EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
Journal of the European Hematology Association

Risk of cardiovascular events and pulmonary hypertension following splenectomy – a Danish population-based cohort study from 1996-2012

by Marianne Rørholt, Waleed Ghanima, Dora Körmendiné Farkas, and Mette Nørgaard

Haematologica 2017 [Epub ahead of print]

Citation: Rørholt M, Ghanima W, Farkas DK, and Nørgaard M. Risk of cardiovascular events and pulmonary hypertension following splenectomy – a Danish population-based cohort study from 1996-2012. Haematologica. 2017; 102:xxx
doi:10.3324/haematol.2016.157008

Risk of cardiovascular events and pulmonary hypertension following splenectomy – a Danish population-based cohort study from 1996-2012

Marianne Rørholt[1], Waleed Ghanima[2,3], Dora Körmendiné Farkas[4], and Mette Nørgaard[4]

[1]Department of Research and Otorhinolaryngology, Østfold Hospital Trust, Norway
[2]Department of Research and Medicine, Østfold Hospital Trust, Norway
[3]Institute of Clinical Medicine, University of Oslo, and department of haematology Oslo University Hospital, Norway
[4]Department of Clinical Epidemiology, Aarhus University Hospital, Denmark

Corresponding author:
Dr. Mette Nørgaard, mn@clin.au.dk
Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, Aarhus N, DK 8200, Denmark

Abstract

Splenectomised patients are at increased risk of cardiovascular events, but it remains unclear whether this is due to lack of the spleen or due to the underlying disease leading to splenectomy. We aimed to assess the risk of myocardial infarction, pulmonary hypertension, and stroke following splenectomy. We identified patients splenectomised in Denmark during 1996-2012. We constructed two comparison cohorts: an age- and sex-matched general population cohort and a disease-matched cohort based on the splenectomy-related underlying disease. We computed 5-year cumulative incidences, and adjusted hazard ratios of myocardial infarction, pulmonary hypertension, and stroke for the three cohorts. The study included 5,306 splenectomised patients, 53,060 members of the general population, and 11,651 disease-matched patients. Within 5 years follow-up, 1.3% of splenectomised had myocardial infarction versus 1.8% of the population cohort. The adjusted hazard ratio for splenectomised patients versus population cohort was 1.24 (95% CI 1.01-1.52). The 5-year cumulative incidence of pulmonary hypertension was 0.4% among splenectomised and 0.2% in the population cohort [adjusted hazard ratio 3.25 (95% CI 1.93-5.45)] and of stroke it was 3.3% among splenectomised versus 2.6% in the population cohort [adjusted hazard ratio 2.04 (95% CI 1.78-2.35)]. When comparing splenectomised with the disease-matched cohort, only stroke risk was elevated. Five-year risk was 3.0% in splenectomised and 2.3% in disease-matched [adjusted hazard ratio 1.56 (95% CI 1.26-1.92)]. In conclusion, splenectomised patients were at increased risk of stroke. Additionally, we found that underlying splenectomy-related diseases explained the increased risk for myocardial infarction, pulmonary hypertension following splenectomy.

Keywords:
splenectomy, myocardial infarction, pulmonary hypertension, stroke, spleen, risk

Introduction

Splenectomy is a relatively common surgical procedure performed for various medical and surgical conditions (1). According to the National Hospital Discharge Survey, approximately 22,000 splenectomies are performed annually in the United States, with trauma and incidental splenectomy as the primary surgical indications and haematological disorders as the primary medical indications (2).

Splenectomy is known to be associated with both post-operative and long-term complications (1, 3-5). Common short-term complications are well described, including postoperative infections, bleeding, and venous thromboembolism (3, 6). The most serious long-term consequence is lifelong increased susceptibility to encapsulated bacterial infections. Among these infections, pneumococcal sepsis has a particularly high case fatality rate (1, 5).

Over the past 40 years, research has suggested that splenectomised patients also are at increased long-term risk of atherosclerotic events and pulmonary hypertension (PH) (4, 5, 7). Suggested underlying mechanisms include hypercoagulability, increased platelet counts, platelet activation, disturbance and activation of the endothelium, and altered lipid profiles (4). Thus, loss of the filtering function of the spleen may permit particulate matter and damaged cells to persist in the bloodstream, thereby perturbing and activating the vascular endothelium and shifting vascular homeostasis towards enhanced coagulation (4, 7).

Since several underlying diseases for which splenectomy is performed may be associated with increased risk of venous and arterial thrombosis (8-10), it remains unclear whether increased cardiovascular risk arises from removal of the spleen or from the underlying indication for the splenectomy (11). If lack of a spleen is the cause, then effects would be expected across the underlying reasons for splenectomy. Yet, Kristinsson *et al.* found no increased risks of MI or ischemic stroke in 8,149 cancer-free veterans who underwent splenectomy for various reasons compared with 4 million hospitalised veterans (5). They did not, however, take into account the underlying reason for splenectomy. A previous Danish study found more than one year after splenectomy a two-fold increased mortality risk among splenectomised patients, regardless of indication, compared with the general population. Compared with un-splenectomised patients with similar indications, the risk of death associated with splenectomy was not increased (12).

Elevated risks of cardiovascular complications may have important clinical implications. Data on these risks are needed to understand and potentially prevent post-splenectomy death. We therefore conducted a nationwide population-based cohort study on the long-term risks of cardiovascular events following splenectomy. We investigated the risks of myocardial infarction (MI), PH, and stroke among patients splenectomised for a variety of indications and compared their risks with those for the general population. We then examined whether the risks were related to the splenectomy and its consequences or to the underlying diseases, by comparing outcomes among patients who underwent splenectomy with outcomes among non-splenectomised patients with similar diseases.

Methods

We used the Danish National Patient Registry (DNPR) to identify patients who underwent splenectomy between January 1, 1996 and December 31, 2012. The DNPR contains information on all admissions to Danish hospitals and hospital outpatient clinic visits since 1995. Data include dates of admission and discharge, surgical procedures coded according to the Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures, and up to 20 discharge diagnoses coded by physicians according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993, and thereafter ICD-10. We classified splenectomised patients into eight subgroups, according to all previous diagnoses recorded in the patient registry, using the following hierarchy: (1) traumatic rupture of the spleen; (2) idiopathic thrombocytopenic purpura (ITP); (3) other/unspecified thrombocytopenia; (4) hematopoietic cancer; (5) hereditary haemolytic anaemia; (6) abdominal cancer; (7) splenomegaly/other splenic diseases only; and (8) other indications (6, 12). Accordingly, if a patient had traumatic splenic rupture before date of splenectomy, he/she was categorized into this first indication group, regardless the presence/absence of the other indications. Patients in the "other indications" group had none of the selected indications before splenectomy. We excluded splenectomised patients with a prior diagnosis of coronary artery disease (CAD), MI, PH, or stroke before the surgery date. Surgical and diagnostic codes are summarized in the Supplementary Table.

We used the Danish Civil Registration System (CRS) (13) to select 10 members of the general population for each splenectomised patient, matched by age, sex, and

calendar year of splenectomy. We also constructed a disease-matched comparison cohort, using the CRS and DNPR to identify up to 5 patients diagnosed with the same underlying disease in the same calendar year as the corresponding splenectomised patient. Members of this comparison cohort could not have a procedure code for splenectomy, or a diagnosis code for CAD, MI, PH, or stroke before study inclusion. As a comparison group for patients splenectomised due to trauma, we identified trauma patients who underwent surgery for acute injury of the spleen, liver, or gallbladder, with no recorded splenectomy. In our comparison of the splenectomy and disease-matched cohorts, we excluded the "other indications" subgroup from the splenectomy cohort. The date of splenectomy represented the "index date" for the matched sets of patients.

To address potential confounding, we retrieved information on presence of the following diagnoses recorded prior to the splenectomy/index date: chronic obstructive pulmonary disease (COPD), pulmonary embolism (PE), heart failure (HF), diabetes, atrial fibrillation, hypertension and obesity (see Supplementary Table for diagnostic codes). We also retrieved information on all diagnoses of venous thromboembolism (VTE) recorded prior to cardiovascular outcomes.

Splenectomised patients and members of their comparison cohorts were followed from their surgery/index dates to occurrence of any long-term outcomes of interest, death, or end of follow-up (31 December 2012), whichever occurred first.

We used cumulative incidence functions with death as a competing event, and plotted the cumulative risks of MI, PH and stroke for the three study cohorts. Only the first of these outcomes were included in the analyses. We computed the 5-year mortality

and 5-year cumulative incidence of MI, PH, and stroke in the three cohorts as a measure of 5-year risk, treating death as a competing event. We used stratified Cox regression analysis to compute the adjusted hazard ratio (aHR) overall and separately for all indications for splenectomy (with corresponding 95% confidence intervals [CIs]) for each outcome, with adjustment for age, sex, and the following comorbid conditions: COPD, PE, HF, diabetes, hypertension, and obesity while we censored patients who died. In the PH analysis, we additionally included VTE as a time-varying covariate. As well, we analysed the data categorising stroke as ischemic or haemorrhagic because of their different underlying mechanisms. Because more than two-thirds of all unspecified strokes are known to be ischemic strokes, we recategorised unspecified strokes as ischemic strokes. (14) In a separate analysis, we additionally adjusted for atrial fibrillation to explore if this could be an intermediate step.

All analyses were conducted using SAS 9.2 software. The study was approved by the Danish Data Protection Agency (Jr nr. 1-16-02-1-08).

Results

Patient characteristics

We identified 5,306 patients who had undergone splenectomy, 53,060 matched members of the general population cohort, and 11,651 members of a disease-matched cohort. Their characteristics and 5-year mortality rates are summarized in Table 1. The four most frequently recorded indications for splenectomy were traumatic rupture of the spleen [1,033 patients (19.5%)], abdominal cancers [880 patients (16.6%)], hematopoietic cancers [417 patients (7.9%)], and ITP [379 patients (7.1%)]. In total,

1,985 patients (37.4%) had none of the specified indications. Of the comorbid conditions examined, hypertension and COPD were most frequently reported, with a prevalence of 8.2% and 6.2%, respectively among splenectomised patients overall. The prevalence of comorbidity was generally higher than in the general population comparison cohort (Table 1). Among the general population comparisons, 4.9% had hypertension and 4.1% had COPD. Patients with other indications were older and had high prevalence of comorbid conditions. The splenectomy cohort and the disease-matched cohort had almost equal rates of the specified comorbid conditions (Table 1).

Study outcomes

We followed the splenectomised cohort for a median of 3.8 years (maximum 17.0 years). Figure 1 illustrates the cumulative risk of MI for the splenectomy and comparison cohorts over the entire follow-up period. After 5 years of follow-up, the risk of a first-time MI was 1.3% (95% CI: 1.0%-1.6%) among splenectomised patients compared with 1.8% (95% CI: 1.6%-1.9%) among members of the general population cohort, taking death into account as a competing event. However, the unadjusted HR comparing splenectomised patients with the general population cohort was 1.28 (95% CI: 1.04 - 1.57) and the aHR was 1.24 (95% CI: 1.01-1.52) (Table 2). In contrast, splenectomised patients and the disease-matched cohort had a similar 5-year risk of MI (Table 3). Considering death as a competing event, the 5-year risk of MI was 1.2% (95% CI: 0.8%-1.6%) in the splenectomy cohort and 1.4% (95% CI: 1.2%-1.6%) in the disease-matched cohort, with an unadjusted HR for MI of 0.92 (95% CI: 0.68 - 1.24) and aHR of 0.95 (95% CI: 0.70-1.28). Compared with the disease-matched cohort, the

relative risk of MI did not vary substantially between subgroups of splenectomised patients.

The 5-year risk of PH was 0.4% (95% CI: 0.2%-0.6%) in splenectomised patients compared with 0.2% (95% CI 0.1%-0.2%) in the general population cohort (Figure 2), with an aHR of 3.25 (95% CI: 1.93-5.46) (Table 2). However, the cumulative incidences were similar in the splenectomy and disease-matched cohorts (Figure 2) with an aHR of 1.03 (95% CI: 0.55-1.93) (Table 3). Comparing splenectomised patients with those in the disease-matched cohort, the aHR of PH was 7.89 (95% CI 0.71-87.99) among patients with splenomegaly/splenic disease and 4.16 (95% CI 0.58-29.88) for patients with ITP. However, the statistical precision of these estimates was low (Table 3).

Among splenectomised patients, 3.3% (95% CI: 2.9%-3.9%) had a stroke within the first 5 years of follow-up, compared with 2.6% (95% CI: 2.5%-2.8%) of persons in the general population cohort (Table 2 and Figure 3), taking death into account as a competing event. The unadjusted HR was 2.05 (95% CI: 1.79-2.36) and aHR was 2.04 (95% CI: 1.78-2.35) (Table 2). Compared with the general population cohort, the 5-year risk of stroke was consistently higher in all splenectomy indication subgroups, except for the subgroup with non-specific thrombocytopenia (Table 2). The cumulative incidence of stroke was higher in splenectomised patients than in the disease-matched cohort (Figure 3). The five-year stroke risk was 3.0% (95% CI: 2.4%-3.7%) and 2.3% (95% CI: 2.0%-2.6%) in the two groups, respectively (Table 3). After 10 years of follow-up the stroke risk remained higher in splenectomised than in the disease matched cohort (4.9% (95% CI, 4.1-5.8) vs 4.0 % (95% CI, 3.5-4.4), respectively). The

unadjusted HR was 1.48 (95% CI: 1.22-1.80) and aHR was 1.53 (95% CI; 1.26-1.86) (Table 3). In the disease-matched comparisons, the 5-year stroke risk was higher in splenectomised than in non-splenectomised patients in all sub-groups except for those with ITP or non-specific thrombocytopenia (Table 3). For patients splenectomised due to traumatic rupture of the spleen, the aHR for stroke was 3.12 (95% CI 2.19-4.47) compared with the general population cohort (Table 2) and 1.95 (95 % CI 1.06-3.58) compared with disease-matched patients who underwent surgery for acute injury of the spleen, liver, or gallbladder, with no recorded splenectomy (Table 3).

When we analysed the risk of ischemic and haemorrhagic stroke separately, we found that splenectomised patients had a two-fold increased risk of ischemic stroke compared with the general population cohort (aHR 2.05 (95% CI, 1.76 - 2.37)) (Table 4) and a 50% increased risk of ischemic stroke, compared with the disease-matched cohort (aHR 1.56 (95% CI, 1.26 - 1.92)). For haemorrhagic stroke, the aHRs were similarly increased: 1.77 (95% CI 1.17 - 2.70) for the splenectomy cohort compared with the general population cohort and 1.37 (95% CI 0.81 - 2.31) for the splenectomy cohort compared with the disease-matched cohort.

Including atrial fibrillation as a covariate did not substantially change the aHRs for stroke overall, ischaemic stroke, or haemorrhagic stroke (data not shown).

Discussion

Our nationwide population-based study showed that splenectomised patients had as

expected higher risks of MI, PH, and stroke than persons in the general population. When we compared splenectomised patients with a disease-matched cohort, we found similar risks of MI and PH. This indicated that the underlying medical conditions for which the splenectomy was performed caused the increased risk of MI and PH. However, splenectomised patients had a 50% higher risk of ischemic stroke and a 30% increased risk of haemorrhagic stroke compared with persons in the disease-matched cohort. This suggests that the increased risk of stroke was a consequence of the splenectomy, rather than of the underlying disease leading to splenectomy.

The increased risk of cardiovascular events following splenectomy was first suggested in a study of 745 World War II servicemen who had been splenectomised because of trauma (15). By the end of 1974, the risk of death due to ischaemic heart disease was nearly doubled following splenectomy (15). However, the majority of cardiovascular deaths in splenectomised servicemen (36 out of a total of 41) occurred more than 15 years after the splenectomy. This accords with our finding that splenectomised patients did not have higher risk of MI than the general population cohort during our 17-year follow-up period. When we took death into account as a competing event the 5-year risk of MI was in fact slightly higher in the background population than in splenectomised. Still, we found an overall increased hazard ratio of MI and PH when comparing splenectomised with the background population illustrating that although splenectomised have a higher risk of MI, they also have a higher mortality than the background population and therefore fewer of them will live long enough to actually develop MI or PH.

Two previous studies both restricted to patients with hereditary spherocytosis

indicated that splenectomy increased the risk of arteriosclerotic events (stroke, MI, and coronary or carotid artery surgery) 5-7 –fold (16, 17). In our study, we categorized hereditary spherocytosis with other hereditary haemolytic anaemias and found that the risks of MI and stroke were less than 70% increased, when comparing splenectomised and non-splenectomised haemolytic anaemia patients. This was substantially lower than previous findings (16, 17). Still, due to our low statistical precision, we could not rule out a 7-fold increased risk.

Latency since splenectomy and risk of cardiovascular outcomes were addressed in the large study based on US Veterans Affairs data with up to 27 years of follow-up (5). Comparing splenectomised veterans with other veterans, the risk of being hospitalised with MI was not increased at any time during the follow-up period. Our study thus corroborates earlier findings that the absolute risk of MI in general is not increased following splenectomy. Because we stratified splenectomy by underlying indication, our study extended these findings. We observed that, compared with the general population, the risk of MI following splenectomy was only increased for patients who were splenectomised due to haematological disorders. The effect nearly vanished in comparisons with patients with similar haematological disorders.

Increased incidence of PH following splenectomy previously was observed in patients with sickle cell anaemia and thalassaemia (18) and also in patients referred for lung transplantation (7). When we compared our splenectomised and disease-matched cohorts, we found no increased risk of PH. This also suggests that it is not the absence of a spleen, but factors related to the underlying indication for splenectomy, that may be the primary causes of PH. Pulmonary embolism is a risk factor for PH, and it is well

documented that many of the underlying conditions for which splenectomy is performed are associated with increased risk of venous thromboembolism and/or PH including malignancies, trauma, myeloproliferative neoplasms, ITP, and haemolytic anaemia (19, 20). Some studies also have shown that splenectomy is a risk factor for chronic thromboembolic pulmonary hypertension (defined by the absence of thrombus resolution after acute pulmonary embolism), particularly in patients splenectomised for a haemolytic disorder (11, 21). Unfortunately, even our large cohort did not allow us to study specific types of PH such as chronic thromboembolic pulmonary hypertension. (10). Moreover, a previous case series demonstrated that chronic thromboembolic pulmonary hypertension may occur more than 20 years after a traumatic splenectomy (21). Accordingly, our follow-up time may not have been sufficiently long to capture such cases. Still, when we included VTE as a time-varying covariate in comparisons of the splenectomised and general population cohorts, the HR was not substantially lowered. Our study additionally highlighted that the absolute risk of PH was very low.

Our finding of a nearly 2-fold increased risk of stroke among splenectomised patients compared to a disease-matched cohort with traumatic rupture of the spleen, and a nearly 3-fold increased risk of stroke compared with the general population are in line with previous research (18, 22) . A nationwide cohort study form Taiwan included 11,273 splenic injury patients during 1998-2010, among whom 5294 patients were splenectomised. Compared with a control cohort from the background population splenectomised had a two-fold higher incidence of stroke while patients with splenic injury but no splenectomy only had a 20% increased incidence (22). As comparisons for those splenectomised due to trauma we similarly used patients with traumatic injury of

the spleen, the liver or the gallbladder who were not splenectomised and found a higher risk of stroke in splenectomised. Although we cannot completely rule out confounding by disease severity our study extends the findings from the Taiwanese study by showing an increased risk of stroke across varying underlying reasons for splenectomy. In the Taiwanese study, patients with splenectomy had higher prevalence of liver cirrhosis, hypertension, hyperlipidaemia, diabetes, and COPD compared with the control cohort. This suggests that lifestyle may differ between splenectomised and the general population and thus may confound comparisons between splenectomised and the background population. Still, the prevalence of these factors did not differ between splenectomised and those with splenic injury who were not splenectomised (22). The US veterans study found no increase in risk of hospitalisation due to ischaemic stroke (5), however, the risk of death due to stroke was nearly doubled in splenectomised veterans (standardised mortality ratio 1.89; 95% CI; 0.91-3.90).

The mechanisms behind the increased risk of stroke following splenectomy remain unclear. MI and stroke broadly have comparable risk-factors (23). We did not, however, observe an increased risk of MI, which speaks against a generally increased risk of arteriosclerosis caused by platelet activation, disturbance and activation of the endothelium, and altered lipid profiles (4).

Several potential study weaknesses should be considered in interpreting our data. As discussed above one major weakness is that we cannot rule out confounding by disease severity. Also, our study relied on diagnoses recorded in the DNPR and it is well known that coding errors occur (24). We did not validate the underlying diagnoses in splenectomised or disease matched. However, in DNPR, diagnoses are validated on

an *ad hoc* basis (24), and it has been shown that the surgical procedures used to identify splenectomised patients have high validity (25). Moreover, the positive predictive value (PPV) of a diagnosis of MI in the DNPR previously has been found to be above 90% (26), and the PPV of acute stroke diagnoses has been found to be 97% for ischaemic stroke (14). We, therefore, do not think that misclassification of the underlying disease constitutes a major source of bias in our study. We were able to adjust for selected comorbid conditions such as COPD, diabetes, hypertension, and obesity, which are known to be associated with increased risk of cardiovascular events. However, we based our comorbidity information on hospital-related diagnoses and did not capture diagnoses made by general practitioners. It has been recognized that the diagnosis of obesity may be severely underreported in the DNPR (27). Also, we found a prevalence of hypertension in our general population cohort of 5% which is lower than expected based on an age the age-adjusted prevalence (28). Consequently, residual confounding is likely to be present in comparisons of splenectomised patients with the general population. Although we cannot rule out residual confounding in the comparison with a disease-matched cohort either the reported prevalence of comorbid diseases was almost similar between splenectomised and disease-matched comparisons so we assume residual confounding to be smaller in these estimates. More than 30% of the patients in our splenectomy cohort had another underlying diagnosis than the indications that we *a priori* had specified as the major underlying causes of splenectomy. This "other group" was not included in the indication-matched analyses; yet, when compared with their matched cohort from the general population the relative estimates did not suggest that this group had a higher relative risk of the outcomes than those with selected underlying

indications. Finally, even in our nationwide study, the statistical precision in some of our strata did not allow us to make firm conclusions.

In conclusion, our study showed that splenectomy is associated with increased risk of stroke, across the underlying indications for splenectomy. In contrast, any increased risk of MI and PH in splenectomised patients seemed to be related to the underlying indication rather than to the splenectomy itself.

Conflict of interest Statement

Dr. Ghanima reports grants from Bayer, BMS and Novartis and honoraria for participation in advisory board meetings and lectures from Bayer, Novartis, Amgen, Pfizer and BMS. None of the other authors reported receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, Denmark.

Acknowledgements

WG and MN conceived the study. All authors contributed to the study design and conduct. DKF analysed the data. MR and MN drafted the manuscript. All authors took part in interpreting the results and critical revision of the manuscript.

References

1. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. Lancet. 2011;378(9785):86-97.
2. DeFrances CJ, Cullen KA, Kozak LJ. National Hospital Discharge Survey: 2005 annual summary with detailed diagnosis and procedure data. Vital Health Stat. 2007;(165):1-209.
3. Cadili A, de Gara C. Complications of splenectomy. Am J Med. 2008;121(5):371-375.
4. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. Blood. 2009;114(14):2861-2868.
5. Kristinsson SY, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. Haematologica. 2014;99(2):392-398.
6. Thomsen RW, Schoonen WM, Farkas DK, Riis A, Fryzek JP, Sorensen HT. Risk of venous thromboembolism in splenectomized patients compared with the general population and appendectomized patients: a 10-year nationwide cohort study. J Thromb Haemost. 2010;8(6):1413-1416.
7. Hoeper MM, Niedermeyer J, Hoffmeyer F, Flemming P, Fabel H. Pulmonary hypertension after splenectomy? Ann Intern Med. 1999;130(6):506-509.
8. Yusuf HR, Hooper WC, Grosse SD, Parker CS, Boulet SL, Ortel TL. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. Thromb Res. 2015;135(1):50-57.
9. Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med. 2011;9:1.
10. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
11. Peacock AJ. Pulmonary hypertension after splenectomy: a consequence of loss of the splenic filter or is there something more? Thorax. 2005;60(12):983-984.
12. Yong M, Thomsen RW, Schoonen WM, Farkas DK, Riis A, Fryzek JP, et al. Mortality risk in splenectomised patients: a Danish population-based cohort study. Eur J Intern Med. 2010;21(1):12-16.
13. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-549.
14. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28(3):150-154.

15. Robinette CD, Fraumeni JF, Jr. Splenectomy and subsequent mortality in veterans of the 1939-45 war. Lancet. 1977;2(8029):127-129.
16. Schilling RF, Gangnon RE, Traver MI. Delayed adverse vascular events after splenectomy in hereditary spherocytosis. J Thromb Haemost. 2008;6(8):1289-1295.
17. Schilling RF. Spherocytosis, splenectomy, strokes, and heat attacks. Lancet. 1997;350(9092):1677-1678.
18. Taher A, Isma'eel H, Mehio G, et al. Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran. Thromb Haemost. 2006;96(4):488-491.
19. Severinsen MT, Engebjerg MC, Farkas DK, et al. Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. Br J Haematol. 2011;152(3):360-362.
20. Blann AD, Lip GY. Venous thromboembolism. BMJ. 2006;332(7535):215-219.
21. Jais X, Ioos V, Jardim C, et al. Splenectomy and chronic thromboembolic pulmonary hypertension. Thorax. 2005;60(12):1031-1034.
22. Lin JN, Lin CL, Lin MC, et al. Increased Risk of Hemorrhagic and Ischemic Strokes in Patients With Splenic Injury and Splenectomy: A Nationwide Cohort Study. Medicine (Baltimore). 2015;94(35):e1458.
23. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005;162(10):975-982.
24. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-490.
25. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol. 1996;25(2):435-442.
26. Buch P, Rasmussen S, Gislason GH, et al. Temporal decline in the prognostic impact of a recurrent acute myocardial infarction 1985 to 2002. Heart. 2007;93(2):210-215.
27. Sogaard M, Heide-Jorgensen U, Norgaard M, Johnsen SP, Thomsen RW. Evidence for the low recording of weight status and lifestyle risk factors in the Danish National Registry of Patients, 1999-2012. BMC Public Health. 2015;15:1320.
28. Kronborg CN, Hallas J, Jacobsen IA. Prevalence, awareness, and control of arterial hypertension in Denmark. J Am Soc Hypertens. 2009;3(1):19-24.e2.

.

Table 1. Demographic characteristics of the splenectomised cohort (overall and by indication for splenectomy), the disease-matched comparison cohort, and the general population comparison cohort.

					INDICATION FOR SPLENECTOMY, N (%)							
		Overall splenectomised cohort, N (%)	Population comparison cohort, N (%)	Disease-matched Comparison cohort, N (%)	Traumatic Rupture N (%)	Abdominal Cancers N (%)	ITP** N (%)	Hematopoietic Cancers N (%)	Splenomegaly/ other splenic disease N (%)	Hereditary haemolytic anaemias N (%)	Nonspecific thrombocytopenia N (%)	Other N (%)
Total, n (%)		5306 (100)	53,060 (100)	11,651 (100)	1033 (19.5)	880 (16.6)	379 (7.1)	417 (7.9)	321 (6.0)	216 (4.1)	75 (1.4)	1985 (37.4)
Age – years at	Median (IQR)	58.4 (40.1-70.3)	58.4 (40.2-70.3)	58.4 (40.2-70.3)	36.6 (22.1-53.9)	70.8 (78.5-95.2)	46.4 (28.9-60.8)	63.9 (55.5-71.7)	48.0 (32.6-63.0)	13.1 (9.7-26.7)	56.0 (43.7-66.5)	62.9 (51.6-71.8)
Sex	Female	2485 (46.8)	24,850 (46.8)	5700 (48.9)	300 (29.0)	439 (49.9)	239 (63.0)	183 (43.9)	149 (46.4)	121 (56.0)	38 (50.6)	1016 (51.2)
	Male	2821 (53.2)	28,210 (53.2)	5951 (51.1)	733 (71.0)	441 (50.1)	140 (36.9)	234 (56.1)	172 (53.6)	95 (44.0)	37 (49.3)	969 (48.8)
Year of splenectomy/ index date	1996-2001	2113 (39.8)	21,130 (39.8)	4645 (39.9)	427 (41.3)	392 (44.6)	176 (46.4)	137 (32.9)	100 (31.2)	79 (36.6)	29 (38.7)	773 (38.9)
	2002-2007	1796 (33.9)	17,960 (33.9)	3935 (33.8)	399 (38.6)	298 (32.8)	117 (30.9)	144 (34.5)	124 (38.6)	90 (41.7)	30 (40.0)	603 (30.4)
	2008-2012	1397 (26.3)	13,970 (26.3)	3071 (26.4)	207 (20.0)	199 (22.6)	86 (22.7)	136 (32.6)	97 (30.2)	47 (21.8)	16 (21.3)	609 (30.7)
Comorbid condition												
	COPD*	329 (6.2)	2197 (4.1)	746 (6.4)	37 (3.6)	58 (6.6)	12 (3.2)	28 (6.7)	23 (7.2)	14 (6.5)	8 (10.7)	149 (7.5)
	Diabetes	210 (4.0)	1282 (2.4)	503 (4.3)	16 (1.5)	31 (3.5)	15 (4.0)	18 (4.3)	12 (3.7)	3 (1.4)	8 (10.7)	107 (5.4)
	Hypertension	437 (8.2)	2610 (4.9)	972 (8.3)	31 (3.0)	93 (10.6)	21 (5.5)	30 (7.2)	23 (7.2)	0 (0)	6 (8.0)	233 (11.7)
	Atrial fibrillation	130 (2.5)	1034 (1.9)	399 (3.4)	14 (1.4)	27 (3.1)	8 (2.1)	11 (2.6)	8 (2.5)	0 (0)	3 (4.0)	59 (3.0)
	Pulmonary embolus	54 (1.0)	187 (0.4)	117 (1.0)	3 (0.3)	14 (1.6)	0 (0)	11 (2.6)	2 (0.6)	0 (0)	2 (2.7)	22 (1.1)
	Heart failure	64 (1.2)	436 (0.8)	205 (1.8)	5 (0.5)	16 (1.8)	4 (1.1)	6 (1.4)	2 (0.6)	1 (0.5)	0 (0)	30 (1.5)
	Obesity	123 (2.3)	742 (1.4)	270 (2.3)	13 (1.3)	15 (1.7)	12 (3.2)	8 (1.9)	8 (2.5)	2 (0.9)	4 (5.3)	61 (3.1)
5-year mortality		39.4 %	9.5%	38.3%	17.3%	66.4%	7.2%	50.4%	22.3%	4.1%	44.0%	50.1%

IQR = Interquartile range

Table 2. Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios, with 95% confidence intervals, of myocardial infarction, pulmonary arterial hypertension, and stroke in 5306 splenectomised patients compared with 53,060 age- and gender-matched members of the general population, overall and stratified by indication for splenectomy.

	Myocardial infarction			**Pulmonary arterial hypertension**			**Stroke**		
	Splenectomised patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomised patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomised patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio**
Overall	1.28 (0.99-1.63)	1.75 (1.64-1.88)	1.24 (1.01-1.52)	0.35 (0.21-0.56)	0.16 (0.12-0.20)	3.25 (1.93-5.46)	3.34 (2.86-3.89)	2.62 (2.47-2.77)	2.04 (1.78-2.35)
Traumatic rupture	0.54 (0.21-1.21)	0.57 (0.43-0.74)	0.74 (0.34-1.60)	0.21 (0.05-0.74)	0.06 (0.02-0.13)	1.75 (0.31-10.01)	2.78 (1.88-3.96)	0.95 (0.76-1.16)	3.12 (2.19-4.47)
Abdominal cancer	1.50 (0.82-2.55)	2.92 (2.56-3.31)	0.79 (0.47-1.33)	0.12 (0.01-0.68)	0.29 (0.19-0.43)	2.21 (0.46-10.58)	3.08 (2.03-4.48)	4.58 (4.13-5.06)	1.34 (0.96-1.87)
Idiopathic thrombocytopenic purpura	1.13 (0.38-2.71)	1.00 (0.70-1.39)	1.51 (0.70-3.25)	-	0.03 (0.00-0.15)	2.47 (0.25-24.08)	2.09 (0.93-4.09)	1.24 (0.90-1.66)	1.70 (0.99-2.91)
Hematopoietic cancers	1.86 (0.83-3.66)	2.14 (1.69-2.67)	1.12 (0.53-2.38)	0.58 (0.12-1.94)	0.14 (0.05-0.31)	5.13 (0.53 - 49.28)	4.40 (2.62-6.88)	2.83 (2.32-3.42)	2.15 (1.30-3.54)
Splenomegaly/splenic disease	1.73 (0.66-3.79)	0.81 (0.52-1.21)	2.59 (1.15-5.83)	0.77 (0.15-2.57)	0.18 (0.07-0.42)	9.44 (0.95-94.29)	4.51 (2.52-7.36)	1.59 (1.16-2.13)	5.00 (2.85-8.75)
Non-specific thrombocytopenia	2.95 (0.56-9.17)	0.94 (0.39-1.97)	1.73 (0.35-8.43)	-	-	-	3.08 (0.58-9.51)	2.14 (1.23-3.48)	1.02 (0.23-4.52)
Hereditary haemolytic anaemia	-	0.17 (0.05-0.47)	3.35 (0.65-17.36)	-	0.56 (0.05-2.86)	-	0.49 (0.05-2.52)	0.57 (0.31-1.00)	4.69 (1.65-13.29
Other indications	1.50 (1.00-2.16)	2.31 (2.08-2.54)	1.44 (1.08-1.93)	0.49 (0.23-0.94)	0.20 (0.14-0.27)	2.92 (1.33 - 6.43)	3.98 (3.12-5.00)	3.27 (3.01-3.55)	1.96 (1.57-2.44)

*adjusted for age, sex, chronic obstructive lung disease, pulmonary embolism, heart failure, diabetes, hypertension, and obesity.

**additionally adjusted for venous thromboembolism as a time-varying covariate

Table 3. Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios with 95% confidence intervals of myocardial infarction, pulmonary arterial hypertension, and stroke in 3321 splenectomised patients with a known underlying indication compared with 11,651 members of a disease-matched cohort. Patients with other indications for splenectomy (N=1985) were not included in the overall analyses.

	Myocardial infarction			**Pulmonary arterial hypertension**			**Stroke**		
	Splenectomised patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomised patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomised patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio*'
Overall	1.16 (0.82-1.59)	1.40 (1.18-1.64)	0.95 (0.70-1.28)	0.28 (0.13-0.53)	0.28 (0.19-0.40)	1.03 (0.55-1.93)	2.99 (2.42-3.65)	2.32 (2.04-2.64)	1.53 (1.26-1.86)
Traumatic rupture	0.54 (0.21-1.21)	0.69 (0.27-1.55)	0.55 (0.18-1.70)	0.21 (0.05-0.74)	0.14 (0.01-0.74)	1.27 (0.11 - 15.17)	2.78 (1.88-3.96)	1.53 (0.78-2.73)	1.95 (1.06-3.58)
Abdominal cancer	1.50 (0.82-2.55)	1.59 (1.24-2.02)	1.07 (0.58-1.99)	0.12 (0.01-0.68)	0.28 (0.15-0.49)	0.86 (0.17-4.32)	3.08 (2.03-4.48)	2.53 (2.06-3.06)	1.37 (0.90-2.09)
Idiopathic thrombocytopenic purpura	1.13 (0.38-2.71)	1.30 (0.83-1.95)	0.75 (0.33-1.74)	-	0.37 (0.16-0.79)	4.16 (0.58-29.88)	2.09 (0.93-4.09)	2.56 (1.87-3.42)	1.02 (0.57-1.80)
Hematopoietic cancers	1.86 (0.83-3.66)	1.80 (1.26-2.51)	1.04 (0.46-2.37)	0.58 (0.12-1.94)	0.12 (0.03-0.43)	-	4.40 (2.62-6.88)	2.46 (1.80-3.29)	1.63 (0.91-2.91)
Splenomegaly/Splenic disease	1.73 (0.66-3.79)	1.22 (0.68-2.04)	2.20 (0.79-6.09	0.77 (0.15-2.57)	0.39 (0.13-0.97)	7.89 (0.71-87.99)	4.51 (2.52-7.36)	2.33 (1.53-3.40)	1.99 (1.02-3.85)
Non-specific thrombocytopenia	2.95 (0.56-9.17)	1.49 (0.57-3.28)	0.65 (0.08-5.67)	-	0.27 (0.03-1.42)	-	3.08 (0.58-9.51)	2.46 (1.16-4.61)	0.92 (0.19-4.40)
Hereditary haemolytic anaemia	-	0.29 (0.06-1.03)	1.57 (0.13-15.15)	0.56 (0.05-2.86)	0.45 (0.13-1.25)	1.30 (0.13-12.60)	0.49 (0.05-2.52)	0.82 (0.34-1.72)	2.00 (0.65- 6.10)

*adjusted for age, sex, chronic obstructive lung disease, pulmonary embolism, heart failure, diabetes, hypertension, and obesity.

**additionally adjusted for venous thromboembolism as a time-varying covariate

Table 4. Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios with 95% confidence intervals of ischaemic stroke and haemorrhagic stroke in 5306 splenectomised patients compared with 53,060 members of an age- and gender-matched general population comparison cohort, overall and stratified by indication for splenectomy.

	Ischaemic stroke			**Haemorrhagic stroke**		
	Splenectomised patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio* (95% CI)	Splenectomised patients, 5-year risk, %	General population comparison cohort 5-year risk, %	Adjusted hazard ratio* (95% CI)
Overall	2.94 (2.48-3.46)	2.35 (2.21-2.49)	2.05 (1.76-2.35)	0.40 (0.25-0.61)	0.27 (0.22-0.32)	1.77 (1.17-2.70)
Traumatic rupture	1.98 (1.23-3.02)	0.80 (0.64-1.00)	2.82 (1.90-4.19)	0.80 (0.38-1.52)	0.14 (0.08-0.24)	5.05 (2.06-12.35)
Abdominal cancer	2.96 (1.93-4.34)	4.17 (3.74-4.63)	1.47 (1.05-2.06)	0.12 (0.01-0.68)	0.41 (0.29-0.58)	0.28 (0.04-2.08)
Immune Thrombocytopenia	1.56 (0.59-3.43)	1.03 (0.73-1.43)	1.41 (0.76-2.64)	0.53 (0.11-1.79)	0.20 (0.09-0.41)	3.27 (0.81-13.13)
Hematopoietic cancers	3.67 (2.05-6.01)	2.62 (2.12-3.18)	2.09 (1.21-3.60)	0.74 (0.21-2.02)	0.22 (0.10-0.42)	2.92 (0.78-11.01)
Splenomegaly/splenic disease	3.87 (2.04-6.59)	1.41 (1.01-1.92)	5.18 (2.82-9.50)	0.64 (0.13-2.15)	0.18 (0.07-0.42)	7.98 (1.44-44.12)
Non-specific thrombocytopenia	3.08 (0.58-9.51)	1.98 (1.11-3.28)	1.21 (0.27-5.46)	-	-	-
Hereditary haemolytic anaemia	0.49 (0.05-2.52)	0.47 (0.23-0.87)	6.29 (2.18-18.20)	-	0.10 (0.02-0.35)	-
Other indications	3.74 (2.91-4.72)	2.95 (2.69-3.21)	2.02 (1.60-2.40)	0.25 (0.08-0.61)	0.33 (0.25-0.43)	1.10 (0.51-2.40)

Figure 1.

Title: Cumulative risk of myocardial infarction (MI) following splenectomy (in years).

Legend: Upper panel shows cumulative risk of MI in splenectomised patients compared with the risk in the general population cohort, while lower panel shows cumulative risk of MI in splenectomised patients compared with the risk in the disease-matched cohort.

Figure 2.

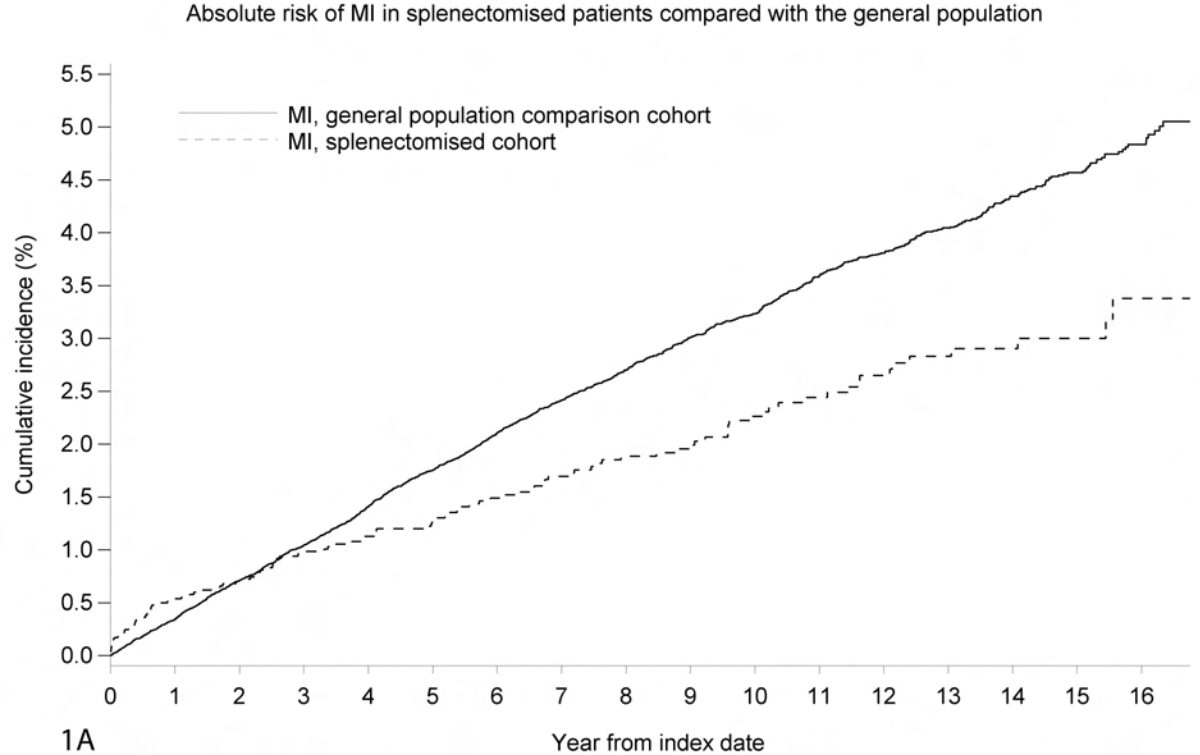
Title: Cumulative risk of pulmonary hypertension (PH) following splenectomy (in years).

Legend: Upper panel shows cumulative risk of PH in splenectomised patients compared with the risk in the general population cohort, while lower panel shows cumulative risk of PH in splenectomised patients compared with the risk in the disease-matched cohort.

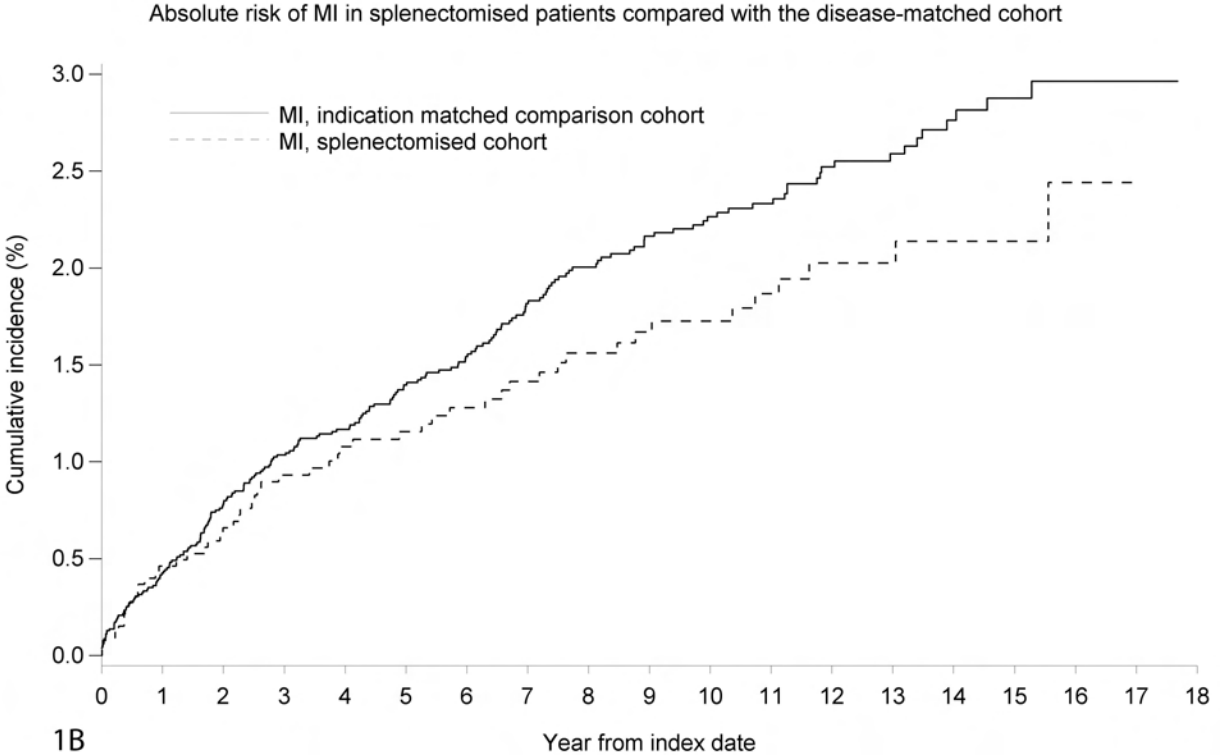
Figure 3.

Title: Cumulative risk of stroke following splenectomy (in years).

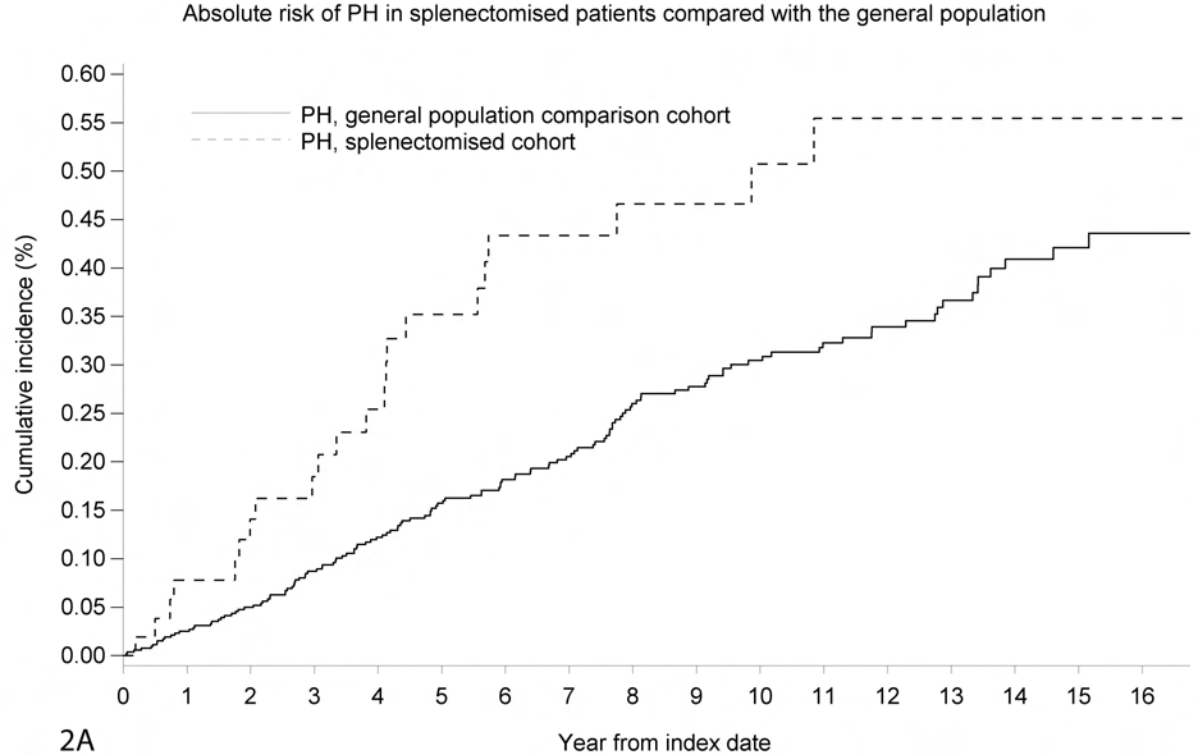
Legend: Upper panel shows cumulative risk of stroke in splenectomised patients compared with the risk in the general population cohort, while lower panel shows cumulative risk of stroke in splenectomised patients compared with the risk in the disease-matched cohort.


Absolute risk of MI in splenectomised patients compared with the general population
MI, general population comparison cohort
MI, splenectomised cohort
Cumulative incidence (%)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Year from index date

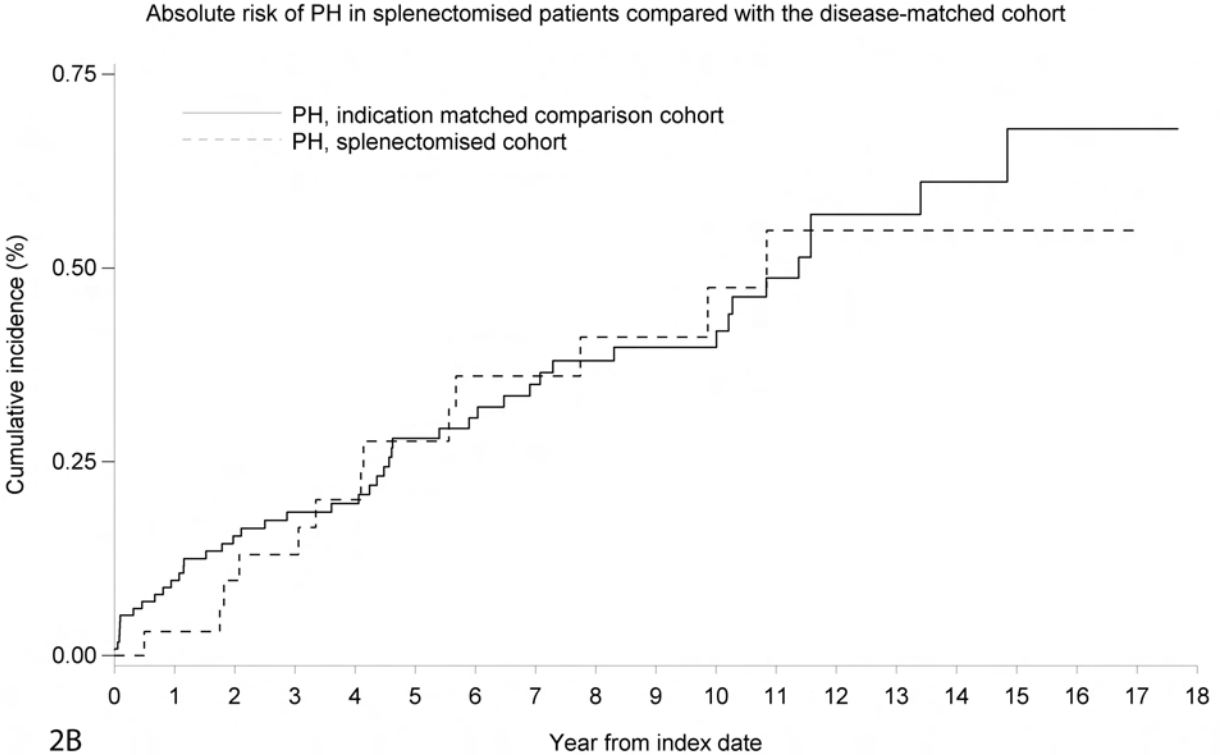
1A


Absolute risk of MI in splenectomised patients compared with the disease-matched cohort
MI, indication matched comparison cohort
MI, splenectomised cohort
Cumulative incidence (%)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Year from index date

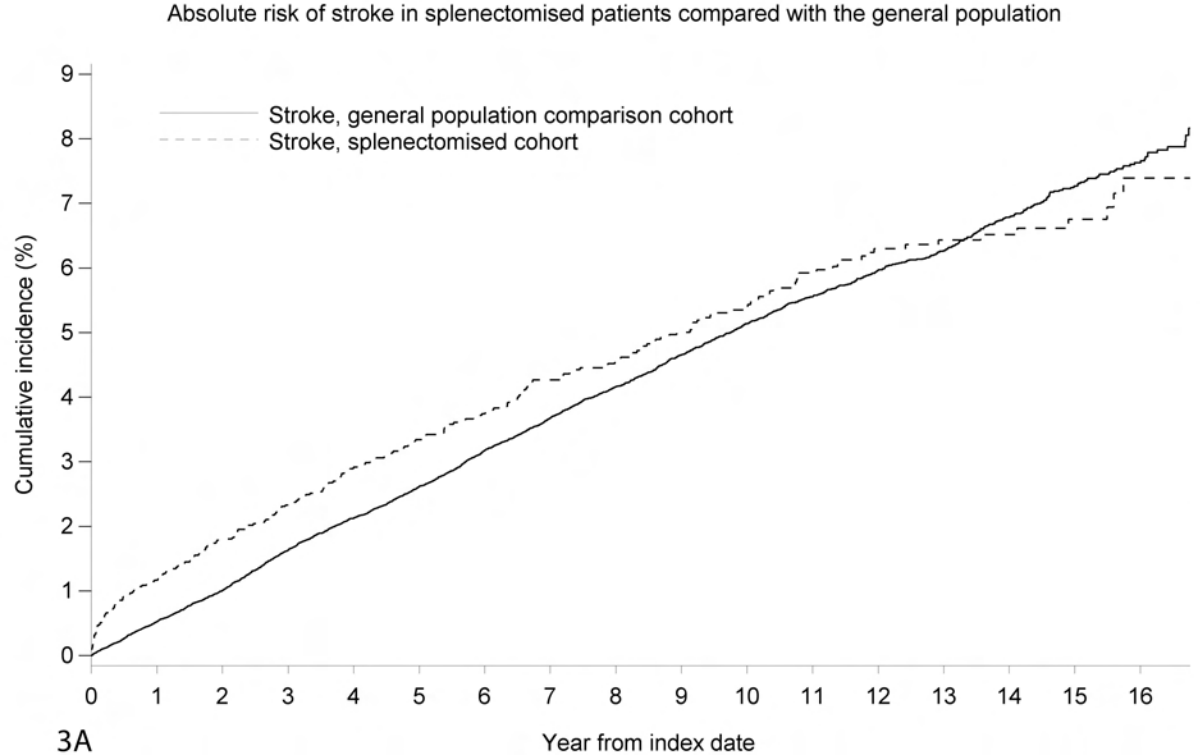
1B


Absolute risk of PH in splenectomised patients compared with the general population
PH, general population comparison cohort
PH, splenectomised cohort
Cumulative incidence (%)
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Year from index date

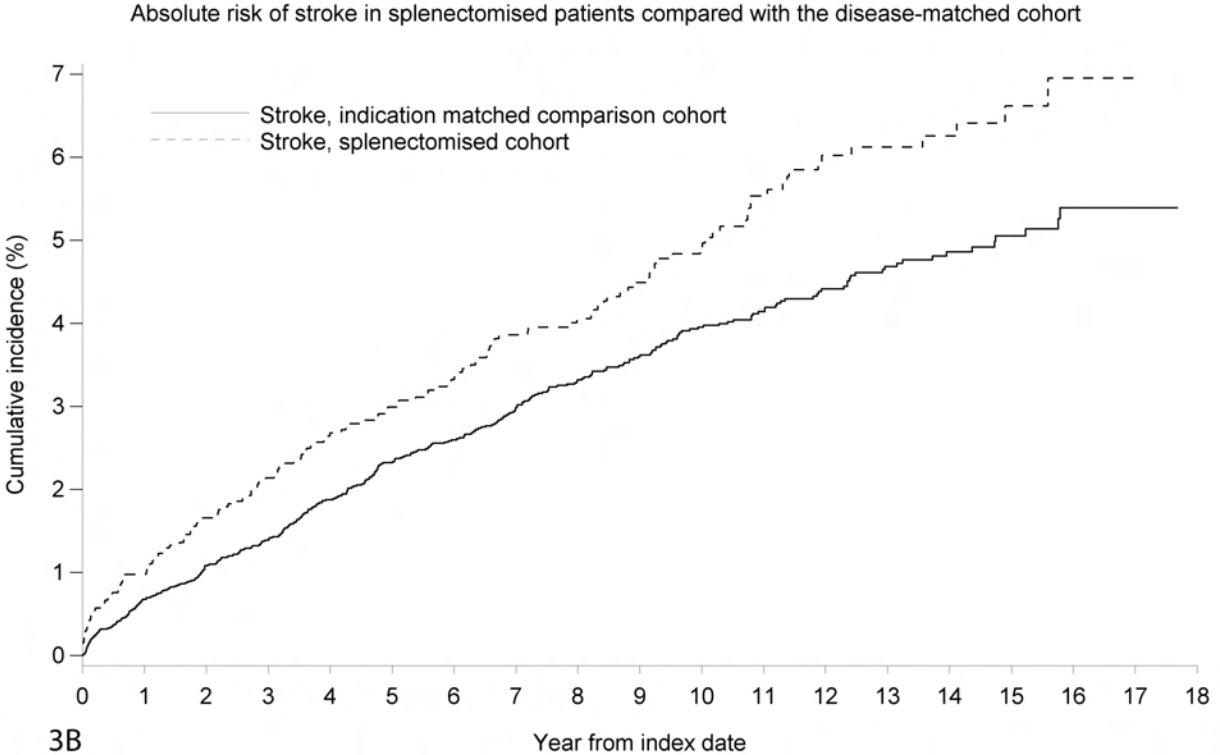
2A


Absolute risk of PH in splenectomised patients compared with the disease-matched cohort
PH, indication matched comparison cohort
PH, splenectomised cohort
Cumulative incidence (%)
0.75
0.50
0.25
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Year from index date

2B


Absolute risk of stroke in splenectomised patients compared with the general population
Stroke, general population comparison cohort
Stroke, splenectomised cohort
Cumulative incidence (%)
0
1
2
3
4
5
6
7
8
9
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Year from index date

3A


Absolute risk of stroke in splenectomised patients compared with the disease-matched cohort
Stroke, indication matched comparison cohort
Stroke, splenectomised cohort
Cumulative incidence (%)
0
1
2
3
4
5
6
7
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Year from index date

3B

Supplementary table:
Table V: Surgical codes (NMCP and NMSP) and diagnostic codes (ICD-8 and ICD-10) used in the study.

		CODES USED TO DEFINE COHORTS, COMORBIDITIES AND OUTCOMES
Splenectomised		
	Splenectomy	JMA 00, 10, 11, 20, JMA 99, JMA 96
Indications		
	Traumatic rupture of the spleen	S36.0 (ICD-10), 865.9 (ICD-8)
	Hematopoietic cancer	C81–C96 (ICD-10); 200-207, 275.59 (ICD-8)
	Hereditary hemolytic anaemias	D55–D58 (ICD-10); 282 (ICD-8)
	ITP	D69.3 (ICD-10); 287.10 (ICD-8)
	Other or nonspecific thrombocytopenia	D69.4, D69.5, D69.6 (ICD-10); 287.11, 287.18, 287.19, 287.29 (ICD-8)
	Splenic diseases and splenomegaly	D73, R16.1, R16.2 (ICD-10); 289.4, 782.89 (ICD-8)
	Abdominal cancers	C16, C18 (ICD-10); 151, 153 (ICD-8)
	Other or unknown indications	Various codes (ICD-10); various codes (ICD-8)
Outcomes		
	Pulmonary hypertension	I27.0, I27.2, I27.8, I27.9 (ICD-10); 426 (ICD-8)
	Coronary artery disease	I20.0-I25.9 (ICD-10); 410-414 (ICD-8)
	Myocardial infarction	I21 (ICD-10); 410 (ICD-8)
	Stroke, ischemic	I63, I64 (ICD-10); 432-434 (ICD-8)
	Stroke, haemorrhagic	I61, (ICD-10); 432 (ICD-8)
Comorbidities		
	COPD	J41-J47 (ICD-10); 490-493, 518 (ICD-8)
	Pulmonary Embolus	I26 (ICD-10); 450.99 (ICD-8)
	Heart failure	I50, I11.0 (ICD-10); 428.99 (ICD-8)
	Obesity (BMI)	E66 (ICD-10); 277 (ICD-8)