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Familial Factors in Mortality with Control of Epidemiological Covariables. Swedish Twins Born 1886-1925

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Abstract. A Cox proportional hazard regression analysis was carried out that evaluated age-specific death risk among 21,890 twins born in Sweden during 1886 through 1925 and followed during 1962 through 1980. Cotwin's survival was used as the primary covariable, and auxiliary covariables were smoking, marital status and, among men, police registration for alcohol abuse. In each age, sex and zygosity group, except the oldest DZ males, cotwin's mortality had a significant, independent, positive relationship to the mortality risk of the individual. The auxiliary covariables, except marital status among females, had significant, independent, positive relationships to mortality among the youngest twins of both zygosity groups and in the middle age group of MZ twins. In the oldest age group, the death of MZ cotwins was the only variable significantly related to the individual's mortality. Heritability estimates for the age-specific probability or death risk, developed by different methods for different analysis groups, range between 0.4 and 0.6. They have reasonable internal consistency, are not much affected by the covariates, and are in agreement with other studies that did not control covariates.

Key words: Mortality, Twins, Risk factors, Familial factors, Smoking, Alcohol abuse, Marital status

INTRODUCTION

Twin concordance for death regardless of cause, that is, the risk of death of a twin if the cotwin is deceased, relates closely to the question of genetic determination of life span and the extent to which it can be extended by appropriate environmental interventions. The subject has been studied by Hrubec and Neel [8], Jarvik et al [9] and Wyshak [11], but none of those analyses considered the effect of covariables associated with mortality. Only the study by Wyshak [11] covered the complete life span, with no surviving twins at

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the conclusion of follow-up, but because of that, those twins could not be classified by zygosity. All three studies found evidence of a within-twin pair association for mortality. However, they could not evaluate the extent to which this association was due to environmental factors, probably shared to a different degree between members of monozygotic (MZ) and dizygotic (DZ) twin pairs. Thus, an investigation of twin concordance that considers important external covariables is of interest.

The study presented here examines the mortality of Swedish twins in relation to that of their cotwins, and accounts in that evaluation for the covariables of tobacco smoking, marital status and, among men, alcohol abuse as determined by records of associated law infractions. Standard methods are not available for genetic analyses of censored mortality observations together with environmental covariables. We present below an application of the Cox proportional hazards regression [3] which attempts to clarify interactions of genetic and environmental factors in twin mortality. We then compare the results to estimates of the heritability of age-specific death risk obtained from a conventional analysis that did not consider covariates.

MATERIALS AND METHODS

The construction and the composition of the Swedish Twin Registry has been described by Cederlöf [2]. The registry was compiled from certificates of twin births during 1886 through 1925. Included have been 10,945 pairs with both twins answering a questionnaire in 1961 through which was obtained the information on smoking and marital status used here. The questionnaire has also been used to determine the zygosity of the twins as described by Cederlöf et al [1]. Validations of this zygosity classification indicate that about 95% of the twins classify themselves in the same category as are classified there by laboratory methods.

Since 1932, a registry has been maintained in Sweden in which are recorded judgments of law violations related to alcohol use, as described by Helander [6]. This includes being drunk in public, drunken driving, committing crimes while under the influence of alcohol, and its illegal sale or manufacture. Among persons born 1915-1919, approximately 40 times more men than women have been registered [6], and therefore this information is being obtained only for the male twins. Although registration is related to alcohol consumption reported on the questionnaire, registration is thought to be a more direct measure of alcohol abuse that includes the social correlates of alcoholism.

Subjects in the Swedish twin registry are matched regularly against a registry of all deaths in Sweden. By this means, twin deaths occurring through 31 December 1980 have been identified and death certificates have been obtained and reviewed for them. The follow-up period starts on 1 January 1962. In this period, 2832, or 29.3% of the males, and 2747, or 22.5% of the females became deceased. The analyses presented here omit 416 males and 462 females for whom zygosity could not be determined and of whom, respectively, 32.2% and 24.2% became deceased during follow-up. To accommodate the wide range of ages during the follow-up period, the analysis was carried out separately in the year of birth groups 1886-1895, 1896-1905, and 1906-1925, constructed so as to contain approximately equal numbers of deaths. Table 1 shows the number of individuals in these groups by age, zygosity, and survival, as well as percent mortality, and percent casewise twin concordance of death. The latter is obtained by dividing the number of individuals in concordant pairs by the number of all affected individuals. Unlike the proband rate, it does not make use of a secondary investigation of affected pairs identified through probands [7]. In this application, such an investigation would be irrelevant since mortality ascertainment is virtually complete.

Multivariate analyses were carried out by applying the Cox proportional hazards model to these data [3]. To avoid the double counting of pairs and correlations between observations on individuals, one individual was selected at random from each pair, and the cotwin's information was used to determine within-pair correlations. The total number of study subjects so selected and the number of deaths that occurred among them in the follow-up period is shown by sex, zygosity and year of birth group in Table 2. The Cox regression procedure does not require knowledge of the mortality func-

Table 1 - Number of Twin Individals, Number of Deaths, 1 Jan 1962-31 Dec 1980, Percent Mortality, and Percent Casewise Concordance, by Year-of-Birth Group, Zygosity and Sex

	1886 - 1895		1896 - 1905		1906 - 1925	
	MZ	DZ	MZ	DZ	MZ	DZ
			MALES			
Total number	380	436	660	1150	2258	4380
Number of deaths	319	372	322	626	353	706
Percent mortality	83.9	85.3	48.8	54.4	15.6	16.1
Percent concordance	87.8	87.1	61.5	60.4	36.8	26.3
			FEMALES			
Total number	424	776	810	1620	2780	5338
Number of deaths	321	581	304	603	277	549
Percent mortality	75.7	74.9	37.5	37.2	10.0	10.3
Percent concordance	82.2	78.1	53.3	47.1	26.0	20.4

Table 2 - Sample for Cox Regression Analysis, One Twin from Each Pair: Number of Subjects at Start of Follow-up[a] and Number of Deaths by Zygosity, Sex and Year-of-Birth Group

Year-of-birth group	MZ twins Total number	MZ twins Deaths	DZ twins Total number	DZ twins Deaths
		MALES		
1886 - 1895	190	160	218	182
1896 - 1905	330	159	575	311
1906 - 1925	1129	177	2190	356
Total	1649	496	2983	849
		FEMALES		
1886 - 1895	212	167	388	295
1896 - 1905	405	163	810	306
1906 - 1025	1390	138	2669	264
Total	2007	468	3867	865

[a]Follow-up is from 1 January 1962 to 31 December 1980.

tion, and it deals with right-censored survival ages. Our application of this model for males is described in Table 3. The model assumes an unspecified hazard function that depends on time (t) and covariables $Z_1, Z_2, ..., Z_n$. Age during follow-up has been used for t, the primary covariable is cotwin's mortality, and auxiliary covariables are the subject's smoking and marital status and the cotwin's smoking and marital status. For males, the subject's and the cotwin's alcohol registration status have also been included as auxiliary covariables. Thus the full model contains 6 auxiliary covariables for males and 4 for females. The percent of twins in the groups with score >0 is shown for each auxiliary variable by year of birth, zygosity and sex in Table 4.

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Table 3 - The Cox Proportional Hazard Model as Applied to Data for Male[a] Twins

$$h(t,Z_1,Z_2,Z_3,Z_4,Z_5,Z_6,Z_7) = h_0(t)\ \exp(\beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_3 + \beta_4 Z_4 + \beta_5 Z_5 + \beta_6 Z_6 + \beta_7 Z_7), \text{ or}$$

$$\ln \frac{h(t,Z_1,Z_2,Z_3,Z_4,Z_5,Z_6,Z_7)}{h_0(t)} = \beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_3 + \beta_4 Z_4 + \beta_5 Z_5 + \beta_6 Z_6 + \beta_7 Z_7$$

Definitions

$h(t, Z_1, ..., Z_7)$	An unspecific mortality function
$h_0(t)$	The mortality function for base values of the covariables
t	Age at follow-up in years

Primary covariable

Z_1	Value for cotwin's death, coded as 0 = living, 1 = deceased

Auxiliary covariables

Z_2	Value for subject's smoking, coded as 0 = never smoked, 1 = ever smoked
Z_3	Value for cotwin's smoking, coded as for subject
Z_4	Value for marital status, coded as 0 = currently married, 1 = never married, 2 = previously married, including widowed
Z_5	Value for cotwin's marital status, coded as for subject
Z_6	Value for alcohol registration, coded as 0 = not registered, 1 = registered
Z_7	Value for cotwin's alcohol registration, coded as for subject
$\beta_{1 \ldots 7}$	Regression parameters for the respective $Z_i \neq 0$ so that

$$RR_i = \text{Relative risk of death for } \frac{Z_i \neq 0}{Z_i = 0} = e^{\beta (Z_i \neq 0)}$$

[a]The alcohol registration covariables Z_6, Z_7 have been omitted for females.

Table 4 - Percent of Individuals in High-Score Groups by Auxiliary Covariable Status, Year-of-Birth Group, Zygosity and Sex

Auxiliary covariable status	1886 - 1895		1896 - 1905		1906 - 1925	
	MZ	DZ	MZ	DZ	MZ	DZ
			MALES			
Ever smoked	56.8	55.7	69.8	65.5	68.6	67.4
Never married	12.6	19.3	13.2	18.3	15.6	19.3
Previously married	12.6	13.5	8.3	6.6	4.2	4.4
Alcohol registration	6.3	8.9	14.5	11.9	14.3	16.7
			FEMALES			
Ever smoked	6.6	6.4	8.6	10.7	26.9	24.7
Never married	21.9	27.2	22.5	24.8	13.2	14.8
Previously married	30.2	26.3	15.7	14.1	7.5	7.3

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The model will produce a satisfactory fit if death rates can be modeled as log-linear functions of the covariables, which then have a multiplicative effect on the underlying hazard function. For each covariable in the equation, the regression coefficients provide a means of estimating relative risk, standardized for its association with the other covariables. The analysis corrects for possible associations of risk factors between twin pair members, who are of the same or similar genotype. Thus, we obtained estimates of relative mortality due to the cotwin's status on the risk factor being evaluated, standardized for the other covariables of the twin and of the cotwin. The analysis was carried out for specific sex, zygosity and year of birth groups. Coefficients were tested for significance by the Wald test, based on the asymptotic normality of maximum likelihood estimates [10].

In additional analyses, the model, as described in Table 3, has been simplified by excluding all the auxiliary covariables for the cotwin from the model, so that altogether 4 independent variables were evaluated for males and 3 for females. In the simplest application of the model, only cotwin's survival has been considered and all other covariables have been omitted.

Before the model presented here was developed, an alternative approach evaluated mortality of twins who survived the first death in the pair from the time of that death. It included a regression coefficient for zygosity that provided a direct comparison of MZ and DZ twins, standardized for the auxiliary covariables. Age was included as an additional covariable. An analysis of residuals indicated that the earlier model could not be fitted satisfactorily to the data and those results have not been presented.

Conventional analyses of heritability have been carried out using methods proposed by Edwards [4] and Falconer [5]. These estimate h^2, the heritability of liability to the event of interest, by examining its prevalence among individuals and the casewise concordance among affected pairs. In this application, the event of interest is defined as survival to the end of the follow-up period among those born 1886 to 1895, and as mortality during follow-up among those born 1896 and later.

RESULTS

Survival of individuals, estimated from the proportional hazard model, is shown by zygosity and sex in the Figure. The estimated functions have been standardized for the distribution of covariables by setting the values equal to sample means for males and females, respectively. Over the entire follow-up period, the standardized survival of MZ male twins is somewhat higher than for DZ male twins. The difference is small, but statistically significant ($P < 0.05$). The standardized survival of female MZ twins is almost identical to that of female DZ twins.

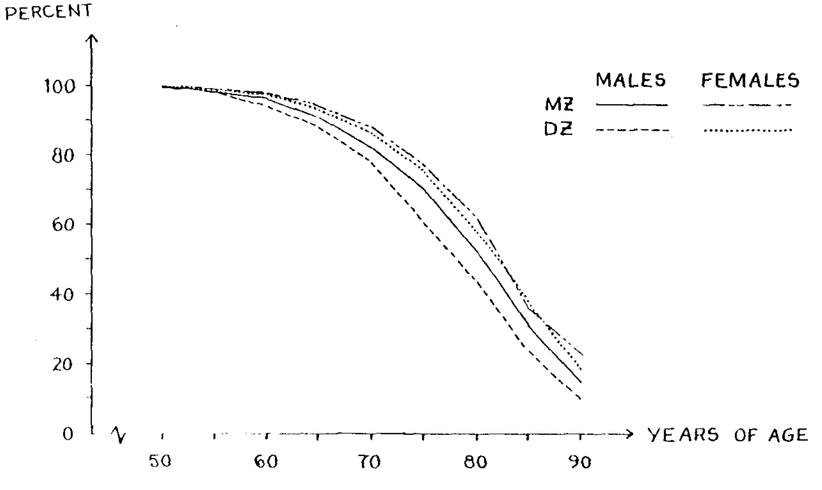

Figure - Estimated percent surviving by age at follow-up, zygosity and sex.

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Table 5 - Standardized Relative Risk of Death from All Causes with Cotwin's Death, Statistical Significance of Coefficient for Cotwin's Mortality (P value) and 90% Confidence Limits on Relative Risk, by Zygosity, Sex, Year-of-Birth Group, and Extent of Analysis[a]

Year-of-birth group	Auxiliary covariables	MZ twins: Relative risk for "Cotwin deceased"	MZ twins: Confidence limits	MZ twins: P value[b]	DZ twins: Relative risk for "Cotwin deceased"	DZ twins: Confidence limits	DZ twins: P value[b]
MALES							
1886 - 1895	6	1.62	1.09 - 2.42	*	1.24	0.83 - 1.86	–
	3	1.62	1.09 - 2.41	*	1.33	0.90 - 1.96	–
	0	1.68	1.13 - 2.49	*	1.32	0.89 - 1.95	–
1896 - 1905	6	1.78	1.36 - 2.34	***	1.29	1.07 - 1.57	*
	3	1.81	1.38 - 2.37	***	1.29	1.06 - 1.56	*
	0	1.85	1.41 - 2.42	***	1.30	1.07 - 1.58	*
1906 - 1925	6	2.42	1.86 - 3.14	***	1.40	1.15 - 1.72	**
	3	2.48	1.91 - 3.21	***	1.39	1.14 - 1.69	**
	0	2.63	2.03 - 3.40	***	1.46	1.19 - 1.78	***
FEMALES							
1886 - 1895	4	2.19	1.59 - 3.01	***	1.38	1.10 - 1.73	*
	2	2.16	1.57 - 2.96	***	1.38	1.10 - 1.73	**
	0	2.09	1.53 - 2.87	***	1.38	1.10 - 1.74	**
1896 - 1905	4	1.90	1.46 - 2.47	***	1.51	1.25 - 1.82	***
	2	1.95	1.50 - 2.53	***	1.51	1.25 - 1.82	***
	0	1.93	1.49 - 2.50	***	1.49	1.23 - 1.80	***
1906 - 1925	4	2.34	1.69 - 3.22	***	1.57	1.22 - 2.02	**
	2	2.33	1.69 - 3.21	***	1.55	1.21 - 2.00	**
	0	2.42	1.75 - 3.33	***	1.60	1.24 - 2.05	**

[a]Relative risk of individual's death given co-twin's death is shown for multivariate regression holding costant auxiliary covariables of both twin and co-twin (6 for males and 4 for females), or of twin only (3 for males and 2 for females), or without any auxiliary covariable control.

[b]Significance, one-sided test: – $P > 0.05$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 6 - Standardized Relative Risk of Death from All Causes for Specified Covariable, Statistical Significance of Coefficient (P value), and 90% Confidence Limits on Relative Risk by Zygosity, Sex and Year-of-Birth Group

	MZ twins			DZ twins		
Variable and year-of-birth group	Relative risk	Confidence limits	P value[a]	Relative risk	Confidence limits	P value[a]
MALES						
Smoking						
1886 - 1895	0.85	0.65 - 1.12	–	1.15	0.89 - 1.48	–
1896 - 1905	1.81	1.32 - 2.48	***	1.06	0.86 - 1.29	–
1906 - 1925	1.63	1.20 - 2.20	**	1.48	1.20 - 1.81	***
Previously married						
1886 - 1895	1.39	0.95 - 2.04	–	1.35	0.96 - 1.92	–
1896 - 1905	2.23	1.53 - 3.25	***	1.04	0.77 - 1.40	–
1906 - 1925	1.79	1.22 - 2.62	**	1.47	1.11 - 1.96	*
Alcohol registration						
1886 - 1895	0.67	0.25 - 1.77	–	0.73	0.46 - 1.14	–
1896 - 1905	1.40	0.99 - 1.98	–	1.25	0.95 - 1.65	–
1906 - 1925	1.52	1.11 - 2.09	*	1.70	1.39 - 2.09	***
FEMALES						
Smoking						
1886 - 1895	1.07	0.62 - 1.84	–	1.10	0.73 - 1.66	–
1896 - 1905	1.76	1.16 - 2.66	*	1.49	1.14 - 1.95	**
1906 - 1925	1.84	1.37 - 2.47	***	1.49	1.19 - 1.87	**
Previously married						
1886 - 1895	0.68	0.50 - 0.91	–	1.01	0.80 - 1.27	–
1896 - 1905	1.05	0.76 - 1.46	–	0.87	0.67 - 1.12	–
1906 - 1925	1.13	0.75 - 1.71	–	1.19	0.88 - 1.61	–

[a] – $P > 0.05$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. One-sided test for analysis with cotwin's survival and auxiliary covariables of twin only.

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Table 5 shows the effect of cotwin's death, the covariable of primary interest, in terms of relative risk of death for the selected individual. In each sex, zygosity and year of birth group, the top line presents the relative risk with cotwin's death when for each individual his own and his cotwin's auxiliary covariables are included in the model (6 for males, 4 for females). The middle line shows the relative risk when only the individual's auxiliary covariables are included (3 for males, 2 for females). The bottom line shows the relative risk when cotwin's death is the only independent variable considered. The relative risks from the full model that includes the auxiliary covariables for the co-twin are almost identical to those from the model that only includes cotwin's mortality and the individual's own auxiliary covariables. The relative risks are also similar when only cotwin's survival is considered, although they tend to be slightly higher among those born 1906-1925 than in the more complex models. Cotwin's death has a significant positive relationship to mortality in all of the 12 analysis groups except DZ males born 1886-1895.

The contribution of all the auxiliary covariables of the cotwin to the individual's mortality has been tested so that cotwin's survival and the individual's own auxiliary variables were held constant. With these constraints, no relationship could be demonstrated between the individual's mortality and all of the auxiliary covariables of the cotwin considered together. In that analysis, none of the cotwin's auxiliary covariables, when tested individually, showed significant associations to the selected twin's mortality in any of the 12 analysis groups, except for alcohol registration among MZ males born 1906-1925, which produced a $P \sim 0.02$. Thus, the results presented below are based on the model that includes only cotwin's survival and the individual's own auxiliary covariables (3 for males, 2 for females). When cotwin's survival was not included in the regression equation, some of the cotwin's auxiliary covariables did have a significant relationship to mortality in several of the two younger analysis groups.

All the auxiliary covariables of the individual considered together are significantly ($P < 0.05$) related to mortality among those born 1906-1925 in all sex and zygosity groups, and among MZ males and DZ females born 1896-1905, when cotwin's survival is held constant. The relative risks obtained in that analysis for each of the auxiliary covariables, when the effect of the others is also controlled, are shown in Table 6 by sex, zygosity, and year of birth group. Among males born 1906-1925, in both zygosity groups, there is an increased mortality risk with smoking, previously married status and alcohol registration, significant on statistical testing. MZ males born 1896-1905 also have a significantly increased risk with smoking and previously married status. Among females, in both zygosity groups, smoking is related to increased risk for those born 1896-1905 and 1906-1925, but no other statistically significant associations with mortality are found for them. There are no strong or statistically significant associations of mortality with the auxiliary covariables among those born 1886-1896 in any of the sex and zygosity groups.

DISCUSSION

Data on age-specific mortality of twins born in Sweden from 1886 through 1925 were used to evaluate the importance of familial factors in this phenomenon. The measures of intrapair association used can be interpreted as having genetic meaning to the extent that relevant environmental factors have been controlled in these analyses. If genotype-environment interactions exist, our results apply only to the distribution of genotypes included in the study.

The Cox regression proportional hazard model was applied to the data. Survival of the cotwin has been included in the model as the covariable that reflects the familial effect on mortality. This provides estimates of the relative risk of death in the follow-up period given the death of the subject's cotwin. The relative risks so obtained are analogous to the risk estimates produced by conventional genetic segregation analysis, but they have been corrected for the effect of other covariables. The model deals with the problem of censored survival times, and consequently avoids some of the age dependence of heritability estimates from conventional analyses. Estimates of relative risk obtained for the other covariables are in turn corrected for their possible associations with particular genotypes that have an atypical mortality experience. This should reduce spurious associations which could arise in an analysis without such genetic control.

The estimates of the relative risks of death associated with the death of a cotwin, the primary covariable in regression analysis, ranged between 1.62 and 2.63 for MZ twins and between 1.24 and 1.60 in DZ twins, depending upon sex, the year of birth group and the analytical model used (Table 5). In all six sex-age analysis groups, the values for MZ twins exceeded those of DZ twins and most of the comparisons were significant on individual testing ($P < 0.05$). It thus appears that the cotwin's mortality is a strong indication of an increased death risk, and one that is more important for MZ than for DZ twins. In this respect the findings correspond to those of the conventional analysis and of previous studies [8,9,11]. However, the estimates of relative risk from the regression analysis had a narrower spread than those from the conventional analysis of these same data, particularly among DZ twins. This may be due to some extent to the standardization for differences in the distributions of the auxiliary covariables that was accomplished in the multivariate approach.

In the regression analysis, the difference between zygosity groups in the relative risk for death of the cotwin, the primary covariable, was the only completely consistent tendency that was evident. Females tended to have somewhat higher relative risks than males, except in the MZ group born 1906-1925, and risks were higher in the youngest groups than in the oldest, but a clear trend with year of birth was seen only for MZ males. Results from the full model that included the individual's and the cotwin's auxiliary covariables were almost the same as from the model with only the individual's auxiliary covariables. When cotwin's mortality was the only independent variable in the model, the relative risk estimates tended to be higher than in the other two models among males, particularly in the MZ group and among the youngest MZ females. Most of these fluctuations are slight, however, and could reflect sampling variation.

If twins whose genotypes predispose them to an environmental exposure such as smoking or alcohol abuse should also have a genetically increased mortality, the interaction could be best handled by the model that included the cotwin's auxiliary covariables, particularly for DZ twins, for whom the genetic correlations are weaker. The model with only the individual's auxiliary covariables indicated that these exposures led to an increased mortality risk independent of their association with each other and with the survival of the cotwin. The full model that included the cotwin's auxiliary covariables gave results very much like the restricted analysis. The cotwin's auxiliary covariables, individually or all together, did not have a significant, independent relationship to mortality of the individual. This suggests that the auxiliary variables are not associated with high-risk genotypes through a genetic mechanism.

For males, all three auxiliary covariables examined were of roughly equal importance.

Previously married status was not independently associated with increased mortality for females. For both sexes and zygosity groups in the oldest cohort, no meaningful increases in relative risk with the auxiliary covariables were found that were independent of co-twin's survival. At those ages, the genetic determinants may not be as strong as earlier in life, but they appear to be the most important factor among those evaluated in the analysis.

If genetic mechanisms are involved, it would be useful to assess under what circumstances attributable risks, derived from the regression analysis as relative risks for cotwin's survival, can be interpreted as heritability. For MZ twins, the relationship seems fairly direct. Heritability estimates based on the attributable risk values obtained for cotwin's survival are 0.38, 0.45, 0.60 for MZ males, and 0.54, 0.48, 0.58 for MZ females, respectively in the three year-of-birth groups used in the analysis. For both sexes in each of the three MZ year-of-birth groups, except males born 1886-1895, the respective values of h^2 obtained in the univariate analysis were somewhat lower. They ranged from 0.38 to 0.46 and had standard errors comparable to those of the attributable risks. In the univariate analysis the estimates of h^2 for the two zygosity groups combined were even lower, with 0.43 as the highest. These combined estimates exclude the effect of environmental factors shared to the same extent between members of MZ and DZ twin pairs, but they do not account for covariates explicity and they have large sampling errors. Confidence limits (90%) for the value of 0.43 ranged from 0.0 to 0.99 with similar variation in the other analysis groups. Considering the conceptual differences between these methodologies, and the sampling errors inherent in each of their applications, the various estimates obtained are reasonably similar. All the estimates for males correspond rather closely to the estimates of $h^2 = 0.50$ obtained from US data on male twin veterans by Hrubec and Neel [8]. in a conventional analysis of heritability.

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