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Diabetes is not associated with the risk of rupture among patients with abdominal aortic aneurysms – results from a large Danish register-based matched case-control study from 1996-2016

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Abstract

Objectives: Numerous studies have shown a paradoxically protective effect of diabetes on the development and progression of abdominal aortic aneurysm (AAA). The aim of our study was to investigate whether the protective role of diabetes on AAA extends to rupture, given the presence of an AAA.

Design: Register-based case-control study

Materials: Patients with ruptured AAA (RAAA) matched 1:1 with patients undergoing elective surgery for AAA by sex, age, and year of diagnosis.

Methods: Multiple conditional logistic regression to estimate the odds ratio (OR) associating a diagnosis of diabetes with RAAA. No protocol is registered.

Results: From 1996 to 2016, we found 6293 potential people with RAAA. We excluded 898 people with an RAAA since no matching controls existed. This left us with 5395 cases in our study. The cases had a median age of 75, and 85.4% were men. Diabetes was defined by hospital diagnosis or the redemption of antidiabetics within one year. Comparing cases with controls and the presence of diabetes, we found a significant crude OR of 0.82 (95% confidence interval (CI) 0.71-0.95). When adjusting for confounders, OR increased to 0.97 (CI 0.83-1.14). Stratifying by age and year of diagnosis did not change the results markedly. OR associating RAAA with diabetes was significantly elevated in women (adjusted OR 1.82 (CI 1.17-2.81)). Of the 5395 cases, the overall 30-days mortality was 58% (n=3145). Using Cox regression, we found a crude hazard ratio (HR) of 1.06 (CI 0.93-1.22) of the 30-day mortality and having diabetes compared to not having diabetes. Adjusting for index year, male sex, and age had little effect on this estimate (HR 1.11 (CI 0.97-1.28)).

Conclusions: We observed no sign of diabetes protecting against RAAA, given the presence of an AAA. Furthermore, diabetes did not increase the risk of dying within 30 days of RAAA.

Keywords: abdominal aortic aneurysm, ruptured aortic aneurysm, diabetes mellitus, case-control study matched

What this paper adds

In this register-based study of 5395 cases with ruptured abdominal aortic aneurysm (RAAA) matched by sex, age and year of diagnosis with elective AAA repair, we rejected our hypothesis that diabetes protects against rupture of AAA, given the presence of a large AAA. Furthermore, diabetes did not increase the risk of dying within 30 days of RAAA.

Introduction

Abdominal aortic aneurysms (AAA) are a common disease with a prevalence of 2-4 % in people above the age of 60.[1] Known risk factors for the development of AAAs are age, male sex, smoking, hypertension, and atherosclerosis.[2] Ruptured abdominal aortic aneurysm (RAAA) carries high mortality of up to 72% and is the consequence of an untreated and often unknown AAA.[3] The estimated incidence of RAAA is 4.3-11 per 100.000/year.[3,4] The risk of RAAA increases with the size of the aneurysm.[5] Furthermore, smoking, hypertension and female sex are identified as risk factors for rupture.[5]

Diabetes is a well-known risk factor for atherosclerosis.[6] Surprisingly, numerous studies have shown a protective effect of diabetes on the development and progression of AAA.[7,8] The mechanism behind the protective effect is still unknown. We have previously shown that elevated levels of glycated haemoglobin are associated with a reduced growth rate of AAAs.[8] It is thus obvious to assume that diabetes may also protect against RAAA in people with already developed AAA.

Our study aimed to investigate whether the protective role of diabetes on AAAs extends to rupture, given the presence of an AAA. Our primary objective was to compare the prevalence of diabetes in all Danish residents with RAAA and with large AAAs. Secondly, to estimate the risk stratified by sex, and whether diabetes was associated with the 30-days postoperative mortality after rupture. We hypothesised that diabetes protects against rupture of AAAs and therefore is present in a lower prevalence among people with RAAA compared to people with large AAAs.

Materials and Methods

Using nationwide data sources, we performed a retrospective population-based case-control study of cases with RAAA and controls with elective AAA repair, analysing the association between diabetes and the risk of RAAA.

Data sources

We used four nationwide Danish data sources.

The National Patient Register comprises data regarding all hospitalisations in Denmark since 1977 and outpatient visits since 1995.[9] The hospitals report admissions, surgical procedures, and diagnoses, the latter using the International Classification of Diseases (ICD-8 from 1978-1993 and ICD-10 thereafter). Surgical procedures are recorded by the Nordic Classification of Surgical Procedures.

The National Prescription Register comprises data on all redeemed prescriptions at an individual user level since 1995.[10] The information includes substance and date among 46 variables in total. The indication is not recorded. Drugs are grouped according to the Anatomical Therapeutic

Chemical (ATC) classification system developed by the World Health Organization.[11] Our "List of included drugs and their ATC codes" are shown in the supplementary material.

The Civil Registration System contains daily updated information on addresses and emigration.[12] The Danish Register of Causes of Death holds data on date of death and causes of death. It is mandatory to fill out a certificate stating the immediate and the underlying cause of death.[13] Not every death in Denmark is followed by an autopsy.[14] Some 40-45% of the deaths occur in hospital settings, while 40-45% die at home or in a nursing home.[14]

The Danish national healthcare system is tax-supported and provides the entire Danish population (5.8 million in 2019) with free, unrestricted access to public health services and partial reimbursement for most prescribed drugs. All Danish residents are assigned a unique ten-digit civil registration number at birth or immigration, and this number enables unambiguous linkage across all healthcare registers at an individual level. Statistics Denmark, a governmental institution, performed anonymous linkage of the data.[15]

Cases and controls

This study included everyone with a diagnosis of RAAA or elective AAA repair in Denmark from 1996 to 2016.

Cases were all Danish residents with a diagnosis of RAAA (ICD10 DI713). Furthermore, data were obtained from the Register of Causes of Death to ensure that people whose cause of death was RAAA without any hospitalisations were included in this study. We excluded people surviving more than 30 days after the diagnosis of RAAA without undergoing any surgery within the first week as we assumed those to be misclassified as RAAA.
Controls were Danish residents with an AAA (ICD10 DI714) and the procedure code for open aortic repair, KPDG10-23 or endovascular repair, KPDQ10-21. The rationale for including people undergoing elective surgery for AAA as controls was, that since we wanted to analyse diabetes as a trigger of RAAA given the presence of an AAA, our controls should represent people in the population having AAAs large enough to potentially rupture. As the size is the very indication for AAA surgery, this choice of control group seemed appropriate. In Denmark, the ESVS guideline is followed regarding the management of AAAs.[2] For each case, we randomly selected one control matched by age, sex and year of diagnosis. We classified people as either case or control according to their first event of either RAAA or AAA-repair, if experiencing both.

Inclusion criterion

Patients were required to be at least 50 years.

Exclusion criteria

Any history of Marfan syndrome, Ehlers-Danlos syndrome, or other known aortic pathology (dissection or thoracoabdominal aortic aneurysm). We were not able to exclude thoracoabdominal aortic aneurysms until 1994 since ICD8 did not include this diagnosis. We excluded anyone with an

AAA-repair or RAAA before 1996. Lastly, we required at least ten years of look-back period for the cases and controls, thereby having a comprehensive diagnostic profile available. People who had immigrated within the last ten years before their index date were thus excluded. Our "List of included ICD-8 and ICD-10 codes" are shown in the supplementary material.

Exposure definition

The exposure was a diagnosis of diabetes. We defined diabetes as the first date of fulfilling either of two criteria: a) any hospital diagnosis of diabetes (ICD10 E10-11) or b) having redeemed at least two prescriptions on any antidiabetic (ATC-code A10) within the last year before the index date.

Confounders

In Denmark, hypertension is primarily diagnosed and managed in primary care, which is not captured by our sources of diagnosis data. Therefore, we based diagnosis of hypertension primarily on redeemed prescriptions on first-choice antihypertensive drugs: thiazide, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-II-receptor antagonists. Likewise, a diagnosis of chronic obstructive pulmonary disease (COPD) is based both on a hospital diagnosis of COPD or use of anti-COPD drugs: inhaled adrenergics, inhaled anticholinergics, inhaled glucocorticoids, inhaled selective beta-2-adrenoreceptor agonists, or xanthines. COPD is a proxy for smoking, which is a known risk factor for the development of AAA as well as RAAA.

The potential confounding effects of age, sex, and calendar year were controlled for using the matched design and conditional analysis. We selected potential confounders based on an automated empirical procedure. We selected a wide range of candidate variables listed in table 1. For each of these variables, we calculated the odds ratio (OR) associating RAAA and diabetes with or without the potential confounder included. If the OR changed by more than 5% in either direction by including the potential confounder, we included it as a covariate in our multivariable analysis. Thus, factors that empirically behaved as confounders were included in our model. These were: a diagnosis of hypertension and COPD, use of statins and platelet inhibitors.

Analyses

Conditional logistic regression was used to compute the OR associating a diagnosis of diabetes with RAAA while including the potential confounders as mentioned above as covariates in the model. Both crude and the adjusted ORs are presented with 95% confidence interval (CI).

A few pre-specified subgroup analyses were performed; a) the main result was analysed stratified by sex, age, and year of diagnosis b) the association between diabetes and 30-days mortality in the case group.

Cox regression was used to compute crude and adjusted hazard ratio (HR) of 30-day mortality and the association with diabetes. The analysis was adjusted for age, sex, calendar year and confounders using the empirical procedure.

As a post-hoc analysis, a quantitative bias analysis was performed to estimate the effect of smoking as an unmeasured confounder. Data from a Danish database regarding RAAA was used. We used the following input in the *biasepi* Stata package; association between smoking and rupture among unexposed 1.28, prevalence of smoking among exposed 0.27, prevalence of smoking among unexposed 0.41 and the prevalence of diabetes in table 1.

All analyses were performed using Stata® Release 15.1 (StataCorp, College Station, TX, USA).

Ethics

This project was approved by the Danish Data Protection Agency (14/40202). Approval from an ethics review board is not required in Denmark for register-based studies.[15]

Results

From 1996 to 2016, we found 6933 potential people with RAAA with a median age of 76 (IQR 70-82). We excluded 640 people diagnosed with RAAA who did not undergo any surgery and were alive after 30 days. Furthermore, we excluded 898 RAAAs who did not have a matching control since the eligible controls had a median age of 72 (IQR 67-77). This left us with 5395 cases in our study with a median age of 75, and 85.4% were men. We matched the cases 1:1 to people undergoing elective repair for an AAA. Of the cases, 6.7% had a known diagnosis of diabetes, with 8.0% for the controls. The use of antidiabetics within one year did not differ significantly in general or for any antidiabetic subgroup except for the use of insulin. The cases and controls differed in almost every aspect of the included data except for the diagnosis of congestive heart failure, renal disease and the use of metformin, sulphonylureas, and thiazide. Demographics are listed in Table 1 — furthermore, an extended version of all the eligible cases and controls in supplementary Table S3.

Given the presence of a large AAA, we found an inverse association between RAAA and diabetes, crude OR 0.82 (CI 0.71-0.95). However, when adjusting for confounders, the OR increased to 0.97 (CI 0.83-1.14).
Stratifying by sex increased the OR among women compared with men (Table 2). Stratifying by age and year of diagnosis did not change the OR significantly (Table 3).

Of the 5 395 cases, 3,079 (57.1%) underwent surgery (either outright repair [n=2902] or an exploratory laparotomy [n=177], Table 1). The overall 30-days mortality was 58% (n=3145 out of 5395), and of the people undergoing either aortic repair, the 30-day mortality was 34.8% (n=1,011 out of 2,902). Using Cox regression, we found a crude HR of 1.06 (CI 0.93-1.22) of the 30-day-mortality and diabetes compared to not having diabetes. Adjusting for index year, male sex and age, we found an adjusted HR of 1.11 (CI 0.97-1.28) of the 30-day mortality and diabetes.

In the post-hoc analysis, we found an OR of 0.86 of diabetes and RAAA adjusted for smoking. In comparison, the crude OR in the main analysis was 0.82.

Discussion

In this nationwide register-based study investigating the association between RAAA and diabetes, diabetes did not increase the risk of RAAA, given the presence of a large AAA. Stratifying by sex, we found that diabetes increased the risk of RAAA in women. Lastly, we found no significant association between diabetes and 30-day-mortality for people with RAAA.

Diabetes is well-known for its protective effect on the development and progression of AAA.[7] Regarding diabetes and the risk of rupture, there are conflicting results. Several studies found no association between diabetes and the risk of RAAA.[5,16-18] Gokani et al. studied people with RAAA and AAA and found no association between RAAA and diabetes.[5] Fillinger et al. demonstrated that matched RAAA and AAA (by diameter, sex and age) did not differ in respect to diabetes.[18] Da Silva et al. studied people both presenting with AAA and RAAA as well as in autopsy and found no association between diabetes and RAAA. Lastly, Lo et al. studied people with AAA or RAAA repair and found no significant adjusted OR for men or women with diabetes undergoing ruptured repair.[17]

On the other hand, Theivacumar et al. studied the risk of RAAA and diabetes.[19] They studied people with RAAA and AAA and found an increased prevalence of diabetes among AAA compared with RAAA.[19] A meta-analysis by Takagi et al. on nine studies found an overall reduced OR; the risk of RAAA was reduced by the presence of diabetes.[20] Interestingly, Nicholls et al. found that diabetes increases the risk of RAAA, but only in aneurysms <5 cm compared with larger aneurysms.[21] Due to the design of our study and the limitations of the registers, it was not possible to comment on the sizes of the aneurysms.Our cases and controls differed in respect to previous hospital-diagnosed comorbidity and previous use of drugs with an overall higher prevalence in the control group. This might not be representative as to conclude that people undergoing elective repair have more comorbidity; it could be underdiagnosed comorbidity in the case group. Furthermore, comorbid people, such as people with diabetes, more often attend examinations and consultations, resulting in a higher chance of incidental finding of their AAA. Moreover, at diagnosis of an AAA, best medical treatment is often initiated (acetylsalicylic acid, statins, blood pressure control and smoking cessation),[2] and this could reflect some of the diversity in the two groups.

We found that diabetes did not affect the 30-day-mortality of RAAA. Vanni et al. found no association between mortality and diabetes after RAAA,[4] neither did Katz et al.[22] nor Aziz et al.[23] On the other hand, Egorova et al. found increased long-term mortality for people with diabetes undergoing open repair, but not EVAR, [24] while Wanhainen et al. found that diabetes was associated with increased mortality.[25]

Our study has some strengths. This study is based on registers with complete coverage and continuously updated data on all Danish citizens, giving us a large sample compared with a single-centre study. Using registers eliminates the risk of recall bias among the study population and minimises the risk of selection bias. If an AAA is known, best medical treatment will often be

initiated, and as we merely focused on diabetes, we included both newly found aneurysms as well as aneurysms under surveillance. The proportion of people with diabetes not included in this study is likely to be small seeing we included people, treated only in the primary health care system, based on redeemed prescriptions of antidiabetics. We have no chance of identifying people with diet-controlled diabetes, however, we assume that the severity of their diabetes was minimal since it did not require antidiabetic therapy. We cannot eliminate the risk of information bias and misclassification of people who stopped using antidiabetics before 1995 as non-users.

Our study also has some potential limitations. We were not able to match all cases. We expected the case group to be older than the controls since everyone with an AAA cannot undergo elective repair. We cannot eliminate the risk of misclassification in the registers. Regarding the causes of death by RAAA for people dying outside hospitals diagnosed with RAAA, the diagnosis is mainly clinical and is often in people with a known AAA. In case of a suspicious, unexpected or unexplained death (no biochemical or imaging explanations), people do have an autopsy. The National Patient Register has been validated,[9,26] and we excluded people surviving more than 30 days without undergoing surgery to avid miscoded RAAA patients. Since this is a register-based study, we were not able to adjust for smoking other than using COPD as a proxy. Lastly, the diagnosis of hypertension was defined by the redemption of first-choice antihypertensive therapy, but many of these have multiple indications. However, we have no reason to think that misclassification would differ markedly between users and non-users of antihypertensives.

The search of the mechanism behind the protective effect continues, and metformin is of great interest. In a previous register-based case-control study nested in a population of people with diabetes, we found no effect of long-term use of metformin on the risk of RAAA.[27] On the other hand, Golledge et al. studied the use of metformin and AAA-related outcomes and found no initial difference in aneurysmal size, but the prevalence of AAA-related risk factors such as current smoking, hypertension and statin-use was increased among metformin-users compared to non-users.[28] Interestingly, Golledge et al. found that the incidence of AAA-related outcomes (surgery or RAAA-related mortality) was reduced in people with diabetes prescribed metformin compared to people with diabetes not prescribed metformin and also compared to people without diabetes.[28] Furthermore, the incidence was similar for people with diabetes not prescribed metformin as for people without diabetes.[28] Similarly, in another publication but in somewhat the same study population, Golledge et al. reported that people with diabetes prescribed metformin had a reduced growth of AAA compared to people with no diabetes, and that people with diabetes and no prescription of metformin did not experience the same reduced growth.[29]

Others have studied the association between metformin and development or growth of AAAs. Hsu et al. found in a nested case-control study among people with diabetes that the use of metformin, thiazolidinedione, and sulphonylureas were associated with a lower risk of developing AAA with both metformin and sulphonylureas having a dose-response effect.[30] Fujimura et al. studied metformin use and the growth of AAAs in people with diabetes in a small study and found that use of metformin was inversely associated with aneurysm enlargement.[31] Furthermore, the use of sulphonylureas was associated with increased enlargement of the AAA, and metformin reduced

aneurysms in their experimental mouse model.[31] Itoga et al. studied aneurysmal growth in people with diabetes and found that the use of metformin significantly decreased the annual growth rate of AAA by 0.2 mm/year.[32] Lastly, Thompson et al. studied the use of commonly prescribed medications and the potential effect on the growth rate of AAA and found that antidiabetics, in general, significantly reduced the growth rate of AAA.[33] When analysing the subgroup of antidiabetics, they, according to their conclusion, did not find any significant subgroup that differed. However, their supplementary table reports a significantly reduced growth for people using either metformin (biguanides) or sulphonylureas.[33]

In conclusion, we did not find that diabetes protects against rupture of AAA, given the presence of an AAA.

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Table 1. Demographics of ruptured abdominal aortic aneurysm (RAAA) and their corresponding controls (elective surgery for abdominal aortic aneurism (AAA)).

Characteristics	***Cases, RAAA***	***Controls, elective AAA surgery***	***P-value***
Total	5395	5395	
Male sex	4609 (85.4%)	4609 (85.4%)	
Age*	75 (69-80)	75 (69-80)	
Year of inclusion			
1996-2000	1385 (25.7%)	1385 (25.7%)	
2001-2005	1450 (26.9%)	1450 (26.9%)	
2006-2010	1292 (23.9%)	1292 (23.9%)	
2011-2016	1268 (23.5%)	1268 (23.5%)	
Preadmission hospital-diagnosed co-morbidity			
Diabetes†	363 (6.7%)	433 (8.0%)	P=0.011
Hypertension‡	2960 (54.9%)	3258 (60.4%)	P<0.000
Acute myocardial infarction	960 (17.8%)	1099 (20.4%)	P=0.001
Congestive heart failure	336 (6.2%)	296 (5.5%)	P=0.110
Peripheral arterial disease	404 (7.5%)	746 (13.8%)	P<0.000
Peripheral vascular disease	296 (5.5%)	534 (9.9%)	P<0.000
Cerebral vascular disease	968 (17.9%)	825 (15.3%)	P<0.000
Chronic obstructive pulmonary disease§	1162 (21.5%)	930 (17.2%)	P<0.000
Renal disease	188 (3.5%)	183 (3.4%)	P=0.833
Cancer‖	644 (11.9%)	862 (16.0%)	P<0.000
Preadmisison drugs			
Antidiabetics	353 (6.5%)	403 (7.5%)	P=0.065
Metformin	193 (3.6%)	222 (4.1%)	P=0.161
Sulphonylureas	178 (3.3%)	190 (3.5%)	P=0.560
Insulin	59 (1.1%)	91 (1.7%)	P=0.011
Anti-platelet therapy¶	2218 (41.1%)	2887 (53.5%)	P<0.000
Statins	1491 (27.6%)	2442 (45.3%)	P<0.000
Thiazide	1147 (21.3%)	1174 (21.8%)	P=0.542
Angiotensin converting enzyme inhibitor	1195 (22.2%)	1346 (24.9%)	P=0.001
Angiotensin-II-receptor-agonist	598 (11.1%)	801 (14.8%)	P<0.000
Calcium channel blockers	1430 (26.5%)	1646 (30.5%)	P<0.000
Beta blockers	1374 (25.5%)	1798 (33.3%)	P<0.000
Non-steroid anti-inflammatory drugs	1365 (25.3%)	1515 (28.1%)	P=0.001
Open surgery	2852 (52.9%)	4236 (78.5%)	
Endovascular aortic repair	50 (0.9%)	1159 (21.5%)	
Exploratory surgery	177 (3.3%)	-	

*Age presented as median, (interquartile range [IQR]). †[a]Diabetes: diagnosis or use of antidiabetics one year before index date. ‡Diagnosis or antihypertensive therapy: thiazide, calcium channel

blockers, ACE-inhibitors, or AT2-antagonists. §Diagnosis or anti-COPD therapy: inhaled adrenergics, anticholinergics, glucocorticoids, selective beta-2-adrenoreceptor agonists, or xanthines. ‖Except from skin cancer. ¶Acetylsalicylic acid, clopidogrel or dipyridamole

Table 2. Main and subgroup analysis. Odds ratio of diabetes and ruptured abdominal aortic aneurysm. Adjusted for the variables in the table. Confidence intervals in brackets.

Odds ratio	***Main analysis***	***Men***	***Women***
Crude OR	0.82 (0.71-0.95)	0.75 (0.64-0.88)	1.42 (0.95-2.13)
Adjusted OR			
Diabetes	0.97 (0.83-1.14)	0.88 (0.74-1.04)	1.82 (1.12-2.81)
Hypertension	0.96 (0.88-1.04)	0.94 (0.86-1.03)	1.05 (0.83-1.32)
COPD	1.30 (1.17-1.44)	1.26 (1.13-1.41)	1.48 (1.14-1.92)
Use of statins	0.39 (0.35-0.43)	0.40 (0.36-0.45)	0.32 (0.24-0.43)
Use of platelet inhibitors	0.80 (0.73-0.88)	0.82 (0.75-0.91)	0.68 (0.54-0.87)

OR, odds ratio. COPD, chronic obstructive pulmonary disease

Table 3. Subgroup analysis stratified by age and year: odds ratio of diabetes and ruptured abdominal aortic aneurysm. Confidence intervals in brackets.

Stratified by	***Crude OR***	***Adjusted OR****
Age		
Age < 60	OR 1.50 (CI 0.67-3.34)	OR 1.48 (CI 0.63-3.50)
Age 60-69	OR 0.71 (CI 0.52-0.97)	OR 0.91 (CI 0.65-1.27)
Age 70-79	OR 0.82 (CI 0.66-1.02)	OR 0.96 (CI 0.77-1.21)
Age 80+	OR 0.86 (CI 0.64-1.15)	OR 0.97 (CI 0.72-1.32)
Year		
1996-2000	OR 1.02 (CI 0.70-1.49)	OR 0.99 (CI 0.68-1.46)
2001-05	OR 1.06 (CI 0.76-1.49)	OR 1.19 (CI 0.84-1.69)
2006-10	OR 0.73 (CI 0.55-0.96)	OR 0.92 (CI 0.68-1.25)
2011-16	OR 0.72 (CI 0.56-0.92)	OR 0.95 (CI 0.72-1.24)

OR, odds ratio. *Adjusted for hypertension (or use of antihypertensive therapy), chronic obstructive pulmonary disease, COPD, (or use of anti-COPD therapy), use of statins, and platelet inhibitors

Supplementary material

Table S1. List of included ICD-8 and ICD-10 codes.
International Classification of Diseases (ICD)-10 and ICD-8 codes used to identify people with ruptured abdominal aortic aneurysms and abdominal aortic aneurysms, to exclude people without aneurysm and to identify comorbidities.

	ICD 8	***ICD 10***
Ruptured abdominal aortic aneurysm	441.21	I713, I718
Abdominal aortic aneurysm	441.20, 441.29	I714
Exclusion		
Aortic dissection	441.09	I710
Thoracic or thoracoabdominal aortic aneurysm	441.10, 441.11, 441.19	I711-712, I715-716
Marfan syndrome	759.80	Q874
Ehlers–Danlos syndrome	757.24	Q796
Comorbidities		
Diabetes mellitus	249, 250	E10-11
Hypertension		I10-13, I15
Myocardial infarction	410	I21, I23, I241
Congestive heart failure	391.29, 427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50, I090, I110, I130, I132
Peripheral vascular disease	440, 442, 443, 444, 445	I70, I72-74, I77
Cerebrovascular disease	430–438	I60–I69, G45-46
Chronic obstructive pulmonary disease	491–492	J41–44
Moderate to severe renal disease	403, 404, 580–583, 584, 590.09, 593.19, 753.10-11, 753.19, 792	I12-13, N00-01, N03-05, N07, N11, N14, N16–19, Q61
Any cancer except from skin cancer	140-172,174-207	C00-C43, C45-96

Table S2. List of included drugs and their ATC codes.
Anatomical Therapeutic Chemical (ATC) prescription codes used to identify preadmission drugs

ATC	*Drug class/name*	*Note*
A10	Antidiabetics	
A10A	Insulins	Change in subgroups in 1997
A10B	Metformin	
A10BD02	Metformin & sulfonamides	
A10BD03	Metformin & rosiglitazone	
A10BD05	Metformin & pioglitazone	
A10BD07	Metformin & sitagliptin	
A10BD08	Metformin & vildagliptin	
A10BD10	Metformin & saxagliptin	
A10BD11	Metformin & linagliptin	
A10BD13	Metformin & alogliptin	
A10BD15	Metformin & dapagliflozin	
A10BD16	Metformin & canagliflozin	
A10BB	Sulphonylureas	
B01AC04	Clopidogrel	
B01AC06	Acetylsalicylic acid	
B01AC07	Dipyridamole	
C03A, C03AB, C03AX, C03EA01	Thiazide, plain and combinations	
C07	Beta blocking agents, plain and combinations	
C08	Calcium channel blockers, plain and combinations	Combination with diuretics changed in 1996 from C02LI
C09A-B	Angiotensin-converting enzyme inhibitors, plain and combinations	C02EA/C02LM before 1996
C09C-D	Angiotensin II antagonists, plain and combinations	Losartan changed in 1996 from C02EX01
C10AA	Statins	
H02	Corticosteroids for systemic use	
M01A	Non-steroidal anti-inflammatory products	
R03AC	Selective beta-2-adrenoreceptor agonists	
R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	
R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	
R03BA	Inhaled glucocorticoids	
R03BB	Inhaled anticholinergics	
R03CC	Selective beta-2-adrenoreceptor agonists	
R03DA	Xanthines	

Table S3. Demographics of all eligible patients with ruptured abdominal aortic aneurysm or abdominal aortic aneurysm with elective repair, 1996-2016. 14.3% of the cases with rupture had no match.

Characteristics	*RAAA matched*	*AAA matched*	*RAAA all eligible cases*	*AAA all eligible controls*
Total	5395	5395	6293	7001
Male sex	4609 (85.4%)	4609 (85.4%)	5045 (80.2%)	5876 (83.9%)
Age*	75 (69-80)	75 (69-80)	76 (70-82)	72 (67-77)
Year of inclusion				
1996-2000	1385 (25.7%)	1385 (25.7%)	1659 (26.4%)	1133 (16.2%)
2001-2005	1450 (26.9%)	1450 (26.9%)	1710 (27.2%)	1297 (18.5%)
2006-2010	1292 (23.9%)	1292 (23.9%)	1442 (22.9%)	1940 (27.7%)
2011-2016	1268 (23.5%)	1268 (23.5%)	1482 (23.5%)	2631 (37.6%)
Preadmission hospital-diagnosed co-morbidity				
Diabetes†	363 (6.7%)	433 (8.0%)	399 (6.3%)	661 (9.4%)
Hypertension‡	2960 (54.9%)	3258 (60.4%)	3442 (54.7%)	4429 (63.3%)
Acute myocardial infarction	960 (17.8%)	1099 (20.4%)	1091 (17.3%)	1340 (19.1%)
Congestive heart failure	336 (6.2%)	296 (5.5%)	385 (6.1%)	363 (5.2%)
Peripheral arterial disease	404 (7.5%)	746 (13.8%)	470 (7.5%)	904 (12.9%)
Peripheral vascular disease	296 (5.5%)	534 (9.9%)	347 (5.5%)	782 (11.2%)
Cerebral vascular disease	968 (17.9%)	825 (15.3%)	1150 (18.3%)	1052 (15.0%)
Chronic obstructive pulmonary disease§	1162 (21.5%)	930 (17.2%)	1343 (21.3%)	1291 (18.4%)
Renal disease	188 (3.5%)	183 (3.4%)	215 (3.4%)	245 (3.5%)
Cancer‖	644 (11.9%)	862 (16.0%)	770 (12.2%)	1155 (16.5%)
Preadmisison drugs				
Antidiabetics	353 (6.5%)	403 (7.5%)	387 (6.1%)	628 (9.0%)
Metformin	193 (3.6%)	222 (4.1%)	212 (3.4%)	444 (6.3%)
Sulphonylureas	178 (3.3%)	190 (3.5%)	192 (3.1%)	224 (3.2%)
Insulin	59 (1.1%)	91 (1.7%)	65 (1.0%)	127 (1.8%)
Anti-platelet therapy¶	2218 (41.1%)	2887 (53.5%)	2607 (41.4%)	4130 (59.0%)
Statins	1491 (27.6%)	2442 (45.3%)	1636 (26.0%)	4078 (58.2%)
Thiazide	1147 (21.3%)	1174 (21.8%)	1370 (21.8%)	1535 (21.9%)
Angiotensin converting enzyme inhibitor	1195 (22.2%)	1346 (24.9%)	1356 (21.5%)	2021 (28.9%)
Angiotensin-II-receptor-agonist	598 (11.1%)	801 (14.8%)	689 (10.9%)	1184 (16.9%)
Calcium channel blockers	1430 (26.5%)	1646 (30.5%)	1646 (26.2%)	2251 (32.2%)
Beta blockers	1374 (25.5%)	1798 (33.3%)	1577 (25.1%)	2589 (37.0%)
Non-steroid anti-inflammatory drugs	1365 (25.3%)	1515 (28.1%)	1572 (25.0%)	1950 (27.9%)
Open surgery	2852 (52.9%)	4236 (78.5%)	3070 (48.8%)	5306 (75.8%)
Endovascular aortic repair	50 (0.9%)	1159 (21.5%)	55 (0.9%)	1695 (24.2%)
Exploratory surgery	177 (3.3%)	-	199 (3.2%)	-

RAAA, ruptured abdominal aortic aneurysm, AAA, abdominal aortic aneurysm. *Age presented as median, (interquartile range [IQR]). †[a]Diabetes: diagnosis or use of antidiabetics one year before index date. ‡Diagnosis or antihypertensive therapy: thiazide, calcium channel blockers, ACE-

inhibitors, or AT2-antagonists. §Diagnosis or anti-COPD therapy: inhaled adrenergics, anticholinergics, glucocorticoids, selective beta-2-adrenoreceptor agonists, or xanthines. ‖Except from skin cancer. ¶Acetylsalicylic acid, clopidogrel or dipyridamole