

A Genealogical Assessment of Heritable Predisposition to Asthma Mortality

Craig C. Teerlink¹, Matthew J. Hegewald², and Lisa A. Cannon-Albright¹

¹Department of Biomedical Informatics, University of Utah, Salt Lake City, Utah; and ²Department of Pulmonary and Critical Care Medicine, University of Utah and LDS Hospital, Salt Lake City, Utah

Rationale: Asthma is a multifactorial disease; genetic factors have been suggested but have not been well defined.

Objectives: This study examined evidence for a heritable component to asthma mortality using a unique data resource consisting of Utah death certificates linked to a genealogy of Utah.

Methods: Cases were defined as individuals whose death certificate listed asthma as a cause of death in a registry of all Utah deaths since 1904 ($n = 1,553$). The genealogical index of familiarity analysis was used to compare the average relatedness of asthma deaths to the expected relatedness in the Utah population. Relative risks for asthma death in relatives of individuals who died of asthma are provided for close and distant relatives.

Measurements and Main Results: The genealogical index of familiarity identified a significantly higher average relatedness in cases ($P < 0.001$), even when close relationships were ignored. In addition, a significantly increased risk of dying of asthma was observed in first-degree relatives of cases (relative risk = 1.69, $P < 0.001$) and in second-degree relatives of cases (relative risk = 1.34, $P = 0.003$).

Conclusions: These results support a heritable contribution to asthma mortality.

Keywords: genetic predisposition; bronchial asthma; genealogy and heredity; relative risk; Utah Population Database

Asthma is a respiratory disease with a complicated heterogeneous phenotype, and various genetic and environmental risk factors, including family history, have been hypothesized as causes (1, 2). Investigations of possible genetic factors have been prompted by evidence of a heritable component to a clinical diagnosis of asthma and related respiratory phenotypes (e.g., bronchodilator hyperresponsiveness, childhood wheeze). Previously published estimations of risk for asthma in relatives of asthma cases reflect a variety of phenotype definitions and have been largely restricted to risk estimates for first-degree relatives or patients' personal knowledge of family health history (3–5). The most severe phenotype, death due to asthma, has not been considered. Asthma mortality is a substantial health problem, resulting in about 5,000 deaths per year in the United States (6).

Our study takes advantage of the Utah Population Database (UPDB), a computerized resource that links genealogy records of Utah pioneers and their descendants with statewide death certificates, to analyze asthma mortality. Computerized death

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The heritable nature of asthma has been documented in various populations but is restricted to analyses concerning first-degree relatives or patient recall of family history. Familial investigations in more distant relatives are not well established.

What This Study Adds to the Field

These findings support the existence of a genetic contribution to a severe asthma phenotype (e.g., death).

certificates representing more than 100 years of deaths in Utah have been linked to the Utah genealogy. This combined data resource allows analysis of a larger population than has been available in other studies (3). The extended genetic relationships, strict phenotype definition, and large homogeneous population provide insight into the magnitude of a heritable contribution to death from asthma.

We hypothesize that concentrating on the most severe asthma phenotype (death) will reduce the noise associated with analysis of the genetics of less severe asthma phenotypes. The large pedigree structures available in the UPDB allowed us to estimate risk of asthma death in both close and distant relatives of individuals who died of asthma, allowing consideration of both common environment and genetics as factors. Some of the results of these studies have been previously reported in the form of an abstract (7).

METHODS

The UPDB is a computerized data resource consisting of genealogical and demographic data representing the Utah population (8). The genealogical data in the UPDB has been record-linked to other statewide data resources, including the Utah Cancer Registry and Utah death certificates. The Utah genealogy database was created in the 1970s to investigate the familial aggregation of cancer and now spans up to 10 generations in some Utah pedigrees (9). Several studies using the genealogy data linked to the Utah Cancer Registry have defined familial cancer predispositions and syndromes (10–17). Other studies using the genealogy data linked to Utah death certificates have demonstrated heritable predisposition to noncancer diseases (18–20).

The original Utah genealogy consisted of data for approximately 1.6 million Utah pioneers and their descendants. It has been extended to current generations using Utah vital statistics data, and now includes over 9 million individuals, not all of whom have linked genealogical data. Our analysis was restricted to the 2.2 million subjects in the UPDB with at least three generations of genealogy records. The Utah population is genetically representative of northern Europe and has low inbreeding levels, similar to other areas of the United States (21, 22). The use of this data resource for this study has been approved by

(Received in original form August 21, 2006; accepted in final form August 6, 2007)

Partial support for all datasets within the Utah Population Database (UPDB) was provided by the University of Utah Huntsman Cancer Institute. C.C.T. was supported by an NLM Training Grant to the University of Utah Department of Biomedical Informatics. Data collection for this publication was supported by a grant from the Utah Department of Health Asthma Program to L.A.C.-A.

Correspondence and requests for reprints should be addressed to Craig C. Teerlink, M.S., Department of Biomedical Informatics, University of Utah, 26 South 2000 East, Room 5775 HSEB, Salt Lake City, UT 84112-5750. E-mail: craig.teerlink@utah.edu

Am J Respir Crit Care Med Vol 176, pp 865–870, 2007

Originally Published in Press as DOI: 10.1164/rccm.200703-448OC on August 9, 2007

Internet address: www.atsjournals.org

the University of Utah Institutional Review Board and by the Utah Resource for Genetic and Epidemiology Research.

The individual data in the UPDB have been record-linked to Utah death certificates containing physician-documented cause-of-death data. The resource currently includes death certificates from 1904 to 2004, and consists of more than 400,000 individuals for whom there is both genealogy data and known cause of death. Death certificates were linked to Utah individuals in the genealogical resource using name and birthdate data; approximately 40 to 50% of the individuals represented on death certificates matched individual records in the UPDB (18). Cause-of-death data were coded with International Classification of Diseases (ICD), revisions 6–10, beginning in 1957. Death certificates for 1904 to 1957 were retrospectively coded with ICD revision 10 codes. The specific ICD codes used to identify asthma deaths appear in Table 1. All individuals with asthma as a cause of death on Utah death certificates were identified ($n = 2,536$). We analyzed only those individuals who died with asthma as a cause of death who also had at least three generations of genealogical data ($n = 1,553$).

The Genealogical Index of Familiarity (GIF) statistic was designed to identify familial aggregation of specific traits within the Utah genealogy (23). The GIF method of analysis has been used in previous studies of familiarity for cancers, aneurysm, and heart disease (10–12, 16–20, 24). A method of analysis similar to the GIF statistic has been used in analyzing extended Icelandic genealogies (25–28). An advantage to the GIF statistic over other methods is that it takes into account all genetic relationships between all cases.

The GIF statistic measures the average relatedness between all pairs of individuals with a specific phenotype (cases). The Malecot coefficient of kinship is used to measure the degree of relatedness between all pairs of cases. The coefficient of kinship is defined as the probability that randomly selected homologous genes from two individuals are identical by descent from a common ancestor and accounts for all possible relationships between a pair of cases (29). The calculation is simplified by use of genetic path diagrams. For any two individuals, the coefficient of kinship is equal to the sum of $(1/2)^n$ for each of all possible pathways between the two individuals, where “ n ” is the number of individuals along the pathway. The case GIF is the mean of all coefficients of kinship between all possible pairs of cases. The coefficient of kinship for any two individuals in an outbred population is expected to be close to zero. The case GIF is multiplied by 10^5 for ease of presentation.

To test the hypothesis of no excess relatedness among cases, an empirical control distribution was created. For each asthma case, a control was selected at random from the genealogy resource, matched according to sex, 5-year birth cohort, and place of birth (in or out of Utah), resulting in a control set of the same size as the case set. The matching strategy is used to account for potential differences in kinship based on differences in birth year, sex, and place of birth. One thousand independent control sets were selected and the GIF measured for each

set to create an empirical distribution of average relatedness under the null hypothesis of no excess relatedness among cases. The hypothesis is tested by comparing the case GIF to the empirical distribution of the 1,000 control GIFs.

The degree of shared genetic composition between pairs of cases representing different genetic distances is quantifiable through the GIF analysis. We assume that the degree of shared environment among individuals diminishes to a population level of sharing beyond second- or third-degree relatives for the Utah population. Among close relationships, it remains difficult to identify whether excess familiarity is due to shared environment or shared genetic composition or a combination of both. However, among more distant relationships, significant excess relatedness is indicative of a genetic contribution. We compared contributions to the GIF statistic for cases and control sets across genetic distance. In the GIF analysis, genetic distance is approximated by path length between individuals in a pair. For example, a parent and a child are assigned a genetic distance of 1, siblings a genetic distance of 2, an aunt and a niece a genetic distance of 3, and so forth. The empirical significance of the GIF test tells us whether overall excess familiarity is observed. This same test is also performed excluding all close relationships (first- and second-degree relatives) to determine whether the excess familiarity is also significant when ignoring all close relationships, further supporting the hypothesis of a genetic contribution.

Estimation of relative risks (RRs) in relatives is an alternative approach to testing the hypothesis of a familial contribution to disease. Although the GIF analysis uses all relationships between all cases regardless of genetic distance, the RR analysis typically relies on comparisons in close relatives only. The RR approach compares observed asthma mortality in relatives of probands with the expected rates of asthma mortality as represented in the UPDB. All individuals in the UPDB with genealogy data and with known cause of death were used to estimate cohort-specific asthma mortality rates.

We estimated RR as follows: All 2.2 million individuals in the UPDB with at least three generations of genealogy were assigned to 1 of 132 cohorts based on birthplace (in/out of Utah), sex, and 5-year birth-year cohorts. For each cohort, internal cohort-specific asthma mortality rates are calculated by summing the number of individuals in each cohort with asthma as a cause of death and dividing by the total number of individuals in the cohort with a death certificate. These internal cohort-specific asthma mortality rates estimate the expected rate of asthma death for each cohort. The expected number of asthma deaths among deceased first-degree relatives of probands is calculated by multiplying the number of deceased first-degree relatives of probands (counted without duplication) in each cohort by the cohort-specific internal rate of asthma mortality, and then summing over all cohorts. The number of observed asthma deaths among relatives is a count (without duplication) of all of the relatives of asthma deaths who also died of asthma. The first-degree RR statistic is the ratio of the number of observed asthma deaths among first-degree relatives of asthma deaths to the number of expected asthma deaths among first-degree relatives. The RR was similarly estimated for second- and third-degree relatives. The ratio of observed deaths to expected deaths is an unbiased estimator of RR (also termed “standardized morbidity rate”). One-sided probabilities for the alternative hypothesis test of $RR > 1.0$ were calculated under the null hypothesis $RR = 1.0$, under the assumption that the number of observed deaths follows a Poisson distribution with the mean equal to the expected number of deaths. The Poisson distribution is an approximation of a sum of multiple binomial distributions, representing the number of expected deaths in each cohort. This Poisson approximation is appropriate for both rare and common phenotypes, being more conservative for common diseases.

Although significantly elevated risks in first-degree relatives suggest a genetic contribution to disease, they may also result from shared environment, or a combination of both genes and environment. Significantly elevated risks for second- or third-degree relatives are strongly suggestive of a heritable component.

RESULTS

Table 1 provides sample sizes according to the specific ICD codes used to identify the 1,553 cases analyzed. The observed drop in the number of asthma deaths in the 1960s and 1970s appears to

TABLE 1. ASTHMA DEATHS WITH GENEALOGY DATA AS IDENTIFIED BY INTERNATIONAL CLASSIFICATION OF DISEASES, REVISIONS 6–10, CODES ON UTAH DEATH CERTIFICATES

Decade of Death	ICD Revision (Code)						Decade Total
	ICD 6 (241)	ICD 7 (241)	ICD 8 (493)	ICD 9 (493)	ICD 10 (J45)	ICD 10 (J46)	
1904–1909					38		38
1910–1919					93		93
1920–1929					99		99
1930–1939					118	1	119
1940–1949					171	5	176
1950–1959	26	24			75	5	130
1960–1969		106	19				125
1970–1979			54	8			62
1980–1989				135			135
1990–1999				223	55		278
2000–2004					298		298
Total							1,553

Definition of abbreviation: ICD = International Classification of Diseases.

Numbers in parentheses indicate ICD code used to identify a death certificate.

result from coding changes or differences in coding among ICD revisions 7, 8, and 9, and has been observed elsewhere (30). This drop is observed not only in the set of 1,553 asthma deaths analyzed here but also in all 2,536 asthma deaths reported in Utah. The increased number of reported deaths from asthma observed in more recent decades appears to result from including more than one cause of death on these later death certificates.

To determine whether the asthma cases analyzed in this study (those with linked genealogy data) were representative of all asthma deaths in Utah in the same time period, we compared the two groups according to average age at death, sex, and ICD codes used to identify asthma as a cause of death (shown in Table 1). Asthma accounted for 2,536 deaths among all Utah death certificates. The average age at death for all Utah asthma deaths was 66.6 years, with 51.0% males ($n = 1,294$). The 1,553 Utah individuals who died of asthma and who also had genealogy data accounted for 43.9% of all Utah asthma deaths. The average age at death for the cases we analyzed was 68.1 years of age; 52.1% of these deaths were males ($n = 809$). Age at death was significantly higher for the asthma deaths we analyzed ($P = 0.02$), with an observed difference of 1.5 years. The groups were not significantly different in sex composition ($\chi^2 P$ value = 0.52), or in ICD codes used to identify asthma as a cause of death ($\chi^2 P$ value = 0.32). The number of asthma deaths per decade in the entire death certificate resource is not statistically different from the number of asthma deaths per decade for those with genealogy data ($\chi^2 P$ value = 0.392).

Table 2 shows the results of the GIF analysis for cases and control sets, and the empirical P value for the hypothesis test of no excess relatedness. Two separate analyses are shown: the GIF analysis of all cases and the GIF analysis ignoring close relationships (genetic distance < 4). Each analysis showed significant excess relatedness among cases ($P < 0.001$ and $P = 0.02$, respectively). The excess relatedness among cases when compared to control sets is illustrated in Figure 1, which plots the contribution to the GIF statistic for each type of paired relationship (genetic distance). The contribution to the GIF statistic at each genetic distance is the number of pairs identified with that particular genetic distance weighted by the value of the Malecot kinship coefficient for that genetic distance. The contribution to the GIF statistic for all asthma mortality cases exceeds that for the control sets up to a genetic distance of 6, which represents second-cousin relationships. We analyzed the 1,222 individuals with asthma reported as the primary cause of death separately. The results obtained in this subset were similar to those of all cases examined together.

The RR analysis used to test the hypothesis of increased risk of asthma mortality for first-, second-, and third-degree relatives of individuals who died of asthma is summarized in Table 3. For each category of relative, Table 3 provides the number of deceased relatives of probands, the observed and expected number of asthma deaths among these relatives, one-sided significance values for the test of the alternative hypothesis $RR > 1.0$, the estimated RR to relatives, and 95% confidence intervals for the RR estimates. RRs were significantly elevated for first- and

second-degree relatives ($P < 0.001$ and $P = 0.003$, respectively), and suggestive for third-degree relatives ($P = 0.065$). Similar results were obtained in the 1,222 individuals in whom asthma was reported as the primary cause of death (data not shown).

DISCUSSION

The familial component of asthma has been previously investigated in many study populations around the world (3, 31–40). Studies have considered several asthma phenotypes, including wheezing as a symptom of asthma, exercise-induced bronchospasm, and bronchial hyperresponsiveness (3, 31–42).

Previous investigations have relied on three major methodologies to determine the extent of a familial contribution. Studies using twins have shown evidence of a genetic predisposition to asthma phenotypes (43, 44). Family history has been confirmed as a risk factor for asthma in several studies (4, 36–42). These studies are characterized by a heavy reliance on patient report of family history and wide range of definitions for positive family history (5). Familial aggregation of asthma-related phenotypes has been reported (3, 33–35, 43, 44). Although these studies show evidence of a familial component to asthma, all of the studies were restricted to first-degree relatives. The restriction of analysis to first-degree relatives does not allow discrimination of shared environmental factors from shared genetic factors, or joint effects of both. In addition, previous studies have not investigated the most severe phenotype of asthma mortality.

The use of the GIF and RR methodologies are well established within population-wide genealogy resources as a means to describe the heritable component to a disease phenotype. The use of the UPDB genealogy data linked to death certificates allows an examination of familial aggregation of disease traits among distant relationships. This increases the power of the study and reduces recall bias. Using death certificates to identify cases eliminates the possibility of patient misreporting or patient memory error because the diagnoses are made by a physician at the time of death. A potential shortcoming of this study is the use of death certificates to diagnose asthma as the cause of death. The accuracy of death certification in asthma deaths decreases with advancing age, due to the misclassification of asthma with chronic obstructive pulmonary disease (COPD) (45–47). However, other studies of death certificate diagnoses of asthma as an underlying cause of death have noted a low sensitivity but high specificity (38, 48). This suggests that many cases were missed but that the cases that were identified were correct. Utah also has the lowest smoking rate in the United States, at approximately 10%, and one of the lowest COPD mortality rates (49, 50). The lower COPD prevalence and mortality in Utah may decrease the misidentification of COPD deaths as asthma in this study. The methods presented are robust to incomplete ascertainment and false positives are well tolerated (18). Because Utah's founding population originated from northern Europe, results of familial studies using the UPDB genealogy records can be generalized to other populations of northern European descent. Population-based genealogy resources also allow for ascertainment of high-risk pedigrees, which may be used in further study of genetic factors of disease. Perhaps the greatest impact of the data resource is the ability to distinguish between shared environment and genetics by extending analyses beyond first-degree relatives where shared environment is likely to be the most acute (18, 19).

Despite these benefits, relying on death certificates for ascertainment of cases has several limitations. The ICD codes used to categorize cause of death on Utah death certificates lack sufficient granularity to distinguish asthma phenotypes and do not describe the clinical features of identified asthma cases.

TABLE 2. GENEALOGICAL INDEX OF FAMILIALITY RESULTS FOR 1,553 ASTHMA DEATHS, CONTROLS VERSUS CASES

	All Cases	Ignoring First- and Second-degree Relationships
Case GIF	3.16	1.95
Control GIF	2.42	1.73
Empirical P value	<0.001	0.026

Definition of abbreviation: GIF = Genealogical Index of Familiarity.

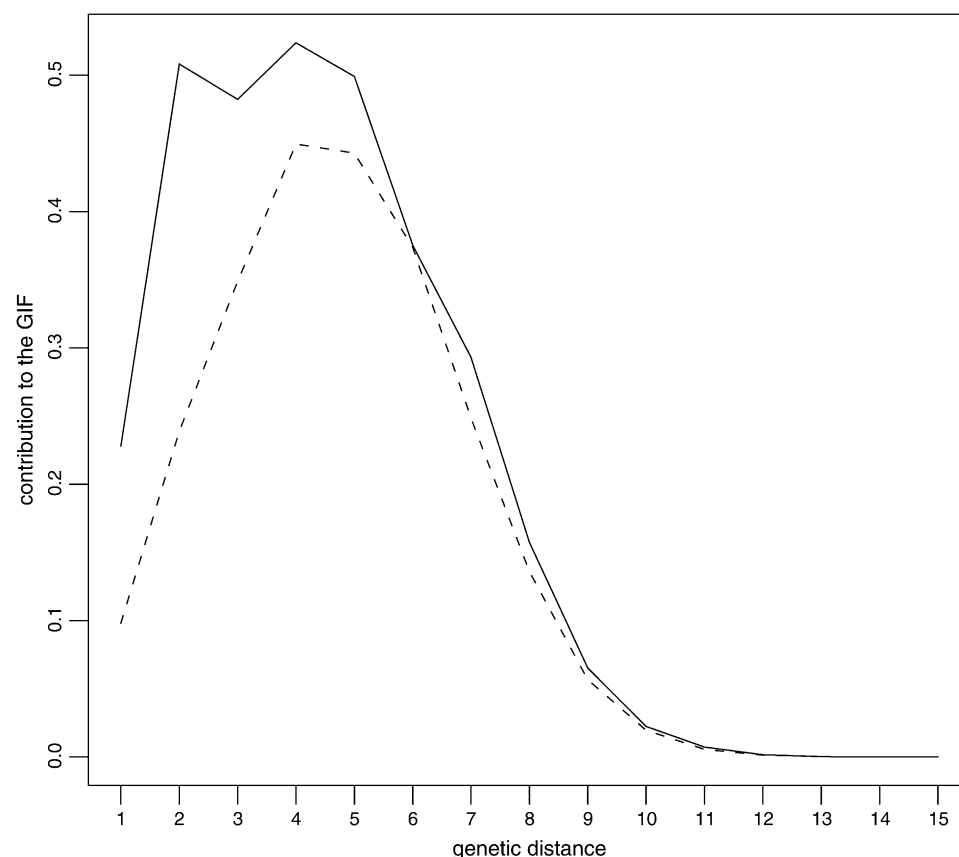


Figure 1. Contribution to the Genealogical Index of Familiarity (GIF) statistic by genetic distance between pairs of individuals for asthma mortality: 1,553 cases (solid line) and 1,000 sets of matched control subjects (dashed line).

There is a potential for misdiagnosis of cause of death on a death certificate, particularly with diseases that are clinically difficult to distinguish, as is the case with asthma. The definition of asthma may have changed over the 100-year span of the death certificate resource. This may be further complicated by the retrospective coding for all death certificates before 1957. Asthma is generally considered to be an underdiagnosed disease (51). The possibilities of misdiagnosis or underdiagnosis of asthma are mitigated by the robust qualities of the analytical methods. The effects are likely conservative.

A further limitation to the study is the inability to measure the impact of smoking on asthma mortality among cases or controls. Although smoking is a known risk factor for asthma, our data resources do not allow direct measurement of smoking status. Therefore, smoking is a potential confounding factor in the present study if smoking habits are consistent among distant relatives (i.e., second- and third-degree relatives). As discussed, smoking rates in Utah are the lowest in the United States, which would decrease the confounding effects of smoking in this population (50).

TABLE 3. RELATIVE RISKS FOR CATEGORIES OF RELATIVES OF ASTHMA DEATHS

	No. of Deceased Relatives	Observed Asthma Deaths	Expected Asthma Deaths	One-sided P Value	RR	95% Lower CI	95% Upper CI
First-degree relatives	7,936	52	30.7	<0.001	1.69	1.26	2.22
Second-degree relatives	19,319	100	74.8	0.003	1.34	1.09	1.62
Third-degree relatives	28,601	129	112.2	0.065	1.15	0.96	1.37

Definition of abbreviations: CI = confidence interval; RR = relative risk.

Asthma mortality as recorded by death certificates does not detect severity indicators for asthma, with the exception of death. Although asthma mortality represents a severe phenotype, it should not be confused with asthma severity phenotypes defined by clinical stages of disease. As a result, our conclusions may not be generalizable to other asthma severity phenotypes.

The results of the analyses support a heritable contribution to predisposition to asthma mortality. The GIF results indicate excess relatedness of individuals dying of asthma which are above that expected in this population at both close and distant degrees of relationship. Although the extent of shared environment is not quantifiable in this analysis, it will likely be less at distant relationships, supporting the conclusion of a genetic contribution. The RR results also indicate significantly increased risks in both close and more distant relationships (i.e., second- and third-degree relatives), although results did not achieve significance for third-degree relatives. The significantly elevated risk to distant relatives of cases supports the conclusion that a heritable predisposition contributes to asthma mortality. The magnitudes of estimated risk for different categories of relatives are modest but meaningful when considered on a population basis, given the extreme nature of the phenotype definition. Given the origins of the Utah population, estimates of risk are best generalized to populations of northern European descent and may not be generalizable to other populations.

These results add to the mounting evidence for a heritable component to asthma, particularly for a severe phenotype. The results should provide further incentive for asthma providers to thoroughly question their patients about family history as it is a risk factor for asthma mortality. The results encourage investigation of other asthma phenotypes within large population-based data resources such as the UPDB. Such studies could increase the possibility of improved detection and prevention

strategies for asthma, provide identification of resources for gene discovery, and encourage further investigation of the genetic factors of asthma.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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