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Editor's Choice – High Heritability of Liability to Abdominal Aortic Aneurysms: A Population Based Twin Study

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WHAT THIS PAPER ADDS

This study includes the largest number of twins affected with abdominal aortic aneurysm (AAA). The results support screening of co-twins (and other siblings) of twins with AAA as their risk of AAA was found to be very high (12% in dizygotic (DZ), twins and 30% in monozygotic (MZ) twins). This study did not include investigations of the risk of AAA among other siblings of AAA-affected twins, but it is expected that the risk would be comparable with that of DZ twins.

Objective: First degree relatives of patients with abdominal aortic aneurysm (AAA) have an increased risk of developing AAA; however, despite intensive investigation, the specific genetic factors involved in the development of the disease are still largely unknown. In twin studies the influence of genetic and environmental factors can be assessed by comparing concordance rates between monozygotic (MZ) and dizygotic (DZ) twins. Higher phenotypic similarity between MZ than DZ twins indicates a genetic attribution to the etiology. The objective of this study was to investigate the heritability of AAA among Danish twins using concordance rates and heritability estimates.

Methods: The Danish Twin Registry was used to identify all Danish twin pairs (born 1880–1971) where both twins were alive on January 1, 1977. AAA cases were then identified using the National Patient Registry and the Registry of Cause of Death. Probandwise concordance rates were calculated and heritability estimated using structural equation modeling.

Results: The study identified 414 twins with AAA; 69.8% (289/414) were men and 30.2% (125/414) women. The probandwise concordance rate in MZ twins was 30% (95% CI 20.3–43.3%) compared with 12% (95% CI 7.0–20.1%) in DZ twins. In the heritability analysis 77% (95% CI 67–85%) of the total variance was explained by additive genetic components and 23% (95% CI 15–33%) was explained by non-shared environmental factors.

Conclusions: The probandwise concordance rate was found to be 2.5 times higher in MZ compared with DZ twins. An overall heritability of 77% was determined.

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INTRODUCTION

It has long been known that the risk of developing abdominal aortic aneurysm (AAA) is increased in first degree relatives of AAA patients,[1–6] but despite intensive investigation, the specific genetic factors involved in the development of the disease are still largely unknown.[7,8]

The increased risk of developing AAA among first degree relatives of AAA patients may be a result of genetic susceptibility as well as a shared environment with subsequent accumulation of known risk factors within affected families. A well known method for studying the relative etiological importance of genetic and environmental factors is the classic twin study: as twins share environment before birth and to a large extent after, the genetic influence on a particular trait may be assessed by comparing concordance rates in monozygotic (MZ) twins, who for practical purposes are genetically identical, and dizygotic twins (DZ), who on average share genes as other siblings. A Swedish twin study[9] found concordance rates to be five times higher for

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AAA in MZ twins compared with DZ twins, and a heritability of 70% of the total variance of liability for AAA. However, the number of identified twins was limited and the findings have not yet been confirmed by other studies.

Objective

The aim of this study was to investigate the heritability of AAA among Danish twins using concordance rates and heritability estimates.

METHOD

A registry based historical follow up twin study was conducted. Data from the Danish Twin Registry was linked with data from the National Patient Register and the Cause of Death Register, via the unique personal identification code assigned to all Danish residents by the Danish Civil Registration System, to get information about all Danish twins with AAA.

Registries

The Danish Twin Registry is one of the oldest and largest twin registries in the world with more than 85 000 pairs registered from 1870. It is a nationwide and population based register established in 1954 and comprises twins born between 1870 and 1930 and surviving for at least 6 years, as well as the birth cohorts 1931–2000.[10] It contains information on zygosity established using a questionnaire regarding the similarity of twins in a pair. This was later validated using DNA analysis, and the misclassification was found to be less than 5%.[11]

The National Patient Register (NPR) was established in 1977 and contains information on all hospital contacts, including hospitalization time and department, main and secondary diagnoses, operations and procedures, place of residence, and personal identification number.[12] Diagnoses are classified according to the International Classification of Diseases (ICD). ICD-8 was used until 1993, ICD-10 thereafter. Operations and procedures are classified according to the NOMESCO Classification of Surgical Procedures (NCSP). AAA was coded as 441.20 or 441.29 in ICD-8 with procedure codes 86550–86555 and I714 in ICD-10 with procedure codes KPDG10, KPDG20, KPDG21, KPDG23, KPDG24, KPDQ, and KPDQ10. Ruptured AAA was coded as 441.21 in ICD-8 and I713 in ICD-10. Main and secondary diagnoses were used.

The National Patient Register has been validated with regards to vascular diagnoses including AAA diagnoses through the Danish Vascular Registry Karbase, where a 99.2% compliance between the two registries has been reported.[13]

The Cause of Death Register (CD) was established in 1973 and includes personal identification number, place and time of death, and one primary, as well as up to three contributing, causes of death.[14] AAA was coded as 441.20 or 441.29 in ICD-8 and I714 in ICD-10. Ruptured AAA was coded as 441.21 in ICD-8 and I713 in ICD-10.

All residents in Denmark are given a unique personal identification number, which is registered in the Danish Central Personal Registration System (CPR). The registry was established in 1968 and includes individual information on personal identification number, sex, date of birth, place of birth, place of residence, citizenship, continuously updated information on vital status, and the identity of parents and spouses.[15]

In the study database all twin pairs were included in which both twins had had a possibility of having a record in the NPR (i.e. both twins in a pair should be alive on January 1, 1977). Furthermore, the sample was restricted to only contain twin pairs up to the birth year of the youngest identified AAA affected twins. An AAA case is defined as an individual with an AAA diagnosis in NPR (updated until March 10, 2014) or AAA as cause of death in CD (updated until August 15, 2012). In total the study database consisted of 32 910 twin pairs born between 1880 and 1971; both males and females were included.

Analysis of twin similarity

Heritability is the proportion of observed phenotypic differences in a population that can be explained by genetic variance. Twin studies offer a unique possibility to distinguish between the genetic and environmental contributions to phenotypic variance of a particular trait by looking at concordance rates for MZ and DZ twins, respectively. Higher phenotypic similarity between MZ than DZ twins indicates a genetic attribution to the etiology.

In the analysis of concordance rates, probandwise concordance rates were used.[16] A proband is in this case defined as each individually identified twin with AAA and the probandwise concordance rate is the proportion of affected co-twins of probands. In other words, the probandwise concordance rate estimates recurrence risk in the co-twin of the proband.

The heritability was estimated using structural equation modeling assuming equal prevalence of AAA for twin 1 and twin 2 as well as for MZ and DZ.[17] According to standard biometric practice the total phenotypic variance in the population (V) can be separated into four different variance components: $V = A + D + C + E$. A refers to the variance contribution from additive genetic components (average sum of effects of alleles across and within loci), D refers to the effects on variance from genetic dominance (interaction of alleles within loci), C refers to the effects of shared environment, and E to the effects of non-shared environment. Generally speaking, the shared environmental effects (all the environmental effects that twins reared together share, such as prenatal and early family environment) are a part of what makes twins similar, whereas non-shared environmental effects contribute to their differences.

The genetic and environmental components of liability for AAA can be estimated by structural equation modeling. In the full standard biometric model D and C cannot be estimated at the same time, therefore ADE and ACE models were fitted separately. Simpler models, AE, CE, and E were also tested, as simpler models may describe data equally well. The models were each evaluated for how well they