality per 100,000 white men by year. For
1951 to 1978, rates are standardized to the US 1960 population as calculated by Lilienfeld et al. and from 1979 onward to the US
1970 population from CDC Wonder. Rates include abdominal, thoracoabdominal, and unspecified aortic aneurysm, both ruptured and
unruptured (ICD8: 441.2, 441.9, ICD9: 441.3 to 441.6, ICD10: I71.3 to I71.9), and exclude thoracic aneurysm and dissection. Because
all nonsyphilitic aortic aneurysms and dissection were combined before 1968, and 1967 to 1968 data indicate that thoracic aneurysm
and dissection accounted for 20% of this total, pre-1968 values were reduced by 20% for consistent display. AAA indicates abdominal
The lifetime prevalence of abdominal aortic aneurysms among siblings of aneurysm patients is eightfold higher than among siblings of spouses: An analysis of 187 aneurysm families in Nova Scotia, Canada

Toru Ogata, MD, Gerald L. MacKean, MD, C. William Cole, MD, Claudette Arthur, BN, MBA, Pantelis Andreou, PhD, Gerard Tromp, PhD, and Helena Kuivaniemi, MD, PhD, Detroit, Mich; and Halifax, Nova Scotia, Canada
A population-based case-control study of the familial risk of abdominal aortic aneurysm

Emma Larsson, MD, a,b Fredrik Granath, PhD, Asst. Prof, c Jesper Swedenborg, MD, PhD, a,b and Rebecka Hultgren, MD, PhD, a,b Stockholm, Sweden

- J Vasc Surg 2009
- The Swedish Multigeneration Registry
- 3183 patients with AAA were compared with 15,943 matched controls
- The risk to have an AAA was 1.9 (1.6-2.2) if you had a first degree relative with AAA
High prevalence of abdominal aortic aneurysms in brothers and sisters of patients despite a low prevalence in the population

Anneli Linné, MD, David Lindström, MD, PhD, and Rebecka Hultgren, MD, PhD
Stockholm, Sweden

- J Vasc Surg 2012
- 150 siblings were investigated
- 11% of the siblings were found to have an AAA, 17% of the brothers, 6% of the sisters
- 81% of the siblings with AAA were ever smokers, vs 59% of those without AAA
150/778 = 19.3%

Selection bias is a problem in all these studies.

What did the deceased siblings die from?

How about those >80?
Gene-environment interaction in a population with high prevalence

• 1992-2001 I was the only consultant of VS in an area in Northern Sweden
• We operated on 4 times as many AAAs per population than the rest of Sweden
• 2/3 were ruptured AAA
• The rationale behind performing the first population based AAA screening in Sweden in 1999 in this area
“We people of Norsjö have a special kind of giant hernias of the vessels in the stomach. They tend to burst, that is what we die from”
Wanhainen A et al. J Vasc Surg

555 men and women 65-75 years old were invited, 504 (91%) accepted

All with an US aortic diameter > 27 mm were examined with CT

16.9% of men, and 3.6% of women had an aortic diameter of 30 mm or more

The highest prevalence ever reported!
Table 1 - Interactions of three major factors (history of cardiovascular disease, ever smoked and having a 1st degree relative with AAA) associated with AAA among 242 men in the Norsjö municipality.

<table>
<thead>
<tr>
<th>Numbers of risk factors present</th>
<th>N</th>
<th>No. of patients with AAA</th>
<th>Prevalence</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>4</td>
<td>4%</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>89</td>
<td>11</td>
<td>12%</td>
<td>3</td>
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<td>2</td>
<td>45</td>
<td>10</td>
<td>22%</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4</td>
<td>57%</td>
<td>32</td>
</tr>
</tbody>
</table>
Learn more about modifiable environmental risk factors and AAA later during this session.
Possible mechanisms between genetic and environmental factors

- Epigenetic mechanisms, in particular methylation of DNA
- Effect on telomere length
- Gene-environmental interactions
- Gene-gene-environmental interactions