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Original Contribution

Genetic and Environmental Influences on Risk of Death due to Infections Assessed in Danish Twins, 1943–2001

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Genetic differences have been proposed to play a strong role in risk of death from infectious diseases. The study base of 44,005 included all same-sex twin pairs born in 1870–2001, with both twins alive on January 1, 1943, or those born thereafter. Cause of death was obtained from the Danish Cause of Death Register and was available for 18,359 deaths. The authors classified death due to infections by 3 definitions (narrow, broader, and broadest) and calculated concordance rates for same-sex monozygotic and dizygotic twin pairs. Heritability was estimated by using structural equation models. When the 3 definitions were applied, 211 (1.1%), 1,089 (5.9%), and 2,907 (15.8%) deaths, respectively, were due to infections. The probandwise concordance rates for monozygotic twin pairs were consistently higher than for dizygotic twin pairs regardless of the definition (9% vs. 0% ($P = 0.04$), 10% vs. 3% ($P < 0.01$), and 19% vs. 15% ($P = 0.07$), respectively). For the broader and broadest definitions, heritability was 40% (95% confidence interval: 12, 50) and 19% (95% confidence interval: 3, 35), respectively. The concordance rates were generally low, and, although a genetic influence on the risk of death from infectious diseases could be demonstrated, the absolute effect of the genetic component on mortality was small.

cause of death; genetics; infection; twins

Abbreviation: ICD, *International Classification of Diseases*.

Susceptibility to and prognosis of infectious diseases are presumed to have a strong genetic component (1). Genotype may predispose an individual to death from infectious diseases by either monogenetic or multigenetic mechanisms. Simple Mendelian inheritance has been demonstrated for many severe, but rare immune defects (2, 3). Genetics also seem to play a role in susceptibility to common global diseases such as tuberculosis, malaria, and human immunodeficiency virus (4–6). However, it is still controversial whether genetic variation in the human population in general predisposes to death from infectious diseases in a modern Western World setting.

In a seminal study published in 1988, Sørensen et al. (1) used a Danish cohort of adoptees to study genetic and environmental influence on risk of death. The authors found that the risk of death due to infectious diseases increased almost 6-fold for the adoptees born in 1924–1926 when one of the biologic parents had died from an infection (1). In contrast, this risk was close to unity when the adoptive parent had died from an infectious disease. In a series of following papers including the entire cohort of adoptees born in 1924–1947, the authors reported some evidence to support the initial results, but the effects were weaker (7–9). In the most recent analyses of siblings of the adoptees (9), the risk of death from infections until age 70 years was doubled for biologic siblings who had shared no postadoptive environment with the adoptees. Independent confirmative studies to support this result are very sparse, and the details of the genetic nature of the phenomenon remain to be established.

In a large, nationwide cohort of twins from the same population as the adoptees, we independently tested the hypothesis that death due to infectious diseases has a strong genetic component. To further elucidate the association, we used several classifications of causes of death.

MATERIALS AND METHODS

Study design

The study was conducted as a twin study. Concordance rates of death from infections among monozygotic twin pairs were compared with concordance rates of death from infections among dizygotic twin pairs in the same twin population registered in the Danish Twin Registry.

The Danish Twin Registry. The Danish Twin Registry is a nationwide and population-based registry established in 1954. It initially included twins born between 1870 and 1930 who had survived to age 6 years (10). Birth cohorts from 1931 through 2004 were later added to the registry, which now holds data on more than 80,000 twin pairs born between 1870 and 2004. Zygosity was established through a questionnaire on the degree of similarity between twins in a pair. The zygosity classification has been evaluated by comparison with blood group determinants, and the proportion of misclassification was less than 5% (11).

The Danish Cause of Death Registers. Since January 1, 1943, causes of death have been registered on a nationwide basis and are available for record linkage. Information on deaths from 1943 to 1969 can be obtained from the Cause of Death Register at the National Institute of Public Health, whereas information on deaths after 1969 can be obtained from the Cause of Death Register at the National Board of Health (12). ''Cause of death'' has been coded according to various editions of the *International Classification of Diseases* (ICD), including the fifth (ICD-5, 1943–1950), sixth (ICD-6, 1951–1957), seventh (ICD-7, 1958–1968), eighth (ICD-8, 1969–1993), and 10th (ICD-10, 1994–). The causes of death are registered by the physician on the death certificate as primary (immediate cause of death), secondary, or tertiary. Causes of death were available for the present study until December 31, 2001.

Follow-up period and cause of death

In the present study, we included same-sex twin pairs born between January 1, 1870, and December 31, 2001, among whom both twins were alive on January 1, 1943, or those born thereafter. Individuals were followed up until December 31, 2001. Altogether, 45,658 male twin individuals and 42,352 female twin individuals were included. A total of 19,052 (22%) of the 88,010 twins died before 2002, and a cause of death could be identified for 18,359 (96%) of them.

Vital status and date of death were obtained from the Danish Civil Registration System (13), and causes of death were obtained by linkage to the 2 Danish Cause of Death Registers. We used 3 different definitions for cause of death due to infections: narrow, broader, and broadest.

Narrow definition (includes what is generally considered contagious diseases). Causes of death were categorized according to the classification used by the World Health Organization. This classification operates with 14 groups; one is infectious diseases in general and one is tuberculosis. A case was classified as an individual who died from an infectious disease if the primary cause of death was grouped as infection or tuberculosis. Essentially, this classification is equivalent to codes 000–0136 in ICD-8 and the A and B groups in ICD-10.

Broader definition (includes what is generally considered of infectious etiology). For this classification, we first created a list including all death categories for the twins (the 1,803 categories are listed in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oupjournals.org/)). From this list, an infectious diseases specialist and an internal medicine specialist categorized the causes of death as infectious or not when the causes were not already defined as infectious according to the narrow definition described above. The categorization was performed blinded with respect to twin relationships and zygosity. This broader classification thereby included the causes defined in the narrow definition but further included specific organ-related causes of death, for example, endocarditis, pneumonia, peritonitis, and osteomyelitis. A case was included in this definition only if the primary cause of death was categorized as infectious.

Broadest definition. In this classification, causes of deaths were categorized according to the list used in the above-mentioned broader definition. However, this definition also included cases for whom infectious diseases were listed as secondary or tertiary causes of death on the death certificate.

Statistical analysis

Analyses of twin similarity. We assessed the similarity of monozygotic and dizygotic twins using probandwise concordance rates and tetrachoric correlations for death due to infection. The classic twin-study methodology is based on the assumption that monozygotic twins have identical genotypes, whereas dizygotic twins share, on average, half of their segregating genes and thus are no more genetically related than biologic full siblings. A greater phenotypic similarity in monozygotic than in dizygotic twins is expected if there is a substantial genetic component in the etiology of the disease.

Concordance rates. The probandwise concordance rate is defined as the proportion of affected twin partners of probands. It reflects the probability that one twin will die from infection, given that the twin partner died from infection. Thus, it is directly comparable with risk rates reported for other relatives (14). We computed the confidence interval using the standard errors of proportions.

Correlation. The correlations attributable to the dichotomous outcome, death from infections, were investigated by assuming an underlying normally distributed liability (susceptibility) to a condition (death due to infection) because of genetic and environmental factors. The manifestation of a condition is established when an individual exceeds the threshold of affliction on the liability distribution, and the impact of genetic and environmental effects is reflected in the similarity of the other twin's liability to the condition (15). We estimated the correlations in liability by using a multifactorial threshold model (16) and the Mx software package (17). Likelihood-based confidence intervals were estimated by structural equation modeling, as described in detail elsewhere (15).

Heritability. According to standard biometric practice when estimating heritability as the proportion of total phenotypic variance attributable to genetic variance in the population, we assumed no epistasis (gene-gene interaction), no gene-environment interaction or correlation, and no assortative mating with respect to loci affecting the risk of death due to infections. The phenotypic variance can then be separated into 4 variance components: variance attributable to additive genetic effects (A), genetic dominance (D), shared environment (C), and nonshared (individual-specific) environment (E) (15). Only nonshared environments contribute to dissimilarity within monozygotic twin pairs because of their presumed genetic identity, whereas the effects of additive genetic factors and genetic dominance may also contribute to dissimilarity within dizygotic pairs, who share, on average, half of the additive and one-quarter of the dominant genetic factors. The method for selecting the best model followed standard procedures (structural-equation analyses) (15).

Because the effects of genetic dominance (D) and shared environment (C) are completely confounded in the classic study of twins reared together, it is not possible to estimate all parameters simultaneously in a single model (15). Thus, we fitted 5 models (ACE, ADE, AE, CE, and E) to the data. The best model is considered one that fits the data well (by a chi-square goodness-of-fit test based on the log-likelihood difference of nested models) and is the most parsimonious (i.e., none of the parameters in the model can be deleted without a substantial increase in the chi-square value).

To compare nonnested models, we used the Akaike Information Criterion (AIC; $-2 \times$ log-likelihood – twice the degrees of freedom). The model with the lowest Akaike Information Criterion represents the best balance of goodness of fit and parsimony (18). To compare nested models, we used the chi-square difference test (i.e., $\Delta\chi^2 = 2 \times \Delta$log-likelihood of the nested models). The difference in chi-square of the models is itself distributed as a chi-square statistic, with the degrees of freedom equal to the difference in the degrees of freedom of the models being compared.

RESULTS

Since 1943, a total of 211 twins born in 1870–2001 were registered as having died from infection when the narrow definition was used. For the broader and broadest definitions of death due to infection, the respective numbers were 1,089 and 2,907 (Table 1), corresponding to 1.1%, 5.9%, and 15.8% of the 18,359 deaths observed in the cohort. For the narrow, broader, and broadest definitions, 78.4%, 82.5%, and 91.2%, respectively, of the deaths occurred after the age of 20 years.

As shown in Table 2, infections of the respiratory system were the dominant causes of death when the broader definition of infectious diseases was used. Regarding the broadest definition, malignant, cardiovascular, neurologic, and respiratory diseases were the predominant primary causes of death.

The probandwise concordance rate for monozygotic twin pairs was consistently higher than for dizygotic twin pairs regardless of the definition used (Table 3) (narrow definition: 9% vs. 0%, broader definition: 10% vs. 3%, broadest definition: 19% vs. 15%). The difference was statistically significant (narrow: $P = 0.04$, broader: $P < 0.01$) except for the broadest definition, for which the difference was borderline significant ($P = 0.07$).

Structural-equation analyses were not possible for the narrow definition because of small numbers (Tables 3 and 4). For the broader definition, a model including additive genetic factors and nonshared environment provided the best fit to the data. Heritability was 40% (95% confidence interval: 12, 50) (Table 4). The remaining variation could be attributed to nonshared environments. For the broadest definition, a model also including shared environmental factors provided the best fit, but, also in this instance, the influence

Table 1. Number of Danish Same-Sex Twins Born in 1870–2001 Who Died and Were Registered as Having a Cause-of-Death Diagnosis of Death due to Infection[a]

Zygosity	Death due to Infection		
	Narrow Definition	Broader Definition	Broadest Definition
Monozygotic	46	274	811
Dizygotic	98	502	1,526
Unknown	67	313	570
Total	211	1,089	2,907

[a] The definitions are categorized as described in the Materials and Methods section of the text and in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oupjournals.org/).

Table 2. Primary Causes of Death in 1943–2001 for Same-Sex Twins of Known Zygosity Who Died From Infectious Diseases, According to 3 Different Definitions of Infectious Diseases[a,b]

Primary Cause of Death	Narrow	Broader	Broadest
Tuberculosis	52	52	52
Infectious diseases (excluding tuberculosis)	92	88	88
Malignant neoplasms		0	490
Apoplexia, dementia, senility		0	292
Diseases of the heart		33	383
Diseases of the respiratory system		423	530
Diseases of the digestive system		56	138
Diseases of the genital-urinary system		91	110
Congenital malformations		0	4
Disorders occurring during the perinatal period		0	1
Violent death (accidents, homicide, suicide)		0	63
All other diseases		33	186
Total	144	776	2,337

[a] Four cases of sarcoidosis Boeck (*International Classification of Diseases*, Eighth Revision, code 135) are included in the narrow definition but not in the broader and broadest definitions.

[b] The definitions are categorized as described in the Materials and Methods section of the text and in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oupjournals.org/).

Table 3. Probandwise Concordance Rates and Tetrachoric Correlation for Death due to Infection in Danish Twin Pairs

Death due to Infection[a]	Zygosity	Concordant for Death due to Infection	Discordant for Death due to Infection	Concordant for not Death due to Infection	Probandwise Concordance Rate	95% CI	*P* Value, Equal MZ-DZ Concordance	Tetrachoric Correlation	95% CI
Narrow definition[b]	MZ	2	42	12,360	0.09	0.01, 0.27	0.04		
	DZ	0	98	21,699	0	0, 0.07			
Broader definition	MZ	13	248	12,143	0.10	0.05, 0.15	<0.01	0.41	0.28, 0.53
	DZ	8	486	21,303	0.03	0.01, 0.06		0.17	0.04, 0.29
Broadest definition	MZ	77	657	11,670	0.19	0.15, 0.23	0.07	0.48	0.41, 0.54
	DZ	115	1,296	20,386	0.15	0.13, 0.17		0.38	0.33, 0.43

Abbreviations: CI, confidence interval; DZ, dizygotic; MZ, monozygotic.

[a] The definitions are categorized as described in the Materials and Methods section of the text and in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oupjournals.org/).

[b] Tetrachoric correlation is not possible to calculate because zero DZ pairs are concordant for death due to infections.

of genetic factors was statistically significant (heritability = 19%, 95% confidence interval: 3, 35) (Table 4). Hence, the probandwise concordance rate comparisons for the 3 definitions and the heritability estimates all suggest that genetic factors influence susceptibility to death due to infection.

Only 7 twin pairs (2 monozygotic, no dizygotic, and 5 of unknown zygosity) were concordant for evident infectious causes of death by the narrow definition. In 3 of these twin pairs, both twins died from tuberculosis; in one pair, both twins died from acquired immunodeficiency syndrome within a 1-year interval; and one pair of twins died on the same day of gastrointestinal intoxication from staphylococcal toxin. In one pair of twins, both died of meningococcal meningitis before the age of 2 years within an interval of almost 1 year. A total of 192 twin pairs of known zygosity were concordant for death due to infectious diseases with the broadest definition. In these twin pairs, malignancies were the primary cause of death for one or both twins in 58 (30%) pairs and cardiovascular disease in 67 (35%) pairs; for 120 (63%) pairs, cardiovascular disease or malignancy was given as the primary cause of death for one or both twins.

DISCUSSION

In a cohort of 44,005 twin pairs with 18,359 registered deaths of known cause, we found a familial aggregation of death from infectious diseases and evidence for the influence of genetic factors. The major strengths of the

Table 4. Model Fit and Heritability Estimates for the Broader and Broadest Definitions[a] of Death due to Infection in Danish Twin Pairs

Definition and Model	a^{2b}		c^{2c}		d^{2d}		e^{2e}		AIC	vs.	Δdf^f	$\Delta\chi^{2g}$	*P* Value
	Heritability	95% CI	Heritability	95% CI	Heritability	95% CI	Heritability	95% CI					
Broader													
ADE	0.26	0.00, 0.50			0.15	0.00, 0.52	0.59	0.47, 0.71	−5.71				
ACE	0.40	0.12, 0.50	0.00	0.00, 0.21			0.60	0.50, 0.72	−5.42				
AE[h]	0.40	0.12, 0.50					0.60	0.50, 0.72	−7.42	ADE	1	0.29	0.59
CE			0.28	0.19, 0.36			0.72	0.64, 0.86	−0.34	ACE	1	7.08	<0.01
E							1.00		31.56	AE	1	40.98	<0.001
Broadest													
ADE	0.54	0.48, 0.59			0.00	0.00, 0.05	0.46	0.41, 0.51	17.22				
ACE[h]	0.19	0.03, 0.35	0.29	0.16, 0.41			0.52	0.46, 0.59	−3.752				
AE	0.54	0.49, 0.59					0.46	0.41, 0.51	15.22	ACE	1	20.97	<0.001
CE			0.42	0.38, 0.46			0.58	0.54, 0.62	−0.64	ACE	1	5.12	0.02
E							1.00		339.99	AE	1	342.62	<0.001

Abbreviations: AIC, Akaike Information Criterion; CI, confidence interval.

[a] The definitions are categorized as described in the Materials and Methods section of the text and in the Web Appendix, which is posted on the *Journal*'s website (http://aje.oupjournals.org/).

[b] Proportion of total variance ascribed to additive genetic effects.

[c] Proportion of total variance ascribed to common environmental effects.

[d] Proportion of total variance ascribed to genetic dominance effects.

[e] Proportion of total variance ascribed to unique environmental effects.

[f] Difference in degrees of freedom between models.

[g] Difference in twice the log-likelihood between compared models.

[h] Best fitting model.

study are 1) the large study population; 2) the nationwide, population-based design; 3) access to complete data sources that specify causes of death in the study population; 4) a high frequency of known zygosity of the twins; and 5) the large number of study endpoints (death accompanied by a registered cause of death). Furthermore, the data available enabled us to use several different classification systems for death due to infectious diseases.

Our study has 2 potential weaknesses (1). First, causes of death were obtained from the information registered by the physician on the death certificate, and it is well known that these causes of death may be misclassified. Second, we had to categorize the ICD codes used to classify causes of death on the death certificate as infectious or not. Strict classification was further complicated by the fact that 5 different ICD systems (ICD-5, ICD-6, ICD-7, ICD-8, and ICD-10) had been used in the Danish Cause of Death Register during the study period. The potential biases that these misclassifications may introduce will underestimate the effect of genetic components. We further explored the data set by using a very stringent and 2 broader classifications of causes of death, but we reached the same overall conclusions irrespective of the definitions of the classes. To define the broader and broadest causes of death, an infectious disease specialist and an internal medicine specialist both categorized the list of 1,803 ICD categories of death, and the categorization was performed blinded to the frequency of zygosity associated with the groups. We are aware that some of the causes of death cannot unambiguously be defined as infectious or not (e.g., pericarditis, peritonitis, appendicitis). To make the definitions open to discussion and to allow for later comparative studies, we have included a list of causes of death in which those categorized as infectious are marked in the Web Appendix.

We used 3 definitions of infectious diseases. The narrow definition included only what is categorized as group A and B in the ICD-10 system (or the equivalent in the ICD-5, ICD-6, ICD-7, or ICD-8 systems). We find this definition very strict because it excludes organ-related infections such as pneumococcal meningitis and endocarditis. As a consequence, we observed few twins in this category. In contrast, the broadest definition included patients who had died of infectious disease even when the disease was listed as a secondary or tertiary cause of death on the death certificate, and this classification probably led to misclassification of some deaths. The broadest classification thereby may induce underestimation of the effects of genetic components; accordingly, we observed a reduced heritability when we used the broadest definition. The broader definition probably reflects the best categorization because it included organ-specific infectious disease diagnoses and included only those cases for whom infectious diseases were considered the primary cause of death. We therefore suggest that the broader definition led to the lowest frequency of misclassifications, which probably explains why we found the highest heritability when we used this definition.

Our results are generally in accordance with those obtained in the studies of the Danish adoption cohort (1, 7–9). In these studies, there appeared to be a secular decline in the strength of genetic influences in the parent-offspring associations (1, 7, 8). Plausible reasons for this finding are the steady decline in risk of acquiring infectious diseases because of better hygiene and vaccinations and in risk of dying of infections because of improved treatment options. The most recent study of the biologic and adoptive siblings of the adoptees, conducted as a case-cohort study (9), showed a doubling of the risk of dying from infections for the biologic siblings when the adoptees had died from infections, whereas there was no increased risk for the adoptive siblings. In agreement with the results from the present twin study, these results suggest a genetic influence and no shared familial environmental influence on risk of dying.

Only a minor fraction of the deaths in our study population occurred in the preantibiotics period; therefore, we cannot exclude the possibility that genetic factors may further predispose to increased risk of death in a setting with no access to antimicrobial chemotherapy. In fact, several studies indicate that some infectious diseases may aggregate in families because of shared genetic predispositions. In a 1978 study, Comstock (19) found a 2.5-fold higher concordance rate for tuberculosis for monozygotic versus dizygotic twins. However, this conclusion was challenged in a later Dutch study (20). In addition, the risks of acquiring human immunodeficiency virus and malaria have genetic components (5, 6).

A genetic predisposition to increased mortality from infectious diseases may be due to an increased risk of acquiring the infection (as with, for example, chronic granulomatous disease) or an increased risk of dying from the infection when acquired (as found in families with X-linked Duncan's syndrome, in whom the male members die from an otherwise-benign Epstein-Barr virus infection). A hospital-based twin study by Marshall et al. (21) indicated a higher concordance rate for acquisition of infections in monozygotic twins. Shared environment increases the risk of transmitting infectious diseases. However, most deaths due to infectious diseases occur in adulthood, and we propose that the risk of one twin transmitting an infectious disease to the twin sibling with deadly consequences is low for both monozygotic and dizygotic twins. Analysis of the risk of acquiring infections and of the risk of dying from infections for those infected (case fatality) among the Danish adoptees and their adoptive and biologic siblings suggested only a small influence of genetic factors on risk of acquiring infections, whereas the risk of dying from infections is under strong genetic influence (L. Pedersen, National Centre for Register-based Research, University of Aarhus, Aarhus, Denmark, unpublished manuscript).

Infections are often secondary to major morbidity causes such as malignancies or cardiovascular diseases. We used 3 systems to identify twins who died from infectious diseases. By using the broadest classification (which also identifies twins with infectious diseases registered as a secondary or tertiary cause of death), we identified 192 twin pairs concordant for death due to infectious diseases. For a major proportion of these twin pairs, malignancy and cardiovascular disease were the immediate causes of death. Although these pairs of twins were classified as having died from infections, they may as well have died from malignancies or cardiovascular disease. These patients may have been predisposed to cancers or cardiovascular diseases, which

secondarily led to infectious diseases. In this context, it is of interest that the studies based on the Danish adoption cohort used a very broad definition of death from infectious diseases, in which they categorized patients with infectious diseases identified as secondary or tertiary causes of death as having died from infections. Vascular diseases and malignancies seem to have genetic components (22, 23). These diseases are, at later stages, associated with secondary infections, and the genetic components of vascular diseases and malignancies may therefore eventually lead to categorization of the death as ''infectious.'' As a consequence, the broader and broadest definitions of causes of death may have confounded and possibly inflated the proposed associations.

Common environmental risk factors may predispose to death from, for example, cardiovascular and malignant diseases. This possibility may clarify the finding that, for the broadest definition, 29% of the deaths were explained by shared environmental factors.

Abuse of drugs, tobacco, and alcohol has a strong familial association, some of which may be linked to genetic predispositions (24). Because such abuse increases susceptibility to and death from infectious diseases, these genetic components may bias our estimates and may also lead to overestimation of the genetic components observed in the present study.

Only 7 pairs of twins were concordant with regard to evident infectious causes of death according to the narrow classification; 3 of these pairs had tuberculosis, one pair had acquired immunodeficiency syndrome, and one pair had intoxication with staphylococcal toxin. For these 5 latter twin pairs, the concordant reasons for death probably also reflect concordant exposition. For one pair of twins, both died of meningococcal meningitis. This pair of twins may have suffered from complement deficiency, which is well known to predispose individuals to meningococcal disease (25). However, in the 64,030 pairs of twins included in our study population, this was the only pair in which both died from a common well-defined infectious disease known to be a potential consequence of inherited immune deficiency. This finding also reflects the fact that the incidence of major monogenetic immune deficiencies is very low (2).

In conclusion, our data indicate that genetic factors predisposed to death from infectious diseases. However, because the concordance rates were generally low, the absolute effect of the genetic component on the mortality risk due to infections is small.

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