Nationwide Study on the Risk of Abdominal Aortic Aneurysms in Patients With Psoriasis

Usman Khalid, Alexander Egeberg, Ole Ahlehoff, Laerke Smedegaard, Gunnar Hilmar Gislason, Peter Riis Hansen

Objective—Abdominal aortic aneurysm (AAA) is a complex multifactorial disease associated with a high morbidity and mortality. Increased inflammation including T-helper 17 cell–mediated effects has been implicated in AAA pathogenesis. Psoriasis is considered to be a T-helper 17-driven chronic inflammatory disease and in view of potentially overlapping inflammatory mechanisms, we investigated the risk of AAA in patients with psoriasis in a nationwide cohort.

Approach and Results—The study comprised all Danish residents aged ≥18 years followed up from January 1, 1997, until diagnosis of AAA, December 31, 2011, migration or death. Information on comorbidity, concomitant medication, and socioeconomic status was identified by individual-level linkage of administrative registers. Incidence rates for AAA were calculated and incidence rate ratios adjusted for age, sex, comorbidity, medications, socioeconomic status, and smoking were estimated in Poisson regression models. A total of 5,495,203 subjects were eligible for analysis. During the study period, we identified 59,423 patients with mild psoriasis and 11,566 patients with severe psoriasis. The overall incidence rates of AAA were 3.72, 7.30, and 9.87 per 10,000 person-years for the reference population (23,696 cases), mild psoriasis (240 cases), and severe psoriasis (50 cases), respectively. The corresponding adjusted incidence rate ratios for AAA were increased in patients with psoriasis with incidence rate ratios of 1.20 (95% confidence interval, 1.03–1.39) and 1.67 (confidence interval, 1.21–2.32) for subjects with mild and severe disease, respectively.

Conclusions—In a nationwide cohort, psoriasis was associated with a disease severity-dependent increased risk of AAA. The mechanisms and consequences of this novel finding require further investigation. (Arterioscler Thromb Vasc Biol. 2016;36:1043-1048. DOI: 10.1161/ATVBAHA.116.307449.)

Key Words: aortic aneurysm, abdominal | cardiovascular diseases | inflammation | psoriasis | Th17 cells

Abdominal aortic aneurysm (AAA) is a complex multifactorial disease associated with increased morbidity and mortality.¹² The prevalence of AAA increases with age and affects ≤2% of men aged ≥65 years.² Emerging evidence suggests that AAA is a focal representation of a systemic disease with a distinct inflammatory component, rather than a mere consequence of atherosclerosis.²⁻⁷ Chronic inflammation in the aortic wall is crucial for AAA formation, and recent evidence has shown striking similarities between central inflammatory pathways involved in AAA and those occurring in psoriasis, a prevalent chronic inflammatory disease, with apparent pivotal roles of T-helper-17 cells and interleukin-17 in both conditions.⁸⁻¹² In view of these overlapping inflammatory pathways and an established increased risk of atherothrombotic disease in patients with psoriasis, it seems plausible that patients with psoriasis may also have increased risk of AAA.¹³,¹⁴ Although limited case series have reported an increased risk of AAA in some other autoimmune disorders including rheumatoid arthritis and systemic lupus erythematosus, no large-scale studies have explored the potential association between AAA and psoriasis.¹⁵,¹⁶ Therefore, we conducted a retrospective cohort study by using Danish national registers to investigate the risk of AAA in patients with psoriasis compared with the general population.

Materials and Methods
Materials and Methods are available in the online-only Data Supplement.

Results
Baseline Characteristics
From January 1, 1997, to December 31, 2011, a total of 5,495,203 eligible subjects were included in the study. Subjects...
with a history of psoriasis (n=14,352) and AAA (n=5,318) were excluded at the study start. During follow-up, we identified a total of 59,423 subjects with mild psoriasis and 11,566 with severe psoriasis. These patients were compared with the reference population of 5,404,544 individuals. During the study period, 23,986 patients were diagnosed with AAA. A flowchart of the study population is illustrated in the Figure, and baseline characteristics for the study population are presented in Table 1.

**Risk of AAA in Patients With Psoriasis**

The results showed a disease–severity–dependent association between psoriasis and AAA (Table 2). The overall incidence rates (IRs) of AAA were 3.72, 7.30, and 9.87 per 10,000 person-years for the reference population (23,696 cases [mean follow-up, 14.4 years]), mild psoriasis (240 cases [mean follow-up, 5.7 years]), and severe psoriasis (50 cases [mean follow-up, 5.7 years]; Table 3). The multivariable and time-dependent Poisson regression analyses, adjusted for age, sex, and calendar year showed increased risk of AAA in patients with psoriasis when compared with the reference population with IR ratio (IRR) of 1.36 (95% confidence interval [CI], 1.19–1.54) and IRR 2.00 (95% CI, 1.51–2.64) for mild and severe psoriasis, respectively. The risk associated with psoriasis remained significant in the fully adjusted statistical models controlling for age, sex, calendar year, comorbidity, concomitant medications, socioeconomic status, and smoking history with IRRs of 1.20 (95% CI, 1.03–1.39) for mild and 1.67 (CI 1.21–2.32) for severe psoriasis (Table 2).

**Discussion**

In this retrospective cohort study of the Danish population, we found an increased risk of AAA in patients with psoriasis, independent of traditional cardiovascular risk factors. Notably, the observed risk increased with increasing severity of psoriasis. The results were supported by the sensitivity analyses. To our knowledge, this is the first study to assess the risk of AAA in patients with psoriasis in a nationwide setting. These results may warrant the need for increased awareness on higher risk of AAA in patients with severe psoriasis.

Psoriasis is a chronic immune-mediated inflammatory disease associated with cardiometabolic comorbidities. Although it is well-established that psoriasis is an independent risk factor for atherosclerotic disease and persistent systemic inflammation is thought to play a contributory role, the risk of AAA in patients with psoriasis has not previously been investigated. AAA is a common and often asymptomatic disease characterized by progressive localized dilation of the abdominal aorta with risk of rupture and fatal outcomes. Several studies have found a positive correlation between cardiovascular disease and AAA, and there is significant overlap of risk factors for atherosclerotic and AAA (eg, male sex, smoking, and a family history) with frequent coexistence of the 2 diseases. However, the traditional view that atherosclerotic disease is the primary driving factor for the development of AAA has been reviewed, and contemporary...
data suggest that atherosclerosis is not the usual factor for AAA. Indeed, the pathogenesis and progression of AAA are considered to be a multifactorial process that comprises, for example, inflammation, matrix degradation, thrombosis, increased biomechanical aortic wall stress, and a host of associated mediator molecules. Evidence has indicated that systemic levels of inflammatory markers, eg, C-reactive protein and tumor necrosis factor-α, are increased in patients with AAA and other chronic inflammatory diseases including psoriasis. Furthermore, a central pathogenic role for tumor necrosis factor has been suggested for both AAA and psoriasis, and more specifically, recent studies have indicated that T-helper-17 cells and interleukin-17 can be of pivotal importance in the inflammatory pathogenesis of AAA, as was established long ago for psoriasis. Also, hemodynamic forces and segmental aortic stiffening probably contribute to AAA development, and in patients with psoriasis, increased arterial stiffness is associated with systemic inflammation. Anti–tumor necrosis factor therapy can attenuate AAA formation in a murine model, and in subjects with psoriasis, these agents decrease aortic stiffness and endothelial dysfunction along with their amelioration of psoriatic lesions. Taken together, these data support the notion that shared inflammatory mechanisms contribute to the psoriasis severity-dependent increased risk of AAA observed in the current study. This finding clearly requires independent replication and the clinical consequences are unclear at present, eg, whether patients with psoriasis should undergo increased ultrasonic screening for AAA, and whether anti–tumor necrosis factor and other anti-inflammatory treatment of psoriasis may reduce the risk of AAA.

### Limitations and Strengths

When interpreting our findings, some limitations and strengths should be considered. Register-based follow-up

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Reference Population (n=5,404,544)</th>
<th>Mild Psoriasis (n=59,423)</th>
<th>Severe Psoriasis (n=11,566)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) age, y</strong></td>
<td>41.0 (19.7)</td>
<td>43.9 (16.6)</td>
<td>42.7 (15.1)</td>
</tr>
<tr>
<td><strong>Men (%)</strong></td>
<td>2,665,667 (49.3)</td>
<td>28,971 (48.7)</td>
<td>5,447 (47.1)</td>
</tr>
<tr>
<td><strong>Mean (SD), socioeconomic status</strong></td>
<td>2.0 (1.4)</td>
<td>2.5 (1.3)</td>
<td>2.5 (1.2)</td>
</tr>
<tr>
<td><strong>Smoking ever (%)</strong></td>
<td>515,021 (9.5)</td>
<td>8,419 (14.2)</td>
<td>2,128 (18.4)</td>
</tr>
</tbody>
</table>

#### Comorbidity (%)

- **Vascular disease** 37,753 (0.7) 431 (0.7) 67 (0.6)
- **Atrial fibrillation** 28,125 (0.5) 235 (0.4) 51 (0.5)
- **Diabetes mellitus** 83,155 (1.5) 968 (1.6) 233 (2.0)
- **Thromboembolism** 43,077 (0.8) 370 (0.6) 70 (0.6)
- **Hypertension** 178,702 (3.3) 2,468 (4.2) 44 (3.8)

#### Medications (%)

- **β-Blockers** 140,382 (2.6) 2,141 (3.6) 363 (3.1)
- **ACEIs/ARBs** 121,029 (2.2) 1,743 (2.9) 309 (2.7)
- **Acetylsalicylic acid** 159,816 (3.0) 1,603 (2.7) 264 (2.3)
- **Loop diuretics** 132,592 (2.5) 1,090 (1.8) 270 (2.3)
- **Vitamin K antagonists** 21,560 (0.4) 216 (0.4) 44 (0.4)
- **Digoxin** 65,223 (1.2) 432 (0.7) 69 (0.6)
- **Cholesterol-lowering drugs** 28,808 (0.5) 525 (0.9) 98 (0.9)
- **Systemic glucocorticoids** 91,121 (1.7) 1,156 (2.0) 378 (3.3)

ACEI indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin 2 receptor blocker.

### Table 2. Risk of AAA Associated With Psoriasis Presented as Incidence Rate Ratios with 95% CIs

<table>
<thead>
<tr>
<th></th>
<th>Incidence Rate Ratio for AAA</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age, sex, and calendar year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild psoriasis</td>
<td>1.36</td>
<td>1.19–1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>2.00</td>
<td>1.51–2.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, sex, calendar year, comorbidity, medication, socioeconomic status, and smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild psoriasis</td>
<td>1.20</td>
<td>1.03–1.39</td>
<td>0.017</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.67</td>
<td>1.21–2.32</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted for age, sex, and calendar year; censored for subjects who developed abdominal atherosclerotic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild psoriasis</td>
<td>1.36</td>
<td>1.20–1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.92</td>
<td>1.46–2.52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurysm; and CI, confidence interval.
studies are susceptible to changes in registration of the data over time, eg, International Classification of Diseases coding practices. However, in Danish National Patient Registry, established International Classification of Diseases codes have been used since 1978 and the Danish Health Authorities and specialty associations continuously monitor registration practices, with no major alterations or administrative changes of coding practices relevant to our study occurring during the 1997 to 2011 study period.38,39 Increased diagnostic activity after the diagnosis of psoriasis increases the risk of surveillance bias and such effects may not have been captured by our adjustments for important covariates including concomitant medication and comorbidity, and even in the sensitivity analyses, respectively. Moreover, we used the third hospital diagnosis as classification of severe psoriasis, and although results of our sensitivity analyses (severe psoriasis classified by first hospital diagnosis) generally were in agreement with our primary findings, the validity of hospitalization numbers for assessment of psoriasis severity has not been formally investigated.

AAA is often asymptomatic and discovered incidentally as a result of screening. Of note, our group has previously validated the AAA diagnoses used in the present study with an overall predictive value of 89%. In 90% of these cases, the diagnoses were established by imaging techniques including ultrasound examination and computer tomographic scans.40 Nevertheless, an element of residual confounding related to our approach with identification of exposures and end points based on hospital diagnoses cannot be ruled out. Also, our method of identifying mild psoriasis by the use of claimed prescriptions of vitamin D derivatives cannot be extrapolated to patients who may have received other topical therapies or ultraviolet phototherapy, in private dermatology clinics. However, we have validated this method in a previous study, where we assessed hospital records of 155 randomly selected patients, who were diagnosed with psoriasis by a hospital dermatologist. In this validation analysis, vitamin D derivatives were found to be the preferred first-line treatment for 73% of the patients with psoriasis.41 Although the results cannot be generalized to the patients who were not captured by our criteria for mild psoriasis, these patients would have been misclassified as controls and hence bias our estimates toward the null hypothesis. Also, given the large sample size, the impact of such misclassification is likely to be small.41 Furthermore, the registries used in the study lacked information on important clinical parameters such as smoking status. Therefore, as a proxy for smoking, we used information on diagnoses of smoking, tobacco use, chronic obstructive lung disease, lung cancer, and pharmacological treatment for smoking cessation. Although this method is likely to have captured some of the effect in the analyses, it is an indirect approximation of smoking status and the results should be interpreted accordingly.42 Finally, the Danish population is primarily of Northern European decent, and extrapolation to other nationalities should be performed with caution. Because of the observational design of our study, we cannot determine causality.

The study strengths include use of nationwide prospectively recorded data with limited loss to follow-up, adjustment for important covariates, and use of validated measures of exposures and outcomes, respectively. The Danish tax financed healthcare system ensures free access to medical care to all citizens, which minimized the risk of selection bias attributed to, eg, age, sex, health insurance, and socioeconomic status. Also, the exclusion of subjects with a history of psoriasis and AAA at the baseline provided a more precise allocation of time at risk.

**Conclusion**

The results of the present study indicate a disease severity-dependent increased risk of AAA in patients with psoriasis. These findings add importantly to current evidence of psoriasis as a clinically relevant risk factor for cardiovascular disease and may require increased focus on heightened risk of AAA in patients with psoriasis. Further research is warranted to delineate the mechanisms and consequences of this association.

**Acknowledgments**

Drs Khalid, Ahlehoff, Gislason, and Hansen conceived and designed the experiments. Drs Khalid, Egeberg, Gislason, and Hansen analyzed the data. Drs Khalid, Ahlehoff, and Hansen wrote the article. Drs Khalid, Egeberg, Ahlehoff, Smedegaard, Gislason, and Hansen revision of article for critical contents. Supervision was done by Drs Hansen, Ahlehoff, and Gislason. All authors approved the final article.

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**Disclosures**

Dr Ahlehoff had received honoraria as speaker for Abbott, Pfizer, and Janssen-Cilag. Dr Hansen had received honoraria as speaker for Abvie and MSD. Dr Gislason had received research grants from Bayer, Pfizer, AstraZeneca Boehringer-Ingelheim and Bristol Meyer Squibb (BMS) and speaker honoraria from Pfizer, AstraZeneca, and BMS. Dr Egeberg was supported by a grant from Pfizer. The other authors report no conflicts.

**References**


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**Table 3.** IRs With 95% CIs Per 10 000 Person-Years of AAA and Number of Events

<table>
<thead>
<tr>
<th></th>
<th>Reference Population</th>
<th>Mild Psoriasis</th>
<th>Severe Psoriasis</th>
<th>Overall IR (CIs) for AAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events (n)</td>
<td>23696</td>
<td>240</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

AAA indicates abdominal aortic aneurism; CI, confidence interval; and IR, incidence rate.
Abdominal Aortic Aneurysms and Psoriasis


The present study attempts to investigate the risk of abdominal aortic aneurysms in patients with psoriasis by using nationwide data. The results show that psoriasis severity is linked with increased risk of abdominal aortic aneurysms independent of the conventional risk factors. These data add significantly to the foregoing evidence with respect to the relationship of cardiovascular disease and psoriasis. The results extend the need of further research to understand the molecular mechanisms of how skin severity promote vascular inflammation and eventually lead to augmented cardiovascular disease burden in these patients. Nevertheless, these results may warrant the need for increased awareness on higher risk of aortic abdominal aneurysms in patients with severe psoriasis.

Significance
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METHODS

Data sources
In Denmark, each citizen is allocated a permanent civil registration number that allows unambiguous linkage of data across the respective administrative registers employed in the present study. We retrieved data on all dispensed drug prescriptions from Danish pharmacies (recorded since 1995 according to Anatomical Therapeutical Chemical classification system) from the National Prescription Registry. This register holds information on dispensing date, strength of the drug, quantity dispensed, and the affiliation of the physician dispensing the prescription. Partial reimbursement of drug expenses by the government ensures complete and accurate registration. We obtained information on morbidity from the Danish National Patient Register, in which data on all in- or outpatient hospital visits, diagnoses, and procedures are recorded according to the International Classification of Diseases (ICD) code (the 8th ICD revision until 1994 and the 10th ICD revision from 1994 and onwards). For administrative reasons the 9th ICD revision was never used in Denmark. Information on age, gender, and vital status were obtained from the Central Population Register, which records all deaths within 14 days. An age-standardized index of socioeconomic status was defined as the individual average yearly gross income during a 5-year period prior to inclusion in the study. The guidelines for cohort studies as defined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations, were followed to conduct the present study.

Study population
The study cohort comprised all Danish citizens aged ≥18 years and subjects were included in the study on January 1, 1997 or on the subsequent day that they reached 18 years of age. These individuals were then followed until December 31, 2011, the diagnosis of AAA, migration or death, whichever came first, respectively. Patients with psoriasis were identified by claimed prescriptions of topical vitamin D derivatives (ATC D05AX). The second claimed prescription was used as the psoriasis index date to ensure persistent medical treatment. Patients were classified as severe psoriasis at the time of their third hospitalisation for psoriasis (ICD-10 L40) or psoriatic arthritis (ICD-10 M070-M073). We have previously validated this identification and classification method for psoriasis and psoriasis severity.

Pharmacotherapy and comorbidity
Baseline treatment was defined by dispensed prescriptions up to 6 months prior to study inclusion with the following medications: beta-blockers (ATC C07), angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers (ACEI/ARB) (ATC C09), vitamin K antagonists (ATC B01AA), digoxin (ATC C01AA), acetylsalicylic acid (ATC B01AC06), cholesterol-lowering drugs (ATC C10A), and glucocorticoids (ATC H02AB). The following comorbidity was assessed: atrial fibrillation (ICD-10 code I48, and ICD-8 code 4279), diabetes (ICD-10 codes E10-E14, and ICD-8...
codes 250), hypertension (ICD-10 codes I10-I15), vascular disease (ICD-10 codes I21-I22, I70, and ICD-8 codes 410,440), and thromboembolism (ICD-10 codes I26, I63, I64, I74, G458, G459, and ICD-8 codes 433-438, 444, 450). Hypertension was identified by hospital diagnoses for hypertension (ICD-10 codes I110-I115, and ICD-8 codes 400-404), or if patient was treated with at least two of the following anti-hypertensive agents inside a 90-day period after receiving the diagnosis: alpha-adrenergic blockers, non-loop diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors. Diabetes was defined by either hospital diagnoses for diabetes (ICD-8 code 250, and ICD-10 codes E10-E14), or initiation of glucose lowering agents (ATC code A10). Smoking history was defined as claimed prescriptions of drugs used for smoking cessation, diagnoses of smoking, tobacco use, chronic obstructive pulmonary disease, lung cancer, or treatments and/or therapeutic interventions aimed at smoking cessation. This method to track smoking history has been described previously. (See the Supplementary table with the pertinent diagnoses and procedure codes).

Outcome

The outcome of interest was defined as the first diagnosis of AAA (ICD-10 codes DI71.4, DI71.6, DI71.9, DI71.9A, DI79.0, and ICD-8 code 441). These diagnostic codes for AAA have recently been validated with an overall positive predictive value of 89%.

Statistical analysis

All statistical analyses were performed by using SAS statistical software version 9.2 (SAS Institute Inc. Cary, NC, USA) and STATA software version 11.2 (StataCorp, College Station, TX, USA). Baseline characteristics were presented as frequencies and percentages for categorical variables and as means with standard deviations for continuous variables. Differences between groups were analysed using unpaired t tests and χ² tests, as appropriate. Psoriasis was included as time-dependent variable and events occurring before the diagnosis of psoriasis were therefore allocated to the reference population. Likewise, patients contributed risk-time in the mild psoriasis group until they (if appropriate) were diagnosed with severe psoriasis. In addition to follow-up, age and calendar year (divided in bands of 1-year periods after January 1, 1997) were included as timescales. Multivariable Poisson regression models adjusted for age, gender, calendar year, comorbidity, concomitant medications, socioeconomic status, and smoking history were fitted to derive incidence rate ratios (IRRs). Incidence rates were calculated as number of new events per 10,000 person-years at risk. For all analyses, a two-tailed p value below 0.05 was considered statistically significant including when testing for interaction and likewise 95% confidence intervals (CIs) were also presented. The model assumptions, including absence of interaction between covariates were tested and found to be valid.
Sensitivity analyses

To address the impact of bias caused by increased health care consumption associated with our definition of psoriasis, we performed analyses with less conservative inclusion criteria for psoriasis. According to these altered criteria, patients with psoriasis were identified by their first claimed prescription for topical vitamin D derivatives and classified with severe psoriasis at the time of their first in- or outpatient hospitalization with the diagnosis of psoriasis. This alternative definition of psoriasis is associated with less frequent health care visits compared with psoriasis diagnosis and severity definition used in the primary analyses. To further evaluate the potential influence of detection bias in our cohort, we performed analyses (identical to our primary analyses) where exposure was a diagnosis of idiopathic osteoarthritis of the knee (ICD-10 codes M17.0, M17.5, M17.9, and ICD-8 code 713.0), as osteoarthritis is primarily a non-inflammatory disease with no apparent relationship with psoriasis which, however, is likely to lead to increased medical surveillance.

Atherosclerotic disease shares similarities with AAA and has been considered as contributory cause of AAA. Moreover, asymptomatic AAA is often discovered incidentally and therefore more frequently diagnosed in patients with cardiovascular disease who are likely to undergo increased medical evaluation. To determine the importance of such bias we conducted a sensitivity analysis where subjects with atherosclerotic disease, i.e., atherosclerotic heart disease (ICD-10 code I251), myocardial infarction (ICD-10 codes I21, I22), stroke (ICD-10 codes I61, I63, I64), and atherosclerotic vascular disease (ICD-10 code I70), were excluded from the study. Also, in this analysis patients who developed atherosclerotic disease throughout the study period were continuously censored. Moreover, to ensure an accurate registration of covariates, which could change over time, we did a supplementary sensitivity analysis where we continuously updated comorbidity (see above) during follow up. To further address the issue of potential detection bias, we performed analyses to examine risk of ruptured AAA (ICD-10 codes DI713, DI715, and ICD-8 codes 441D) in patients with psoriasis, and estimated incidence rates per 10,000 person-years of undergoing surgery for AAA (procedure codes KPCG, KPCP, KPCQ, KPDG, KPDN, KPDP, KPDQ, KFCD, and KPDC10). These procedure codes for surgery for AAA have been validated in the Danish National Vascular Registry to have a reproducibility of 90-100%.

Ethics

The Danish Data Protection Agency approved the present study (ref. 2007-58-0015, int. ref: GEH-2014-018), and data was encrypted and rendered anonymous by Statistics Denmark. Retrospective observational studies do not require ethical approval in Denmark.
Reference list


