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Twin Studies of Disease Heritability Based on Medical Records: Application to Acne Vulgaris

Gary D. Friedman
Department of Medical Methods Research, Kaiser-Permanente Medical Care Program, Oakland, California

Abstract. Establishment of the Kaiser- Permanente Twin Registry permitted the study of disease heritability in twins based on review of the twins' medical records. The records of 930 pairs of twins were reviewed. Based on previous questionnaires, 342 pairs were MZ, 345 were DZ and 243 were of unknown zygosity. Because of the age distribution of these twins and the time period in which they received care, conditions of youth, such as acne vulgaris were most reliably studied. Heritability of acne was assessed in three ways; all indicated a substantial genetic influence. Certain problems with twin studies using medical records became apparent: 1) Zygosity information is often lacking; 2) Differing times and durations of observation of the two twins in each pair must be accounted for; 3) Categorization by diagnosis is difficult and strict criteria for diagnosis may be impractical; 4) Patients' behavior that affects assessment of disease concordance must be considered; 5) The order in which records are reviewed may influence apparent concordance.

Key words: Acne vulgaris, Heritability, Twins, Medical records

INTRODUCTION

The Kaiser-Permanente Twin Registry was assembled mostly in the mid-1970's as previously described in detail [4]. The effort to recruit twin volunteers was directed primarily toward twins who were subscribers of the Kaiser-Permanente Medical Care Program (KPMCP) in Northern California. The KPMCP is a large health maintenance organization which provides both inpatient and outpatient medical care. Altogether 21,967 twins have been recruited so far, representing both members of 9,747 sets and 2,473 single twins. The

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last annual newsletter to our twins was mailed in May, 1983 to 14,770 twins who were still participating and for whom we believed we had mailing addresses that were accurate as of mid-1982.

One of the main reasons for establishing a twin registry in the KPMCP was that this setting would foster studies of medical and health-related questions in twins. In particular, comprehensive longitudinal medical records exist for the KPMCP's subscribers. These records should provide better documentation of the presence of disease than would questionnaire or death certificates.

We have now conducted some studies of disease heritability using these medical records. We would like to report our experience with this type of study to other investigators of twins. Also, this effort led to a substantial set of data concerning the heritability of the common skin condition, acne vulgaris.

MATERIALS AND METHODS

We initially identified 1,144 pairs of same-sex twins, age 18 years and over, who, when they joined the registry, reported that they were both subscribers of the KPMCP. When it came time to review their medical records, we located and abstracted the records of 930 pairs. Of the excluded pairs, almost half proved to contain one or both twins who were not KPMCP subscribers in our region (some of these subscribed in Southern California), about one third appeared twice in our records under two different identification numbers, and there were a few whose records we could not locate or who were only single twins without cotwins in our registry.

Each of the outpatient medical records (which also contain either hospitalization records or hospital discharge summaries, depending on the facility) was abstracted by one of two trained reviewers. At first, and periodically thereafter, records were read in duplicate to maintain accuracy and consistency. The records of the two twins in each set were reviewed at widely separate times (at least several months apart) to minimize any influence of recall of the first twin on the review of the second. The information abstracted included race, birth date, approximate date at which subject entered KPMCP (based on medical record numbers, which are assigned sequentially), date of first and last visit in record, and date at which subject left KPMCP (based on computer search of termination records, which are not always accurate). Each diagnosis mentioned in the chart was recorded and coded according to a sheme we developed to cover the most frequent illnesses. Also abstracted was the calendar year in which each diagnosis was first mentioned, last mentioned, and the number of calendar years in which it was mentioned. If the condition was noted to have been present before the subject joined the KPMCP, the year or approximate year when it was first diagnosed was also recorded. KPMCP records go back to about 1946 for the earliest subscribers.

In the routine analyses heritability was estimated by the classical formula of Holzinger: $H = \frac{C_{MZ} - C_{DZ}}{1 - C_{DZ}}$ where C_{MZ} and C_{DZ} are the proband concordance rates for monozygotic and dizygotic twins, respectively [1]. To conform with more modern genetic theory, heritability (h^2) was computed from the acne data by the method of Reich et al [11] as recently advocated by Gottesman and Carey [6]. Also, observed and expected coincidence rates were computed as suggested by Cederlöf et al [2] for population-based twin studies. The expected coincidence is merely the square of the prevalence rate of the disease under study; it assumes that concordance in twin pairs is purely a chance occurrence.

RESULTS

Characteristics of the Medical-Record-Review Study Group

Zygosity information was obtained from brief questionnaires that were filled out by the twins or their parents when they joined the registry. Zygosity was unknown or the twin pair disagreed for 243 of the 930 pairs and they were thus excluded, leaving 342 MZ pairs and 345 DZ pairs. The racial composition of the 687 usable pairs was as follows: 79.3% white (including Hispanic), 6.1% black, 1.5% Asian, 13.1% unknown. (Race is routinely recorded in our records only when a patient is hospitalized. Physicians' descriptions are the other main source of racial identification in the medical records). Altogether, 63.0% of the twins were female, 37.0% were male. The age distribution at time of first visit is shown in Table 1. Although the group was selected to be aged 18 and over at the time of chart review, so that we could focus on diseases of adulthood, the charts went back to infancy and early childhood in many cases. Eighty-six percent of first visits were recorded below the age of 30 years.

The duration of medical information covered by the charts ranged from less than one year to 33 years, as judged by the interval between the first and last recorded visit. The mean and standard deviation of duration of medical information were 12.5 years and 7.7 years, respectively.

Table 1 - Distribution of Age at First Visit of Each Twin

Age (yrs)	N	%	Age (yrs)	N	%
0-4	290	21.1	40-44	42	3.1
5-9	142	10.3	45-49	34	2.5
10-14	175	12.7	50-54	28	2.0
15-19	169	12.3	55-59	18	1.3
20-24	137	10.0	60-64	8	0.6
25-29	158	11.5	65-69	1	0.1
30-34	104	7.6	70-74	1	0.1
35-39	67	4.9	Total	1374	100.1

Different Coverage for Twins Within a Given Pair

Twins do not necessarily receive medical care at the same time. There were many indications of this when we reviewed their records. For example, Table 2 shows those twin pairs in which the first clinic visit made by either twin occurred below the age of 50 years. The pairs are divided into 5-year age periods according to the age at first medical contact with the first twin to be seen. The distribution of the age at first visit of the second twin is shown to the right of each 5-year age period. Although concordance for age at first visit was reasonably good, some wide discrepancies were noted. For example, among twins in which the first visit of one twin was before the age of 5 years, 6% of first visits of the second twin occurred after the age of 10. A greater tendency for large age discrepancies was noted, as expected, for older twins, who lead more independent lives. This is evident in Table 2 for twins whose first visit was recorded between the ages of 30 and 50.

Heritability of Disease: General Observations

Our main interest in conducting this study was in the leading chronic degenerative diseases of adulthood such as coronary heart disease and cancer. Unfortunately, because of the age composition of the study group, the data on the diseases was very meager. Several examples are shown in Table 3. It can be seen that the chief clinical manifestations of coronary heart disease, ie, myocardial infarction and angina pectoris, were quite infrequent with at most one concordant pair in any sex-zygosity group. A diagnosis of hypertension was more frequent, but even here the numbers were sufficiently unstable to yield bizarre negative heritability value in women. This was not confirmed in our examination study of adult female twins in which heritability values of 0.25 for systolic and 0.32 for diastolic blood pressures were found. There were no cerebral hemorrhages noted and only one cerebral infarction; this occurred in a DZ male.

Table 2 - Age at First Visit of First and Second Twin. Includes all pairs first seen before the age of 50 yrs and excludes any pairs with part of chart of at least one twin missing

Age at first medical encounter of first twin	No of pairs	Percentage* of second twins whose first medical encounter was in:			
		Same 5-year age group	Next 5-year age group	Next 5-year age group	Still later
0-4	145	85	9	3	3
5-9	66	82	17	0	2
10-14	82	84	15	0	1
15-19	85	76	18	4	2
20-24	86	31	45	19	5
25-29	70	57	27	10	6
30-34	47	34	43	13	11
35-39	24	38	21	25	17
40-44	20	30	35	20	15
45-49	11	36	55	9	0

* Some percentages in the row do not add up to 100% because of rounding.

Cancers were also quite infrequent as can be seen with the four ordinarily common cancer sites – lung, colon, breast and skin – shown on Table 3. Only for skin cancer were there any concordant pairs, but never more than two, which leads to low reliability for heritability values.

Some more common conditions also appear on the table, particularly obesity, hemorrhoids, asthma, hay fever, and hernia. These all showed positive heritability values ranging from very small (0.02) to moderate (0.46).

Heritability of Acne

Acne vulgaris had been diagnosed in 263 (19%) of the 1,374 twins whose records we analyzed. The heritability data determined initially without considering duration of observation are shown in the top row of Table 4. The values were 0.58 for males and 0.44 for females. The distribution of twin pairs into concordant negative, discordant, and concordant positive subsets differed significantly between MZ and DZ twins; the probability values resulting from chi-square tests were $P = 0.02$ for males and $P < 0.001$ for females.

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Table 3 - Heritability of Several Chronic Diseases, Based on Diagnoses Recorded in Kaiser-Permanente Medical Records

Condition	No. of concordant, discordant male pairs			No. of concordant, discordant female pairs		
	MZ	DZ	H	MZ	DZ	H
Myocardial infarction	1,1	0,2	0.67	0,1	0,2	0.00
Angina pectoris	0,5	0,3	0.00	0,3	1,2	−1.00
Hypertension	6,6	3,15	0.53	10,26	14,17	−0.50
Cancer of colon	0,0	0,0	–	0,0	0,0	–
Cancer of lung	0,0	0,0	–	0,0	0,0	–
Cancer of breast	0,0	0,0	–	0,2	0,2	0
Cancer of skin (non-melanoma)	2,9	0,9	0.31	1,12	2,10	−0.20
Chronic bronchitis	0,5	1,4	−0.50	2,8	0,7	0.33
Asthma	4,10	5,13	0.02	9,22	3,22	0.30
Hay fever	18,35	11,45	0.27	16,49	16,65	0.10
Hypothyroidism	0,4	0,3	0.00	0,12	1,11	−0.18
Diabetes mellitus	0,7	2,4	−1.00	1,3	0,10	0.40
Gout	0,3	0,2	0.00	0,1	0,0	0.00
Obesity	10,13	4,22	0.46	18,26	21,49	0.22
Migraine	0,4	0,0	0.00	2,14	1,5	0.12
Hernia (inguinal, femoral)	5,16	2,19	0.26	1,3	0,4	0.40
Gallbladder disease	0,2	0,0	0.00	0,11	0,9	0.00
Varicose veins	0,2	0,6	0.00	1,7	4,9	−0.47
Hemorrhoids	7,25	3,18	0.15	4,25	2,26	0.13

Table 4 - Heritability of Acne Vulgaris

When ascertained	Male pairs C+,D,C−		Heritability		Female pairs C+,D,C−		Heritability	
	MZ	DZ	H	h^2	MZ	DZ	H	h^2
No restrictions	19,11,95	11,25,93	.58	.71	22,24,171	18,63,135	.44	.84
Only during observation of both twins (see text)	19,11,95	9,27,93	.63	.92	18,25,174	14,57,145	.39	.82

C+,D,C− = number of concordant positive, discordant, concordant negative pairs.

H = heritability according to Holzinger; h^2 = heritability according to Reich et al.

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Because of the within-pair discrepancies in duration of medical follow-up, we reanalyzed the data, requiring that acne had to be recorded in either twin when or after the second twin had his/her first visit and before either twin stopped having medical visits or before the earliest chart review date. This assured that the "window" of ascertainment was the same for both twins. The findings with this approach are shown in the second row of Table 4. For MZ males there was no change in the number of pairs concordant or discordant for acne. For DZ males there were 2 fewer (9 vs 11) concordant and 2 more (27 vs 25) discordant pairs, compared to the initial unrestricted analysis. This reduction in apparent concordance and increase in apparent discordance for DZ twins led to an increase in the heritability value from 0.58 to 0.63, a small change.

In the MZ females there was a reduction by 4 of concordant pairs and an increase by 1 of discordant pairs. The DZ females showed apparent reductions of both concordant (by 4) and discordant (by 6) pairs. As a result the heritability value was reduced slightly, from 0.44 to 0.39.

When the method of Reich et al [11] was used, heritability values were considerably higher (Table 4) suggesting that heredity plays a major role in the causation of acne. In males, restricting the window of ascertainment substantially increased heritability.

Both MZ and DZ twins exhibited greater than expected coincidence of acne by the method of Cederlöf et al [2] (Table 5). The 4-fold excess in MZ twins was clearly greater than the 1.6- to 2.6-fold excess in DZ twins. There was little change in the findings when the window of ascertainment was made equal for both twins in each pair.

Table 5 - Observed and Expected Coincidence Rates for Acne Vulgaris

When ascertained		Males		Females	
		MZ	DZ	MZ	DZ
No restrictions	Observed coincidence	0.152	0.085	0.101	0.083
	Expected coincidence	0.038	0.033	0.025	0.053
	Ratio: Obs/Exp	4.0	2.6	4.0	1.6
Only during observation of both twins (see text)	Observed coincidence	0.152	0.070	0.083	0.065
	Expected coincidence	0.038	0.030	0.020	0.039
	Ratio: Obs/Exp	4.0	2.3	4.2	1.7

DISCUSSION

The observation that there is a genetic factor in the etiology of acne vulgaris is not new. A tendency for acne to be inherited has been noted before both in pedigree studies and in twin studies [7,10 and Liddell, cited in 12]. Hecht [7] summarized his clinical observations in families as follows: "If the parent whom the child resembles had acne vulgaris, the child will probably get it".

More important is what we have learned from this investigation about conducting studies of twins using the medical records of a health maintenance organization.

First, it should be recognized that zygosity information is not routinely recorded in medical records. There is no reason for it to be recorded, for most twins. It becomes important when one twin develops a disease for which tissue or organ transplantation might be used, but this is rare. If occasionally a doctor notes zygosity in the record, it would probably be based on general appearance as observed by the doctor, a twin, or a parent. Forunately, we also had self-reports concerning zygosity for our participating twins, but missing information and within-pair disagreements as to zygosity led to our discarding 243 (26%) of our 930 pairs. Previous validation studies of our self-reported zygosity data by genetic markers in blood [8] led to the conclusion that self-report of monozygosity was quite accurate in our group, but that 20% of self-reported DZ twins were MZ. Thus, our findings should show somewhat less contrast between MZ and DZ twins than is the true state of affairs and heritability values should be somewhat understated.

Next, duration of observation need not be the same for both twins. Even during childhood, when the twins are living together, one twin may have occasion to go to the doctor earlier, later or more often than the other. If both twins have a similar condition, it is not hard to imagine a harassed mother bringing in just one of two sick twins and using the prescribed medication on both. Or, one twin may dvelop a similar illness after the other does, and be given leftover medicine or other similar nonmedicinal treatments. Of course, such circumstances and, in general, the vagaries of the behavior of patients and thier parents not only affect duration of observation but whether or not an existing condition would *ever* be recorded in a twin's record.

Handling the problem of comparability of duration of observation is not simple. Forcing the duration of observation to be the same can have a variety of effects as was noted with the acne data. Any reduction of the observation period for either twin could result in missed diagnoses, which in turn could convert a concordantly positive pair to either a discordant pair or a concordantly negative pair; it could also convert a discordant pair to a concordantly negative pair. Since heritability is based on the relationship of the proportion of concordantly positive and discordant pairs in MZ and DZ twins, it is easy to see why a variety of effects on heritability could occur when the observation period is manipulated. If one cannot have assurance of observation of both twins through the entire age period when a disease can occur, one has to hope that both twins will be brought in at least once in search of help for the disease. In the real world of medical care there is no guarantee that this will happen. That being the case it is probably wise to analyze the data with and without time restrictions, or excluding certain pairs where there is a marked discordance in membership duration. In this way one could obtain some indication of the stability of findings under varying assumptions.

Attrition of usable twins is a problem that we have found in several types of twin studies, recently documented for our questionnaire-based investigation [5]. In the present study, our main losses came from a technical problem with duplicate records in our registry and lack of reasonably good zygosity information on many twins. Also, some records were missing or not available. Whenever this happens for one twin, the entire pair becomes unusable.

In our chart-review study, so far, we have relied on diagnoses as simply recorded by the attending physicians. As is well known [9], there is considerable variability in physicians' diagnoses, in terminology, in the criteria used, and in the doctor's degree of certainty about the presence of the condition. To reduce this variability and to have greater assurance that a diagnosed condition is actually present, one can establish specific criteria that must be met before the condition is considered to be present (for example of criteria used for acute myocardial infarction, see Friedman et al [3]). Unfortunately, especially in outpatient care where medical notes are often brief, the busy physician frequently does not record all of the information needed to satisfy the criteria required for research purposes. Further, if one is abstracting information concerning hundreds of medical conditions in many hundreds of twin pairs, the establishment and routine application of criteria for all conditions could be an enormous task, even if the recorded data were complete. For these reasons we chose to record the doctors' diagnoses in 160 categories; these had been used in previous studies and were familiar to our chart abstractors.

Considering the obvious uncertainties connected with the data from medical records, it is difficult to place much confidence in the "softer" information about medical diagnoses obtained from questionnaires and death certificates. It would seem that the best approach for studying most medical conditions is to examine the twins for the special purpose of ruling in or ruling out the condition of interest. For certain conditions such as cancer, generally the diagnosis is carefully documented by pathological examination of tissue. If one has access to all such records in a defined population, a special examination is not necessary. Still, I would not want to rely merely on the absence of such a record for the cotwin to conclude that a pair was discordant. I would want to contact the cotwin in some way to confirm the absence of the disease.

In conducting this study we attempted to keep the reviewers blind to the status of one twin while reviewing the record of the cotwin. The method used was to arbitrarily select one twin in each pair and review virtually all of the records of these first twins before reviewing the records of the second twins. In this way, at least several months elapsed between the review of cotwins' records, and the reviewers could not remember the first when the second was reviewed. It is likely that, if both cotwins' records are reviewed at about the same time, there would be a bias toward finding concordance. The presence of a disease in one twin would probably sensitize the reviewer toward finding the same condition in the cotwin. Although a good reviewer generally should not abstract conditions that are not recorded, there is often sufficient ambiguity in what is written to permit this kind of bias to occur. An alternative approach is to employ more than one reviewer and never permit cotwins' records to be abstracted by the same reviewer. A possible problem here is a bias toward discordance, since two persons abstracting the same record will probably exhibit greater differences in results than one person reviewing the same record twice. These are methodological subtleties that will probably not soon be formally investigated, given most investigators' understandable desire to use their limited research resources to obtain substantive findings.

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Correspondence: Dr. Gary D. Friedman, 3451 Piedmont Avenue, Oakland, CA 94611, USA.