Heritability and Familial Aggregation of Diverticular Disease: A Population-Based Study of Twins and Siblings

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this CME activity, successful learners will be able to explain the role for genetic factors in diverticular disease.

BACKGROUND & AIMS: Little is known about the role of heritable factors in diverticular disease. We evaluated the contribution of heritable factors to the development of diverticular disease diagnosed at a hospitalization or outpatient visit. **METHODS:** Using nationwide patient registries, we identified 142,123 incident cases of diverticular disease diagnosed at a hospitalization (1977–2011) or an outpatient hospital visit (1995–2011) in Denmark, including cases in 10,420 index siblings and 923 twins. We calculated standardized incidence ratios for siblings versus the general population and concordance rates for monozygotic versus dizygotic twin pairs as measures of relative risk (RR). **RESULTS:** The RR for diverticular disease in siblings of index cases was 2.92 (95% confidence interval [CI], 2.50–3.39) compared with the general population. The RRs were similar irrespective of the sex of the sibling or index case and were particularly strong in siblings of hospitalized cases and cases that underwent surgery. The proband-wise concordance rate for monozygotic twins was double that of dizygotic twins (0.16 [95% CI, 0.11–0.22] vs 0.07 [95% CI, 0.05−0.11], respectively). The RR of diverticular disease in one twin when the other had diverticular disease was 14.5 (95% CI, 8.9–23) for monozygotic twins compared with 5.5 (95% CI, 3.3–8.6) for dizygotic twins. Associations were stronger in female monozygotic twins compared with male twins (tetrachoric correlation, 0.60 [95% CI, 0.49−0.70] vs 0.33 [95% CI, 0.13−0.51]; $P = .03$ in an analysis stratified by sex and zygosity). We estimate that 53% (95% CI, 45%–61%) of susceptibility to diverticular disease results from genetic factors. **CONCLUSIONS: Based on a population-based study in Denmark, genetic factors appear to contribute to development of diverticular disease.**

Keywords: Diverticulosis; Diverticulitis; Genetics; Risk.

Diverticular disease is a highly prevalent and costly disorder.[1] In Western countries, 30% to 50% of the adult population has colonic diverticulosis,[1] of whom an estimated 15% to 25% will develop diverticulitis or diverticular bleeding.[2] These complications result in more than 780,000 hospital admissions and 23,000 deaths per year in Europe[3] and are the most common gastrointestinal indication for hospital admission in the United States.[4] The majority of patients with uncomplicated diverticulitis (without abscess, perforation, or bleeding) are currently managed in the outpatient setting.[5,6] In 2004 in the United States, the cost of outpatient pharmacotherapy for diverticular disease alone was $100 million.[1]

Environmental factors, chiefly low dietary fiber, and aging have historically been considered major risk factors for the development of diverticulosis. Striking geographical and temporal differences in the prevalence of diverticulosis indicate a possible environmental etiology. For example, diverticulosis is uncommon in Asia and Africa, in contrast to the high prevalence in Western populations, and its prevalence increases with Western acculturation.[7] Environmental exposures including obesity, dietary red meat and fiber intake, physical inactivity, smoking, and nonsteroidal anti-inflammatory and corticosteroid medications have also been associated with diverticular complications.[8–12]

The contribution of heritable factors to the development of diverticulosis and subsequent diverticular complications is not well defined. Therefore, we used data from the nationwide population-based Danish registries to examine the familial aggregation of diverticular disease diagnosed at a hospitalization or an outpatient hospital visit in monozygotic and dizygotic twins and siblings in the entire population of Denmark.

Subjects and Methods

We studied familial aggregation of diverticular disease, including diverticular complications and asymptomatic diverticulosis in siblings, and in a separate analysis compared the phenotypic similarity of monozygotic and dizygotic twins and estimated the heritability of diverticular disease.

Abbreviations used in this paper: CI, confidence interval; ICD, International Classification of Disease; RR, relative risk; SIR, standardized incidence ratio.

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Study Population

We identified cases as those in which diverticular disease was coded for a hospitalization or an outpatient hospital visit in Denmark from 1977 to 2011 using data from the Danish National Registry of Patients. This registry was established in 1977 and includes data on more than 99% of all discharges from nonpsychiatric hospitals in Denmark. Beginning in 1995, outpatient and emergency department visits, including endoscopies, were also included. Information available in the registry includes date of admission and discharge, up to 20 discharge diagnoses (according to the International Classification of Disease [ICD]), and surgical procedures performed. We included patients with either primary or secondary diagnosis codes for diverticulosis or diverticular complications (ICD-8 codes from 1977 to 1993 and ICD-10 codes from 1994 to present; see Supplementary Table 1). The validity of ICD-10 coding for diverticular disease has been shown previously by our group.[13] The 2-level code (DK57) has a positive predictive value of 98% for diverticular disease in general. Ninety-four percent of patients with a 2-level code for diverticular disease and colon surgery recorded during a hospitalization had diverticulitis or diverticular bleeding, as did 70% of those with a 2-level code for diverticular disease recorded during a hospital admission.

Identification of Siblings

From the Danish National Registry of Patients, we identified all incident cases with a diagnostic code for diverticular disease. We then identified incident cases born after 1952 with an identifiable mother in the Civil Registration System. Since April 1, 1968, each resident has been assigned a unique Civil Personal Registration number,[14] which can be used to link records across different medical databases. We limited our study population to cases of diverticular disease born after 1952 because parental information in the Civil Registration System is increasingly complete for individuals born after this date. Forty-three percent of individuals born in 1952, 99% of individuals born in 1960, and 100% of individuals born after 1970 have identifiable parents.[15] We defined siblings as individuals with the same mother, and we included twins as siblings. We considered the first diagnosis of diverticular disease during the study period to indicate an incident case, because individuals in the sibling cohort were young at the start of the study.

Identification of Twins

Through linkage to the Danish Twin Registry, we identified cases of diverticular disease who were members of twin pairs. The Danish Twin Registry is a nationwide population-based registry established in 1954 with twins born between 1870 and 1930 and who survived to 6 years of age.[16] Subsequently, twins born from 1931 to 2010 have been added to the registry. A validated questionnaire is used to establish zygosity with a misclassification rate of less than 5%.[17]

Statistical Analysis in Siblings

We defined the first sibling with a hospital or clinic diagnosis of diverticular disease as the index case. Siblings of index diverticular disease cases were followed forward from the date of diagnosis of the index case (or from birth if it occurred after the index event) until a hospitalization or visit for diverticular disease, emigration, death, or the end of the study follow-up. The Civil Registration System was used to assess the date of death and date of emigration, which are updated continuously.

We compared the incidence of diverticular disease in siblings of index cases with the incidence in the general population using standardized incidence ratios (SIRs) as an estimate of relative risk (RR). We estimated population incidence rates by dividing the total number of incident diagnoses of diverticular disease in Denmark in subgroups defined by sex and age (<40 years, 40–44 years, 45–49 years, ≥50) in each study year by the corresponding number of Danish citizens in the subgroup at the beginning of that year. To derive the expected number of cases, we multiplied the incidence rates by the corresponding person-years of observation. The SIRs were calculated by dividing the number of cases observed in siblings by the expected number. We calculated SIRs by sex of index case and sibling, age of index case (<40 years, 40–44 years, 45–49 years, ≥50), calendar period of index case diagnosis (1977–1996, 1997–2001, 2002–2006, 2007–2011), and time interval between the diagnosis of the index and sibling case (<1 year, 1–2 years, ≥3 years) using Poisson regression with generalized estimating equations and the family as the clustering unit. (The study period was divided into 5-year intervals; the early time periods were collapsed due to small numbers of cases.) We used the likelihood ratio to test for linear trends. *P* values were computed using the likelihood ratio test, and a 2-sided *P* value of <.05 was considered statistically significant.

Statistical Analysis in Twins

In a separate period prevalence analysis, we evaluated the phenotypic similarity of monozygotic and dizygotic twins using classic twin methodology including proband concordance rates and odds ratios. Using these methods,[18] a significant genetic component to diverticular disease would be reflected in greater phenotypic similarity in monozygotic twins than in dizygotic twins, because monozygotic twins are genetically identical whereas dizygotic twins share only half of their genetic material, as is the case with nontwin biological full siblings. Because we performed analyses stratified according to sex, we limited the analysis of dizygotic twins to same-sex pairs.

We first estimated the probability of one twin having the disease given that the partner twin is affected using proband concordance rates,[19] the proportion of affected twin partners of probands. We then computed odds ratios (the relative increase in risk of diverticular disease for one twin given the presence or absence of diverticular disease in the partner twin) using information on both concordant diseased and nondiseased twin pairs.

We calculated tetrachoric correlations for diverticular disease using the liability threshold model for monozygotic and dizygotic twin pairs.[18] This model postulates that the genetic basis of a continuously distributed trait (liability) is composed of numerous small, additive effects. We used structural equation analysis to test biometric models for heritability assuming no gene-gene interaction (epistasis), no gene-environment interaction or correlation, and no assortative mating. Variation in phenotype was divided into 4 components: additive genetic affects (A), genetic dominance (D), shared environment (C), and nonshared environment (E). In monozygotic twins, only nonshared environment contributes to phenotypic differences. However, in dizygotic twins, additive genetic factors and genetic dominance also contribute to dissimilarity within twin pairs. We fit 5 models for heritability (ACE, ADE, AE, CE, and E) and selected the best-fitting model according to the Akaike information criterion for non-nested models and the χ^2 goodness-of-fit test for nested models without adjustment for age or sex. We

Table 1. RRs of Diverticular Disease in Siblings of Index Cases According to Sex, Age, Calendar Period, and Time Since Diagnosis of Index Case

	Observed	Expected	Person-years of follow-up	RR (95% CI)[a]	*P* value
Total	166	56.9	79,241	2.92 (2.50–3.39)	
Sex of index case					
Male	94	32.7	45,729	2.88 (2.35–3.52)	.84
Female	72	24.3	33,512	2.97 (2.35–3.75)	
Age of index case (*y*)					
<40	27	3.9	23,719	7.02 (4.82–10.23)	<.001
40–44	40	9.2	17,862	4.35 (3.17–5.98)	
45–49	51	16.6	19,798	3.06 (2.33–4.03)	
≥50	48	27.3	17,862	1.76 (1.33–2.33)	
Calendar period of index case					
1977–1996	2	0.2	3480	10.07 (2.51–40.52)	.008
1997–2001	11	1.6	7231	6.94 (3.84–12.55)	
2002–2006	34	9.3	19,414	3.66 (2.62–5.13)	
2007–2011	119	45.9	49,117	2.59 (2.17–3.10)	
Years since diagnosis of index case					
<1	25	9.3	13,973	2.69 (1.82–3.98)	.90
1–2	43	14.5	21,324	2.97 (2.20–4.00)	
≥3	98	33.1	43,944	2.96 (2.43–3.60)	

[a]In the sibling cohort, we calculated SIRs as an approximation of RRs. Poisson regression was used to calculate RR by sex, age, calendar period, and year since diagnosis of the index case.

then estimated the proportion of the phenotypic variance attributable to genetic effects or the heritability of the risk of diverticular disease using the best-fitting model. Heritability estimates and tetrachoric correlations were adjusted for sex differences in the prevalence of diverticular disease.

The study was approved by the Danish Protection Agency and was exempt from ethics committee review and participant consent given the nature of the registry data.

Results

Descriptive Data

We identified 142,123 incident cases with diverticular disease recorded at a hospitalization from 1977 to 2011 or an outpatient hospital visit from 1995 to 2011 in Denmark. Of these, 13,268 were born after 1952, 10,586 had an identifiable mother in the Civil Registration System, and 10,420 were index cases with a total of 16,374 siblings. We followed up the siblings for a total of 79,241 person-years. The overall population incidence of a hospital admission or visit for diverticular disease in the study was 0.81 per 1000 person-years compared with 2.1 per 1000 person-years in siblings of index cases. In the overall population, the incidence increased from 0.5 per 1000 person-years in the early period (1977–1981) to 1.3 per 1000 person-years in the last period (2007–2011) and in the siblings from 0 per 1000 person-years to 4.7 per 1000 person-years.

We also identified 11,089 monozygotic and 19,233 same-sex dizygotic twin pairs in the Danish Twin Registry who were alive and living in Denmark on January 1, 1977. A total of 923 twins (330 monozygotic, 593 dizygotic) had a diagnosis of diverticular disease during the study period. In twins, the prevalence of a hospitalization or outpatient hospital visit for diverticular disease during the study period was 1.5%.

Siblings

Siblings of cases were 3 times as likely to have diverticular disease diagnosed at a hospitalization or an outpatient visit as individuals in the general population (RR, 2.92; 95% confidence interval [CI], 2.50–3.39). The RRs were significantly higher for siblings of young index cases (<40 years) than for those of siblings of older cases ($P_{trend} < .001$) (Table 1, Figure 1). There was no significant variation in RR according to the time interval after the diagnosis of the index case ($P_{trend} = .90$) (Table 1). The RR of siblings of cases diagnosed from 1977 to 1996 was greater than for those diagnosed in later time periods (RR of 10.07 [95% CI, 2.51–40.52] compared with RR of 6.94 [95% CI, 3.84–12.55] for 1997–2001, RR of 3.66 [95% CI, 2.62–5.13] for 2002–2006 and RR of 2.59 [95% CI, 2.17–3.10] for 2007–2011; $P_{trend} = .008$) (Figure 2).

We found no differences in the RR according to the sex of the index case or sibling (Table 2). The RRs for male

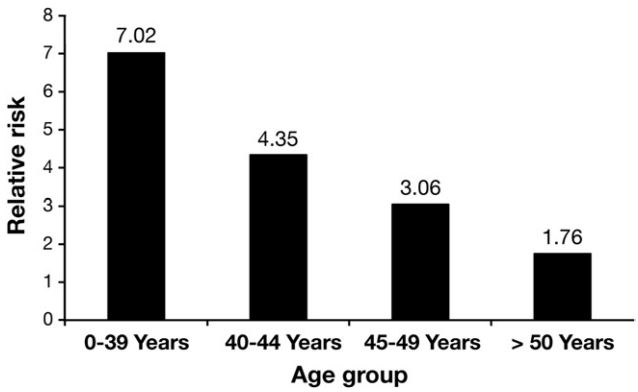

Figure 1. Relative risk (standardized incidence ratio) in siblings according to the age at diagnosis of the index case.

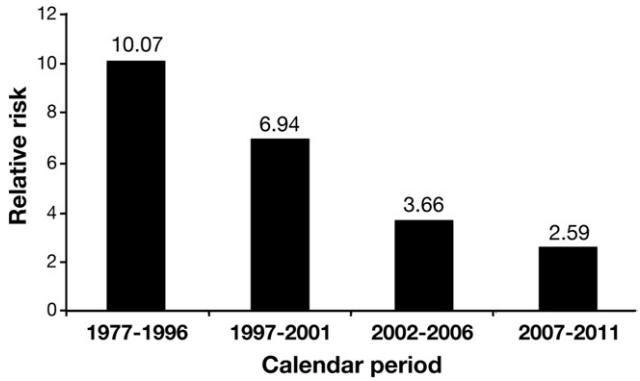

Figure 2. Relative risk (standardized incidence ratio) in siblings according to the calendar period of the index case diagnosis.

siblings of male versus female index cases were 3.26 (95% CI, 2.51–4.22) versus 3.27 (95% CI, 2.42–4.42), respectively ($P = .98$) and for female siblings of male versus female index cases were 2.44 (95% CI, 1.77–3.36) versus 2.59 (95% CI, 1.79–3.75), respectively ($P = .81$).

The RRs were strengthened in siblings of cases likely to have had diverticular complications. The RR was 3.69 (95% CI, 2.94–4.63) in siblings of cases with an inpatient admission, 4.11 (95% CI, 3.24–5.22) in siblings of cases with an inpatient admission with a primary diagnosis of diverticular disease, and 5.37 (95% CI, 2.99–9.67) in siblings of cases with codes for colorectal surgery and diverticular disease during a hospitalization.

Monozygotic and Dizygotic Twins

The proband-wise concordance rate for monozygotic twins was double that for dizygotic twins (0.16 [95% CI, 0.11–0.22] versus 0.07 [0.05–0.11], respectively; $P = .001$) (Table 3). The RR of diverticular disease in one twin given diverticular disease in the co-twin was 14.5 (95% CI, 8.9–23) in monozygotic twins compared with 5.5 (95% CI, 3.3–8.6) in dizygotic twins. Measures of association were similar in monozygotic and dizygotic male and dizygotic female subjects but 2 to 3 times higher in monozygotic female subjects (Table 3); the tetrachoric correlations were 0.33 (95% CI, 0.13–0.51), 0.27 (95% CI, 0.08–0.43), 0.31 (95% CI, 0.19–0.41), and 0.60 (95% CI, 0.49–0.70), respectively ($P = .03$). The associations were similar when the population was limited to hospitalized patients. The concordance rate for monozygotic twins was 0.14 (95% CI, 0.08–0.21) compared with 0.06 (95% CI, 0.03–0.10) for dizygotic twins.

Heritability analyses revealed that the model including additive genetic affects and nonshared environment (AE model) provided the best overall fit to the data ($\chi^2 = 0.4$, $df = 1$; $P = .52$). Using the AE model, the heritability or the proportion of the total phenotypic variance attributable to genetic effects was estimated to be 53% (95% CI, 45%–61%).

Discussion

In this nationwide population-based study, we found strong evidence for a heritable contribution to the etiology of diverticular disease. Siblings of index cases were 3 times more likely to develop diverticular disease than the general population, and measures of twin similarity were consistently higher for monozygotic twin pairs than for dizygotic twin pairs. The RRs were greater among siblings of cases who were hospitalized or had surgery associated with a diagnosis of diverticular disease. We estimated that approximately 50% of the liability to diverticular disease is due to genetic effects.

The genetics of diverticular disease are not well understood. Case reports describe young-onset diverticulitis in otherwise healthy siblings aged 15 and 17 years and in a monozygotic twin pair in their third decade, suggesting the possibility of genetic susceptibility, although such findings might also reflect a shared early environment.[20,21] The low prevalence of diverticulosis in certain ethnic groups despite Western acculturation has also been cited as evidence of a possible genetic predisposition.[8,22,23] For example, first- and second-generation Indian-subcontinent Asian subjects living in England were found to have a lower prevalence of diverticulosis when compared with native white subjects.[22] However, in this study and others, many second-generation subjects were young and may subsequently have developed the disorder, and environmental factors, such as diet, were not taken into account.

As in our data, a recent investigation of diverticular disease in Swedish twins observed stronger measures of association in monozygotic versus dizygotic twins, suggesting a heritable contribution to diverticular disease.[24] An important advantage of our study is the addition of a large, longitudinal, population-based familial aggregation study. Because monozygotic twins tend to share more similar prenatal and postnatal environments than dizygotic twins, greater similarity may not necessarily be attributed to genetic factors.[25] Therefore, our finding of an increased risk of diverticular disease in siblings of cases

Table 2. RRs of Diverticular Disease According to the Sex of the Sibling and Index Case

Sex of sibling	Sex of index case	Observed	Expected	Person-years of follow-up	RR (95% CI)[a]	*P* value
Male	Male	57	17.5	24,083	3.26 (2.51–4.22)	.98
	Female	44	13.5	18,157	3.27 (2.42–4.42)	
Female	Male	37	15.2	21,646	2.44 (1.77–3.36)	.81
	Female	28	10.8	15,355	2.59 (1.79–3.75)	

[a]SIRs were calculated as an approximation of RRs.

Table 3. Proband Concordance Rate, Odds Ratio, and Tetrachoric Correlation for Diverticular Disease According to Zygosity and Sex in Danish Twin Pairs

Zygosity	No. of twin pairs: Disease concordant	Disease discordant	Nondisease concordant	Probandwise concordance rate (95% CI)	Odds ratio (95% CI)	Tetrachoric correlation (95% CI)
Monozygotic						
Total	26	278	10,785	0.16 (0.11–0.22)	14.5 (8.9–23.0)	0.51 (0.41–0.60)
Men	5	124	5333	0.07 (0.03–0.16)	7.1 (2.1–18.3)	0.33 (0.13–0.51)
Women	21	154	5452	0.21 (0.14–0.30)	19.5 (10.8–33.9)	0.60 (0.49–0.70)
Dizygotic						
Total	22	549	18,662	0.07 (0.05–0.11)	5.5 (3.3–8.6)	0.29 (0.20–0.39)
Men	5	198	9740	0.05 (0.02–0.11)	5.0 (1.5–12.4)	0.27 (0.08–0.43)
Women	17	351	8922	0.09 (0.05–0.14)	4.9 (2.7–8.3)	0.31 (0.19–0.41)

versus the general population lends strength and generalizability to the findings in twins. In the longitudinal sibling cohort, we were also able to examine the possibility of diagnostic bias due to a family history (ie, the possibility that siblings are more likely to be diagnosed because of diagnostic bias or heightened investigation based on family history) by comparing the RR according to the time between the index and sibling diagnoses. In addition, we calculated the RR according to the age and time period of the index case, noting that there may be a greater heritable component in patients with young-onset disease. Lastly, our study includes both inpatient and outpatient (from 1995) diagnoses, capturing a broad spectrum of diverticular disease.

The pathogenesis of diverticulosis is incompletely understood but is currently postulated to involve the interplay of increased colon pressures and defects in colon wall integrity.[26] It is therefore plausible that inherited intestinal connective tissue defects predispose to the development of diverticulosis. Diverticulosis is associated with alterations in colon wall collagen structure and content,[27] and early-onset, severe diverticulosis has been observed in the context of several inherited connective tissue disorders, including Marfan, Ehlers–Danlos, Coffin–Lowry, and Williams syndromes.[28–31] In addition, differences in colonic anatomy[32] may account for ethnic differences in the distribution of diverticulosis (individuals of Western origin have predominantly left-sided disease, whereas those of East Asian origin have predominantly right-sided disease)[23] and may have genetic underpinnings. Inherited neuromuscular abnormalities may also contribute to the development of diverticulosis. Recent studies describe alterations of the enteric nervous system in individuals with diverticulosis,[33] and diverticulosis is described in inherited intestinal motility disorders.[34]

Genetics may also influence the pathogenesis of diverticulitis and diverticular bleeding. Diverticulitis is posited to result from luminal trauma, mucosal inflammation, bacterial stasis, and/or tissue ischemia, although the exact mechanisms remain to be elucidated.[26] Diverticular bleeding arises in the setting of characteristic abnormalities in the vasa recta, which are similar to changes seen in other types of vascular injury such as arteriolosclerosis.[26] Therefore, abnormalities in related biologic pathways such as mucosal immunity, vascular remodeling, and the coagulation cascade may contribute to diverticular complications. Further study is needed to determine more precisely how genetic susceptibility plays a role in the development of diverticulosis and its complications.

We found that the RRs of siblings of index cases diagnosed in the earliest study period were higher than those diagnosed in later periods. This may be the result of the increasing use of abdominal imaging and colonoscopy in later years, allowing for the detection of less severe cases and asymptomatic diverticulosis that may have weaker genetic determinants. Similarly, outpatients were included in the later study periods, and these patients may be less likely to have had diverticular complications. Finally, purported environmental risk factors for diverticulitis, including obesity, use of nonsteroidal anti-inflammatory drugs, and physical inactivity, have increased over time, but the effect of such factors very likely would be nondifferential with respect to family history.

In the sibling cohort, the magnitude of risk was greatest in siblings of cases 30 to 39 years of age at diagnosis and declined with each subsequent decade of age, suggesting that genetic factors influence young-onset more than later-onset disease. Early age of onset or diagnosis is associated with increased heritability in many disorders, such as cancer and inflammatory bowel disease.[35,36]

We noted that measures of association were stronger in female monozygotic twins than in female dizygotic twins and were similar in male monozygotic and dizygotic twins, indicating little genetic effect in male twins. The reasons for the sex difference in twins are not clear. We did not find a sex difference in nontwin siblings, suggesting that this could be a chance finding in twins. This finding does not appear to be the result of the higher prevalence of diverticular disease among female as compared with male twins (59% vs 41%, respectively). Tetrachoric correlation is a measure of association that is not influenced by prevalence, and sex-specific tetrachoric correlations, after adjustment for prevalence, remained significantly higher in female twins than in male twins. The literature on sex differences in diverticular disease as a

whole is inconsistent but suggests that diverticulitis is more common in women.[37]

Our study used the robust Danish population-based registries, which provide nearly complete information on all hospitalizations in Denmark and all hospital encounters including emergency department visits and outpatient endoscopies since 1995 and allow accurate identification of twins and siblings. In addition, all Danish citizens have access to free health care. These features make it possible to study the entire country as a cohort, minimizing the possibility of bias and improving the generalizability of the results.[14]

There are several potential limitations of our study, including the use of administrative codes that do not readily distinguish between patients with uncomplicated diverticulosis versus diverticulitis and diverticular bleeding. However, when we limited our analysis to patients likely to have had diverticular complications, our findings were strengthened in the sibling cohort and similar in the twin cohort, confirming our overall results. Many subjects were likely to have undiagnosed asymptomatic diverticulosis; however, this misclassification would be random with respect to zygosity and familial relationship, resulting in a tendency toward a conservative bias. In the study of twins, we are likely to have missed cases diagnosed before 1977. This may have resulted in reporting of some prevalent cases and in misclassification with respect to concordant or discordant disease status. Again, however, any misclassification would be random with respect to zygosity. Left censoring is less likely to have occurred in the sibling cohort because the oldest individuals were only 25 years of age at the start of the study and 43 years of age at the inception of outpatient data. Overall, follow-up was relatively limited in the sibling analysis, with the oldest individuals 59 years of age at the end of the study with an average follow-up of 4.8 years. The young age of our sibling cohort may make it difficult to generalize our findings to older populations who are more likely to have diverticulosis and its complications. Likewise, the Danish population consists largely of white subjects, and therefore our results may not be generalizable to populations with a different racial composition. Lastly, it is possible that environmental factors with inherited or familial tendencies such as smoking and obesity partially explain our data. However, environmental exposures are likely to correlate to a similar degree in monozygotic and dizygotic twins, and such an exposure would have to have had a very strong effect to account for our findings (RR $>$ 10).[38] The published RRs for environmental factors and diverticular complications are generally modest (RR, 1.5–3).[8–12]

In conclusion, our results from this nationwide study of siblings and twins show that diverticulosis, including diverticular complications, aggregates strongly in families and suggest a major role for genetic factors in this common disease. These findings open a new vista on a disease that has previously been regarded as environmental in nature. The elucidation of the genetic basis of diverticular disease should offer insight into the pathogenesis of this prevalent but poorly understood disorder and possibilities for preventative interventions.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.12.030.

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Conflicts of interest

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Supplementary Table 1. ICD Codes for Diverticular Disease and Their Frequency Among Incident Cases

Diagnostic code	Description	Primary diagnosis (n = 8623) (%)	Secondary diagnosis (n = 1797) (%)
ICD-8 codes[a]			
56.210	Diverticulosis of colon	0.6	1.1
56.211	Diverticulitis of colon	0.9	0.3
56.212	Diverticulitis of colon with perforation	0.5	0
56.218	Diverticulosis, diverticulitis of colon, other	0.1	0
562.19	Diverticulosis, diverticulitis, peridiverticulitis, location unspecified	0.3	0.4
ICD-10 codes[a]			
K572	Diverticulosis, diverticulitis coli with perforation or abscess	0.9	0.5
K573	Diverticulosis, diverticulitis coli without perforation or abscess	80	80
K574	Diverticulosis, diverticulitis in small and large intestine with perforation or abscess	0.3	0.3
K575	Diverticulosis, diverticulitis in small and large intestine without perforation or abscess	1	1.8
K578	Diverticulosis, diverticulitis in intestine with perforation or abscess, location unspecified	0.3	0.4
K579	Diverticulosis, diverticulitis in intestine without perforation or abscess, location unspecified	7	8

[a]ICD-8 codes were used from 1977 to 1993, and ICD-10 codes were used from 1994 to 2011.