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CLINICAL RESEARCH

Childhood appendectomy, tonsillectomy, and risk for premature acute myocardial infarction—a nationwide population-based cohort study

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Aims Although inflammation contributes to cardiovascular disease, the associations of appendectomy and tonsillectomy, which remove mucosa-associated lymphoid tissue, with risk of acute myocardial infarction (AMI) are unknown. Our aim was to assess the association between these operations performed in childhood and AMI risk later in life.

Methods and results We conducted a prospective matched cohort study among all Swedish residents born between 1955 and 1970. A national register identified all appendectomies and tonsillectomies. For each patient undergoing appendectomy or tonsillectomy, we randomly selected five controls without the history of the respective operation, matched on sex, age, and county of residence. Participants were followed for fatal and non-fatal AMI for an average of 23.5 years. Because appendiceal and tonsillar tissues have reduced function after adolescence, our primary analyses were restricted to individuals below age 20 at the time of surgery (54 449 appendectomies and 27 284 tonsillectomies). We derived hazard ratios (HRs) from proportional hazard models adjusted for parental occupation and parental history of AMI. Operations before 20 years of age were associated with an increased risk for AMI (417 and 216 events in the appendectomy and tonsillectomy datasets, respectively), with adjusted HRs of 1.33 [95% confidence interval (CI), 1.05–1.70] for appendectomy and 1.44 (95% CI, 1.04–2.01) for tonsillectomy. This association was graded, with the highest risk among those undergoing both procedures, and generally similar among both males and females. Appendectomy and tonsillectomy performed at or above 20 years of age were not associated with the risk of AMI.

Conclusions We found a higher risk of AMI related to surgical removal of the tonsils and appendix before age 20. These results are consistent with the hypothesis that subtle alterations in immune function following these operations may alter the subsequent cardiovascular risk, but further studies are needed to confirm these findings and to explore possible mechanisms.

Keywords Acute myocardial infarction • Epidemiology • Inflammation

Introduction

The cecal appendix and tonsils are secondary lymphoid organs and prominent constituents of the mucosa-associated lymphoid tissue (MALT) system. The lymphoid function of these tissues is particularly pronounced at younger ages.[1–5]

Operative procedures to remove the appendix or tonsils are among the most common surgeries, particularly in children and in young adults,[1,6] with a lifetime risk of appendectomy estimated to be 10–20%[7,8] and a risk nearly as high for tonsillectomy just through to age 20.[9] Concordant with the role of these tissues in immune function in children and adolescents, the long-term health effects of the removal of these secondary lymphoid organs seem to be restricted to operations that occur before adulthood.[10–13] Long-term health effects attributed to such procedures include moderate changes in immune function,[4,14]

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elevated risk for Hodgkin's lymphoma,[10,15] and alteration in risk for some autoimmune disorders.[11–13,16–19]

Given the strong biological and epidemiological evidence linking inflammation with coronary heart disease (CHD),[20] one might anticipate that surgical MALT removal, with its consequent effects on immunity, might also have a long-term effect on CHD. However, we are aware of no studies that have evaluated the potential effects of appendectomy or tonsillectomy on atherosclerosis or CHD risk. To address this possibility, we used Sweden's unique health and administrative registers to investigate whether appendectomy or tonsillectomy, particularly in childhood or adolescence, is associated with acute myocardial infarction (AMI).

Methods

Study population

The study was based on data from the TWELVE-Register, which incorporates 12 of Sweden's national health and administrative registers.[21,22] All persons born between 1955 and 1985 residing in Sweden at any time until 1 January 2003 are included in the TWELVE-Register. To ensure adequate follow-up among the young individuals included in this study, we restricted our analyses to those born between 1955 and 1970.

Appendectomy and tonsillectomy

Appendectomies (operation codes JEA00, JEA01, JEA10, 4510, 4511) and tonsillectomies (operation codes EMB10, EMB20, EMB30, EMB99, 2710, 2720) were identified with a link to the Swedish Inpatient Register, which started regionally in 1964 and since 1987 provides virtually complete information on all inpatient care and corresponding diagnoses in Sweden.

We categorized the underlying diagnoses for appendectomy as follows: (i) perforated or abscessed appendicitis; (ii) acute appendicitis without perforation or abscess; and (iii) appendectomy without underlying appendicitis.

Our primary analyses were restricted to individuals below age 20 at the time of operation, the approximate age at which MALT tissue would be anticipated to become less physiologically significant and used by other studies on long-term health effects of appendectomy.[1,2,11,12] For comparison, we also examined risk in the smaller subset of individuals who underwent these surgeries at age 20 or older and those at below 15 years of age.

Unexposed controls

The present study had a matched cohort design. 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 (in yearly increments), and county of residence at the time of surgery. To identify county of residence at the time of surgery, we used the data from the closest nationwide Population and Housing Census. Censuses were conducted every five years from 1960 until 1990. Participants with missing census data were not included. Unexposed controls who died or emigrated between the census and the operation were excluded.

Outcome ascertainment

Participants were followed with linkage to the respective health or administrative registers from the date of the index operation or the corresponding time for the unexposed controls until fatal or non-fatal AMI, death owing to other causes, emigration from Sweden, or the end of follow-up, i.e. 31 December 2002. Detection method of AMI was identical to that of the national Swedish Myocardial Infarction Register. It was based on record linkage between the Swedish Inpatient Register and the Cause of Death Register using ICD9 code 410 and ICD10 codes I21 and I22 for reasons of hospitalization or underlying cause of death, respectively.[23,24]

In addition to AMI, we also examined total and cardiovascular mortality (ICD codes 410–414, 431, 433, 434, I21, I22, I25, I61, I63 and I64), stroke (ICD codes 431, 433, 434, I61, I63 and I64), and revascularization procedures (operation codes 3105, 3158, 3127, 3066, 3080, 3092, FNA, FNB, FNC, FNE, FNF, FNG) as secondary outcomes.

Hernia operations—an active control group

To determine whether an association of appendectomy and tonsillectomy with risk of AMI reflected early alteration in the immune system or was simply a correlate of early-life surgery, we also examined the association of a second common surgical exposure—herniorrhaphy—with AMI. We identified all operations owing to inguinal (operation codes JAB00-JAB97 and 4200–4206), femoral (operation codes JAC10-JAC97 and 4210–4213), and umbilical (operation codes JAF10-JAF97 and 4260–4263) hernia in our cohort. For each patient undergoing these operations, we randomly selected five controls without history of the respective operation, matched on sex, age, calendar time, and county of residence. Participants were followed for AMI, as those in the appendectomy and tonsillectomy datasets. We then examined the association between hernia operations and AMI separately for operations occurring before 20 years of age and after that.

Although we are aware of no possible immunological consequences related to hernia repair, hernia and AMI might share common risk factors like obesity[25] and smoking.[26] However, confounding from these AMI risk factors should be most apparent in adulthood. Therefore, in contrast to our primary hypothesis concerning the removal of MALT tissues, we hypothesized a similar or stronger relation between AMI and hernia operations in adulthood than in childhood.

Family history of acute myocardial infarction

Family history of AMI was defined as fatal or non-fatal AMI of the biological parents. Biological parents were identified by the Swedish Multigeneration Register.

Socioeconomic status

Because participants were chiefly enrolled as young adults, their socioeconomic status was derived from their parents' occupation. Participants were linked to the parents with whom they lived (biological or adoptive). Information on parents' socioeconomic position was obtained from the censuses closest to the operation. We identified four occupational categories: manual worker, non-manual worker, self-employed/entrepreneur (including farmers), or other (pensioners, part-time workers, those working at home, or not otherwise classified). Paternal data were preferentially used; if missing, we used maternal data. If socioeconomic information was missing from the census closest to the operation, the next closest census was used.

Statistical analyses

We present unadjusted event-free survival curves constructed using the Kaplan–Meier method and evaluated with the log-rank test. We used Cox proportional hazard models to examine the prospective association between appendectomy, tonsillectomy, and hernia operations and AMI with adjustment for potential confounders. We evaluated the proportionality of hazards using formal two-sided tests of interaction with time or log-time. We found no statistical evidence against the proportionality assumption.

In adjusted analyses, we included matching factors of sex, age (indicators for each birth year), county of residency (25 counties), and date of operation or the corresponding date for controls (5-year categories, i.e. time span closest to a census formed a category). We also further adjusted for parents' socioeconomic position and family history of AMI. Matched strata analyses yielded very similar results to the inclusion of matching factors in our models.

Because immigrants may have undergone appendectomy or tonsillectomy prior to immigration, we performed sensitivity analyses restricted to those born in Sweden.

We also examined the joint effects of the removal of MALT organs. We combined the samples of individuals with either operation and their respective controls, and specified the number of MALT organs removed from 0 to 2.

Rothman's synergy index with 95% confidence intervals was used to evaluate biological interactions.[27] Rothman's synergy index allows assessing effect modification on an additive scale using multiplicative models. A synergy index with a value greater than 1 implies synergism, whereas a value below 1 indicates antagonism between two exposures.

For each analysis, a two-tailed *P*-value of <0.05 was considered statistically significant.

Statistical analyses were performed using SAS 9 for Windows.

The study was approved by the Karolinska Ethics committee (ethical approval no. 2008/1650–31).

Results

In *Table 1*, we present characteristics of participants with appendectomy and tonsillectomy before age 20 and their non-exposed controls, respectively. Both operations were more frequent in females than in males. Parents' occupational position and family history of AMI differed little by operative status.

Those suffering from AMI during the follow-up were more often male, were more likely to have a family history of AMI, and their parents were more likely to be manual workers (data not shown).

Figures 1 and *2* show the cumulative proportion of surviving patients who did not have an AMI during the follow-up according to appendectomy and tonsillectomy status, respectively. As expected from the young age of studied individuals, the cumulative risk of AMI was low during the study. Evidence of a slightly higher risk among those who had undergone surgery appeared 15–20 years after the index operation (i.e. at age 35 and older). The average age at AMI was 37.9 (4.2) years for men and 37.9 (4.3) for women in the appendectomy dataset. The corresponding numbers were 38.8 (4.6) and 38.7 (4.5) in the tonsillectomy dataset.

As seen in *Table 2*, appendectomy and tonsillectomy occurring before 20 years of age were associated with an increased relative risk for AMI. Adjustment for matching factors, parental socioeconomic status, and family history of AMI had little influence on the point estimates (*Table 2*).

As a sensitivity analysis, we restricted our analyses to those who were born in Sweden, eliminating 17 805 immigrants from the appendectomy dataset and 8734 from the tonsillectomy dataset. The results were similar, with adjusted HRs of 1.35 (1.06–1.74) for appendectomy and 1.52 (1.09–2.11) for tonsillectomy.

When we analysed appendectomy and tonsillectomy together, the adjusted HR for the increase in risk with each operation was 1.34 (1.10–1.63). When we analysed the effect of appendectomy only ($n = 52\,767$), tonsillectomy only ($n = 25\,602$), and the effect of both operations ($n = 1682$) compared with those who had none of these operations, the adjusted HRs were 1.33 (1.04–1.70) for appendectomy, 1.29 (0.94–1.78) for tonsillectomy, and 2.42 (0.78–7.57) for both. The synergy index for the interaction between the two operations was 2.27 (0.28–18.51).

We found no evidence that secular trends modified the observed associations. For example, the HR for each additional operation was 1.33 (1.05–1.68) for operations up to the census in 1975 and 1.35 (0.92–1.99) for those occurring afterwards.

Appendectomies coded with different accompanying conditions had very similar associations with the risk of AMI. The adjusted HRs for appendectomy owing to perforated appendicitis/appendicitis with abscess, for appendectomy owing to appendicitis without perforation or abscess, and for appendectomy without appendicitis were 1.29 (0.62–2.69, $n = 29\,228$), 1.31 (0.96–1.80, $n = 20\,7213$), and 1.39 (0.90–2.14, $n = 90\,221$), respectively.

We next examined risk stratified by sex. In the case of appendectomy, the associations were similar when men and women were analysed separately. Tonsillectomy had a somewhat stronger association with AMI in men than in women. The adjusted HRs were 1.65 (1.09–2.50) for males and 1.18 (0.68–2.03) for females. The synergy index for the interaction between male gender and tonsillectomy was 1.91 (0.87–4.19).

We also analysed total and cardiovascular mortality, stroke, and coronary revascularization procedures as secondary outcomes. We observed a total of 5594 (289 classified as cardiovascular) and 2794 (159 classified as cardiovascular) deaths in the appendectomy and tonsillectomy datasets, respectively. A total of 615 and 354 participants had stroke and 244 and 111 participants underwent coronary revascularizations in the appendectomy and tonsillectomy datasets, respectively. Both appendectomy and tonsillectomy were associated with an increased risk for total mortality, stroke, and coronary revascularization procedures, but the associations with cardiovascular mortality were less consistent. The multi-adjusted HRs associated with appendectomy were 1.10 (1.02–1.18) for total mortality, 0.85 (0.61–1.20) for cardiovascular mortality, 1.30 (1.06–1.59) for stroke, and 1.47 (1.08–2.00) for revascularization procedures. The corresponding numbers for tonsillectomy were 1.11 (1.00–1.22), 1.40 (0.95–2.06), 1.12 (0.85–1.48), and 1.47 (0.93–2.31), respectively.

Consistent with our hypotheses, there was no evidence for an association between appendectomy or tonsillectomy performed $\geq$20 years of age with AMI in any of the models. For example, in models adjusted for the matching criteria, parents' socioeconomic position, and family history of AMI, the HRs for appendectomy and tonsillectomy were 1.04 (0.85–1.28) and 0.90 (0.66–1.23), respectively. In contrast, when we restricted to operations before age 15, we observed similar results with somewhat higher effect sizes but lower precision than for the main analyses (i.e. restricted to operations before age 20). The HRs were 1.60

Table 1 Characteristics of the population with an appendectomy or tonsillectomy <20 years of age and their controls

n	Appendectomy Yes 54 449	Appendectomy No 272 213	Tonsillectomy Yes 27 284	Tonsillectomy No 136 401
	Mean (SD)			
Age at operation/at entry (years)	14.2 (3.6)	14.2 (3.6)	14.9 (3.7)	14.9 (3.7)
Duration of follow-up (years)[a]	23.4 (5.9)	23.3 (6.1)	23.5 (6.5)	23.6 (6.3)
Person-years of follow-up	1 276 058	6 351 485	642 842	3 200 673
	n (%)			
Male sex	25 593 (47.0)	127 945 (47.0)	10 112 (37.1)	50 551 (37.1)
Parents' socioeconomic position				
Manual	22 119 (42.0)	108 282 (41.4)	11 583 (43.9)	55 184 (42.3)
Non-manual	21 846 (41.5)	110 960 (42.5)	10 955 (41.5)	54 584 (41.8)
Self employed	6300 (12.0)	30 836 (11.8)	2858 (10.8)	15 548 (11.9)
Other	2382 (4.5)	11 258 (4.3)	1001 (3.8)	5168 (4.0)
Family history of AMI	4662 (8.6)	22 340 (8.2)	2535 (9.3)	12 415 (9.1)

AMI, acute myocardial infarction.
[a]Calculated for censored cases.

(1.13–2.27) for appendectomy and 1.55 (0.90–2.68) for tonsillectomy in these secondary analyses.

We also followed patients who underwent hernia operations and their controls for AMI. The HR for AMI was 1.30 (0.75–2.25) in the fully adjusted model for hernia operations occurring before 20 years of age, with a total of 79 cases of AMI among 5550 participants. For operations at 20 years of age and after, the corresponding HR was 1.42 (1.01–1.99) with a total of 228 cases of AMI among 80 884 participants.

Discussion

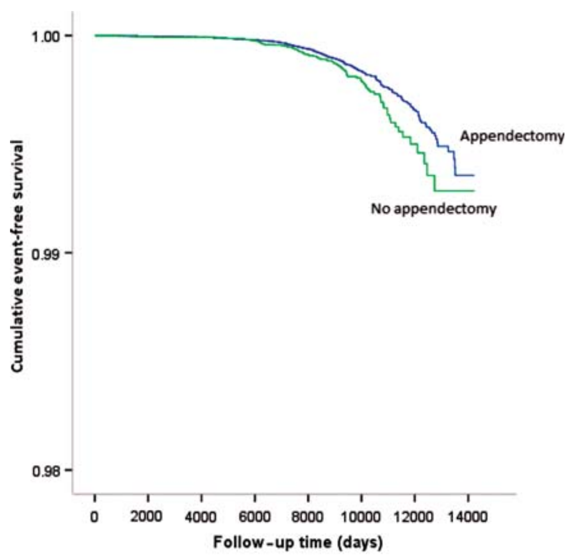
In two population-based cohorts comprising over 400 and 200 cases of AMI accruing over 7.5 million and nearly 4 million person-years of follow-up, respectively, we found that appendectomy and tonsillectomy, when performed before adulthood, were associated with a moderately increased relative risk for subsequent AMI. This association was graded, with the highest risk among those undergoing both procedures, and was consistent in both sexes. As expected from the young age of the population, the observed moderate increases in relative risk corresponded to small risk increases in absolute terms.

Our analyses of secondary outcomes, i.e. total mortality, stroke, and revascularization procedures generally support the hypothesis that appendectomy and tonsillectomy may have subtle effects that increase the risk of CHD. However, the association between appendectomy and tonsillectomy and cardiovascular mortality were less consistent. Apart from the relatively low statistical power to examine cardiovascular mortality, all-cause mortality, revascularization procedures, and AMI are identifiable with greater reliability than cause-specific mortality, and hence, non-differential misclassification might have diluted the observed effects. Alternatively, it is possible but seems less likely that removal of mucosa associated tissues influence cardiovascular risk and prognosis differently.

We found that only operations that occurred before age 20 were associated with higher risk for AMI. Because these operations occurred in childhood and adolescence, traditional risk factors such as diabetes or obesity 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. This substantially limits the range of potential confounders under consideration. Furthermore, the observed associations remained after adjustment for age, sex, county of residency, calendar time of operation, parental history of MI, and parental socioeconomic status. Any remaining potentially confounding risk factor would need to be associated preferentially with operations occurring in children and teens and generally independent of the factors included in our multivariable models.

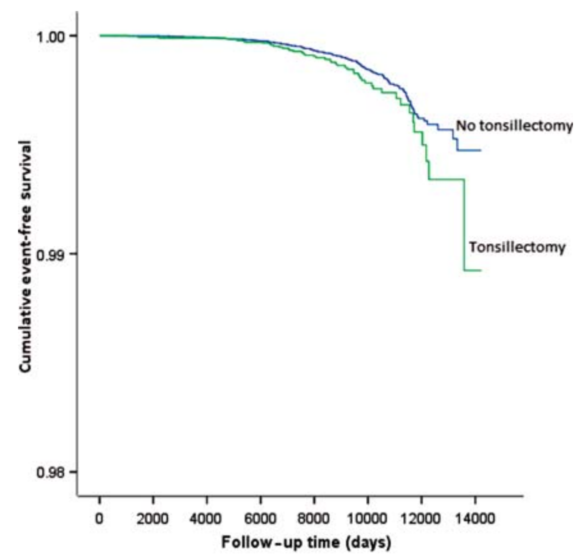
In contrast to our findings concerning appendectomy and tonsillectomy and AMI risk, we found that hernia operations were associated similarly and at least as strongly with AMI if performed in adulthood than if performed in childhood. This may suggest that common AMI risk factors like obesity or smoking[25,26] could confound the relationship between hernia operations with AMI, and that this confounding is at least as strong in adulthood than in childhood. These differences between hernia repair and appendectomy/tonsillectomy—with weaker effects with older age only for the latter—are consistent with our original hypotheses, but ultimately larger studies with greater numbers of endpoints will be needed to test these issues definitively.

An intriguing and biologically plausible explanation for our findings is the possibility that the alteration in immune function mediates the effects of the operations on AMI risk. The appendix and tonsils are secondary lymphoid organs. Their removal can affect several aspects of immune activity, including decreased production of immunoglobulins, especially that of immunoglobulin A.[4,14] This effect seems to be most pronounced when both appendix and tonsils are removed.[4]



Period (years)		Entering	Censored	Exposed to risk	AMI
No appendectomy	0–5	272 213	3545	270440.5	7
	5–10	268 661	3891	266715.5	10
	10–15	264 760	10 557	259481.5	27
	15–20	254 176	55 080	226636	56
	20–25	199 040	89 485	154297.5	105
	25–30	109 450	77 800	70550	82
	30–35	31 568	24 862	19137	34
	35– rest of the follow-up	6672	6665	3339	7
Appendectomy	0–5	54 449	509	54194.5	3
	5–10	53 937	710	53582	1
	10–15	53 226	2099	52176.5	3
	15–20	51 124	11 098	45575	19
	20–25	40 007	17 976	31019	26
	25–30	22 005	15 637	14186.5	25
	30–35	6343	4995	3845.5	12
	35– rest of the follow-up	1336	1336	668	0

Figure 1 Life tables and Kaplan–Meier plots for cumulative proportion of surviving patients who did not have an acute myocardial infarction during the follow-up in relation to appendectomy <20 years of age at the time of surgery (*P* for log-rank test = 0.012).



Period (years)		Entering	Censored	Exposed to risk	AMI
No tonsillectomy	0–5	136 401	1817	135492.5	1
	5–10	134 583	2043	133561.5	8
	10–15	132 532	6181	129441.5	16
	15–20	126 335	31 344	110663	31
	20–25	94 960	34 975	77472.5	41
	25–30	59 944	39 851	40018.5	46
	30–35	20 047	16 774	11660	24
	35– rest of the follow-up	3249	3247	1625.5	2
Tonsillectomy	0–5	27 284	263	27152.5	2
	5–10	27 019	407	26815.5	1
	10–15	26 611	1229	25996.5	5
	15–20	25 377	6248	22253	9
	20–25	19 120	7081	15579.5	10
	25–30	12 029	8003	8027.5	11
	30–35	4015	3354	2338	8
	35– rest of the follow-up	653	652	327	1

Figure 2 Life tables and Kaplan–Meier plots for cumulative proportion of surviving patients who did not have an acute myocardial infarction during the follow-up in relation to tonsillectomy <20 years of age at the time of surgery (*P* for log-rank test = 0.047).

Although relatively few long-term health consequences are clearly established for appendectomy and tonsillectomy, they may specifically alter the risk for diseases where the immune system plays a key role. Several studies suggested that Hodgkin's lymphoma is associated with appendectomy and/or tonsillectomy.[10,15] Appendectomy and tonsillectomy are risk factors for Crohn's disease,[17,18] and appendectomy appears to protect against ulcerative colitis.[11–13] Appendectomy and tonsillectomy may be a risk factor for rheumatoid arthritis as well.[16] Notably, in studies where effect modification by age was considered, these associations seem to be restricted mainly or exclusively to those individuals in whom the appendix and/or the tonsils are removed before adulthood.[10–12] This concords with the fact that the lymphoid mass and function of these organs are most pronounced between 10 and 20 years of age and markedly decrease in adulthood.[1,2]

Atherosclerosis, the underlying pathophysiological mechanism behind AMI, is widely considered to be an inflammatory process. Trapped and oxidatively modified LDL (oxLDL), other autoantigens, and perhaps select microbial pathogens may provoke an immune response.[20,28,29] Several autoimmune diseases and disorders involving chronic inflammation are associated with an increased risk for CHD.[30,31] Epidemiological studies clearly demonstrate that C-reactive protein and other inflammatory markers also predict the risk of CHD nearly as well as more traditional risk factors.[20,28,32] Even mild elevations in C-reactive

Table 2 Appendectomy, tonsillectomy, and risk for AMI among Swedish individuals <20 years of age at the time of surgery

	Total (*n*)	AMI (*n*)	Unadjusted HR (95% CI)	Matching adjusted[a] HR (95% CI)	Multiadjusted[b] HR (95% CI)
No appendectomy	272 213	328	1	1	1
Appendectomy	54 449	89	1.35 (1.07–1.71)	1.35 (1.07–1.70)	1.33 (1.05–1.70)
No tonsillectomy	136 401	169	1	1	1
Tonsillectomy	27 284	47	1.39 (1.00–1.91)	1.39 (1.00–1.91)	1.44 (1.04–2.01)

95% CI indicates 95% confidence interval; HR, hazard ratio, AMI, acute myocardial infarction.
[a]Matching criteria included sex, age (dummies for each birth year), county of residency (25 counties), and time of operation or the corresponding time for controls (5-year categories, i.e. time span closest to a census formed a category).
[b]Adjusted for matching criteria + parents' socioeconomic position and family history of AMI.

protein level, previously considered in the 'normal range', are positively associated with cardiovascular events.[28]

The role of the immune system is complex in atherosclerosis. Some facets of vascular immunity protect against atherosclerosis rather than facilitate it.[28] For example immunization with oxLDL reduces atherogenesis in animal experiments.[33] Several animal experiments and human studies suggest that humoral immunity can protect against atherosclerosis.[28] B-cell deficiency is associated with more pronounced lesions in animal models of atherosclerosis.[34] Removal of the spleen—another secondary lymphoid organ, although not part of the MALT system—is associated with an accelerated atherosclerosis both in experimental animals[35] and in humans.[36] Thus, we hypothesize that the removal of MALT organs might alter atheroprotective immunity. Alternatively, these operations may decrease the capacity of the immune system to eliminate external pathogens and thus lead to increased risk for atherosclerosis. Increased risk of autoimmune disorders, like rheumatoid arthritis, could also be one of the possible pathways of how childhood appendectomy and tonsillectomy might lead to AMI.

Our analyses on the joint effects of the removal of both MALT organs suggested that the joint effect was more pronounced than the independent effects of the two operations. However, our statistical power to detect this interaction was limited. Our results also indicated that there might be a synergism between the effect of male gender and tonsillectomy on AMI risk. In line with this finding, limited evidence suggests that the immunological effects of the removal of tonsils is more pronounced among boys.[14]

Frequently, appendices are removed when operations in the right lower quadrant are performed, on the presumption that treating practitioners in later life will assume that an appendectomy had been performed. Moreover, recent research suggests that not all cases of appendicitis require surgery, as some patients may resolve spontaneously or could be treated with antibiotics alone.[37] Indications for tonsillectomy are also controversial.[5,38] Our findings on increased risk for AMI in association with these operations when performed before age 20—if confirmed and the absolute risk associated with them better established—suggest that the full late burden of illness attributable to these operations, potentially including AMI and autoimmune disorders, may need to be considered during the decision-making process for more elective procedures.

Despite its large size, long duration of follow-up, and population-based design, our study is subjected to important limitations. We relied on Swedish health and administrative registers that provide high-quality information with a high degree of reliability and with complete coverage across Sweden.[39] Nonetheless, the registration of hospital diagnoses started only in 1964, and it did not fully cover all counties of Sweden until 1 January 1987. Because participants were still relatively young in 1987, it is unlikely that we missed substantial numbers of cases of AMI, but we certainly missed some appendectomies and tonsillectomies. To account for this, we matched exposed and non-exposed participants on the county of residence and calendar time, which reflect the probability of being labelled as exposed conditional upon true exposure. More importantly, because this type of exposure misclassification simply makes the non-exposed group more similar to those exposed, it cannot lead to a false finding of association and instead probably have led us to underestimate the true association.

One of our important limitations was that we studied a childhood exposure, with the consequence that our study population was relatively young even at the end of the follow-up. Consequently, we cannot directly extrapolate our findings to cases of AMI that occur among older men or women, in whom risk is highest. However, we found no evidence that risk attenuated over time within the limits of follow-up duration of our study.

As with any observational study, confounding factors for which we did not adjust could explain our findings. For example, low fibre intake[1] and smoking[40] might increase the risk for appendicitis. We could not control for these factors, although socioeconomic status (for which we did adjust) is relatively strongly related to both fibre intake[41] and smoking.[42] Moreover, as highlighted above, it is not clear how such potential confounders could explain why only operations before age 20 were associated with the risk of AMI.

Conclusion

In this prospective matched cohort study, we found an elevated risk for AMI related to the removal of tonsils and appendix before age 20. We hypothesize that subtle alterations in immune function owing to these operations may underlie this relationship. However, further studies are needed to confirm these findings, particularly in cohort studies with characterization of immune and inflammatory status and with information on all cardiovascular risk factors that may present in childhood.

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Conflict of interest: none declared.

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