Childhood appendectomy, tonsillectomy, and risk for premature acute myocardial infarction - a nationwide prospective study

Imre Janszky, Kenneth J Mukamal, Christina Dalman, Niklas Hammar, Staffan Ahnve
Overview

• Appendix, tonsils and their removal

• Hypothesis

• Design and analyses

• Findings

• Concluding remarks
Appendix, tonsils and their removal

• Secondary lymphoid organs

• Prominent constituents of the mucosa-associated lymphoid tissue (MALT) system

• The mass and lymphoid function of these organs are most pronounced between 10 and 20 years of age and markedly decrease in adulthood
Appendix, tonsils and their removal

- Removal of the appendix or tonsils are among the most common surgeries, particularly in children and in young adults.

- Lifetime risk for surgical removal is generally around 10-20% for these organs in the industrialized world.
Appendix, tonsils and their removal

- Removal of these organs is safe

- It is widely believed that the long-term health effects are minimal

- Removal may result in a slightly decreased production of immunoglobulins, especially that of immunoglobulin A
Appendix, tonsils and their removal

• Removal may specifically alter the risk for diseases where the immune system plays a key role

• Removal might increase the risk for Hodgkin’s lymphoma, rheumatoid arthritis, Crohn’s disease but it may decrease the risk for ulcerative colitis

• These associations might be restricted mainly or exclusively to those individuals in whom the appendix and/or the tonsils are removed before adulthood
Hypothesis

Surgical removal of the appendix or tonsils might alter the long-term risk of myocardial infarction.
Design and analyses

- TWELVE-Register incorporates 12 of Sweden’s national health and administrative registers

- All persons born between 1955 and 1970 residing in Sweden at any time until 1 January 2003 were included
Design and analyses

• Appendectomies and tonsillectomies were identified with a link to the Swedish Inpatient Register

• Our primary analyses were restricted to individuals below age 20 at the time of operation
Design and analyses

• For each patient with an appendectomy or tonsillectomy, we randomly selected five matched controls without history of the respective operation

• The matching factors were sex, birth year, county of residence at the time of surgery and date of surgery
Design and analyses

• Participants were followed until fatal or non-fatal acute myocardial infarction (primary outcome), death owing to other causes, emigration, or the end of follow-up, i.e. 31 December 2002.

• In addition to acute myocardial infarction, we also examined total and cardiovascular mortality, stroke and revascularization procedures as secondary outcomes.
Design and analyses

• Standard methods of survival analyses

• We adjusted for the matching factors (sex, birth year, county of residency, date of operation) and for parents’ socioeconomic position and family history of myocardial infarction
Findings – acute myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>AMI</th>
<th>Multiadjusted Hazard Ratios with 95% CI</th>
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<tbody>
<tr>
<td>No Appendectomy</td>
<td>272213</td>
<td>328</td>
<td>1</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>54449</td>
<td>89</td>
<td>1.33 (1.05-1.70)</td>
</tr>
<tr>
<td>No Tonsillectomy</td>
<td>136401</td>
<td>169</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>27284</td>
<td>47</td>
<td>1.44 (1.04-2.01)</td>
</tr>
</tbody>
</table>
Findings

Hazard ratios for secondary outcomes with appendectomy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>1.10 (1.02–1.18)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.85 (0.61–1.20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.30 (1.06–1.59)</td>
</tr>
<tr>
<td>Revascularizations</td>
<td>1.47 (1.08–2.00)</td>
</tr>
</tbody>
</table>
Findings

Hazard ratios for secondary outcomes with tonsillectomy

- Total mortality: $1.11 (1.00–1.22)$
- Cardiovascular mortality: $1.40 (0.95–2.06)$
- Stroke: $1.12 (0.85–1.48)$
- Revascularizations: $1.47 (0.93–2.31)$
Findings

• For operations performed ≥20 years of age: the HRs for AMI were $1.04 \ (0.85–1.28)$ for appendectomy and $0.90 \ (0.66–1.23)$ for tonsillectomy

• For operations performed ≥15 years of age: the HRs for AMI were $1.60 \ (0.85–1.28)$ for appendectomy and $1.55 \ (0.90–2.68)$ for tonsillectomy
Concluding remarks

• Appendectomy and tonsillectomy, when performed before adulthood, were associated with a moderately increased relative risk for subsequent acute myocardial infarction.

• Our analyses of secondary outcomes generally support the hypothesis that these operations before adulthood may be associated with progression of atherosclerosis.
Concluding remarks

• These observed associations are compatible with the hypothesis that subtle alterations in immune function following these operations may alter the subsequent cardiovascular risk

• However, the true nature of these associations and their clinical implications are not clear
Concluding remarks

• Our study population was young even at the end of the follow-up
• As a consequence the observed moderate increases in relative risk corresponded to small risk increases in absolute terms
• We cannot directly extrapolate our findings to cases of myocardial infarctions that occur among older men or women, in whom risk is highest
Concluding remarks

• Confounding factors for which we did not adjust may explain our findings

• However, we believe that traditional risk factors are not likely to confound these relationships unless these risk factors are associated more strongly or exclusively with operations occurring in children and in teens compared with later operations
Concluding remarks

• Further studies are needed to confirm our findings, particularly in cohort studies with characterization of immune status and with information on all cardiovascular risk factors that may present in childhood