A Danish Population-Based Twin Study on General Health in the Elderly

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Objectives: To study the relative influence of genetic and environmental factors on self-rated health and hospitalization patterns in the elderly. Methods: A survey among all 3,099 Danish twins ages 75 years and older identified in the Danish Twin Registry. An interview was conducted with 77% of the twins. The number of hospitalizations in the previous 18 years was obtained through register linkage, thereby obtaining health information on 96% of the study population, including all nonresponders. Results: Structural equation modeling suggested that approximately a quarter of the variation in the liability to self-reported health and the number of hospitalizations could be attributed to genetic factors. The remaining variation was most likely due to nonfamilial environment. Analyses of the hospitalization patterns of proxy responders and nonresponders suggest that the estimates of the genetic influence on health outcomes in the study are conservative. Discussion: The present study indicates that variation in general health among the elderly is partly explained by genetic factors.

General health among the elderly is a complex phenomenon affected by numerous factors. The accumulation of unique exposures during a long life may be expected to be the key determinant of health at older

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ages. However, little information is available on the relative influence of genes and environment on general health in the elderly (Harris, Pedersen, McClearn, Plomin, & Nesselroade, 1992). The twin method is a well-established tool for disentangling the relative importance of genes and environment on complex phenotypes, such as various health outcomes, cognitive abilities, and psychological characteristics (Neale & Cardon, 1992; Plomin, Owens, & McGuffin, 1994).

Among the elderly, common chronic diseases play a major role on general health (Jylhä, Leskinen, Alanen, Leskinen, & Heikkinen, 1986). Twin studies of cardiovascular diseases suggest that at younger ages, death from coronary heart disease is strongly influenced by genetic factors, whereas this genetic effect decreases at older ages (Marenberg, Risch, Berkman, Floderus, & Faire, 1994). Genetic mutations resulting in early-onset dementia have been identified, and studies of dementia among twins suggest persistent genetic influence on the liability to develop dementia at older ages (Breitner et al., 1993; Gatz et al., 1997; Räihä, Kaprio, Koskenvuo, Rajala, & Sourander, 1996).

Here we report on the first wave of a longitudinal study among all Danish same-sexed twins ages 75 and older with a focus on two measurements: self-reported health, and the number of hospitalizations in the previous 18 years. These two measurements reflect complex processes related to health, disposition, and social factors. We obtained information on hospitalization for all nonresponders, which enabled us to evaluate the impact of nonresponders and proxy responders on the results obtained in the twin analyses.

Self-rated health represents an individual's overall sense of physical well-being and has shown to be a predictor of survival at older ages. Researchers of the Manitoba Longitudinal Study on Aging reported that elderly respondents' self-rated health was a better indicator of future survival than objectively measured health status (Mossey & Shapiro, 1982). With a few exceptions, this finding has been confirmed in a number of settings using various designs and survey instruments, indicating a robust association between self-rated health and future survival (Idler, 1992; McCallum, Shadbolt, & Wang, 1994).

In Denmark, all citizens have access to a free national health care system, and the number of private hospital beds is negligible. Since 1977, all discharges from hospital concerning inpatients have been registered on an individual level (Jürgensen, Frølund, Gustafsen, Mosbeck, & Guldkammer, 1984). This provides a unique opportunity to link to the twin study information on disease occurrence requiring hospitalization in an 18-year period. Furthermore, this information is likely to be much less affected by the biasing influence of socioeconomic status on hospitalizations seen in many countries.

Material and Methods

STUDY POPULATION

The study is based on the Danish Twin Registry, which has been described in detail previously (Hauge, 1981; Hauge et al., 1968; Holm, 1983; Kyvik, Christensen, Skytthe, Harvald, & Holm, 1996).This registry was established in 1954 as the first nationwide twin registry in the world and includes all twin pairs born in Denmark between 1870 and 1910 and all same-sex pairs born between 1911 and 1930. The birth registers from all 2,200 parishes of the relevant calendar years were manually scrutinized to identify all twin births. Through regional population registers (in operation since 1924) and other public sources, a search was made for the twins or, whenever needed, their closest relatives. As soon as a twin was traced, a questionnaire was sent to him or her. If neither of the partners was alive, a questionnaire was sent to the closest relative. Specific questions about the degree of similarity between the partners of a pair were included in the questionnaire to assess zygosity in same-sex twins. For twins dying or emigrating at an early age, it was impossible to obtain reliable data to be used in zygosity classification. Consequently, pairs were not followed up if one or both partners died or emigrated before age 6 years.

The validity of zygosity classification based on answers to mailed questionnaires has been evaluated by comparison with the results of later blood group determinants and the misclassification rate has been found to be less than 5% (Hauge, 1981). The present study was restricted to all registered Danish twins age 75 and older who were alive in January 1995 and who had not permanently emigrated—a total of 3,099 individuals.

SURVEY

The residence of all twins in the study population was identified in the Central Person Registry in January 1995 through the personal identification number for each twin. During two weeks in the beginning of February 1995, the twins received a letter explaining the study and asking permission for an interviewer to come to their residence to conduct a health-related, 1-hour, face-to-face interview. A total of 100 interviewers from the Danish National Institute of Social Research were used. In 1958, this institute was set up by law to conduct and disseminate research into social policy, working life, social aspect of housing, health, and living conditions among the Danish population. The interviewers are not medically or paramedically trained. The interviewers from the Danish National Institute of Social Research have substantial experience interviewing the elderly, however (Kjøller, Rasmussen, Keiding, Pedersen, & Nielsen, 1994; Platz, 1989, 1990).

All 100 interviewers received a detailed training program during January and February 1995, and were closely monitored during the 3-month period during which interviews were completed (February-April 1995). When a twin was unable to participate due to physical or mental handicaps, a proxy-responder was sought (closest relative). Only when at least three unsuccessful attempts to contact a twin at his or her residence at different times had been made was the twin considered to be not possible to contact.

Classic twin analysis is based on correlations within pairs, and to avoid inflated estimates of twin similarity due to potential interviewer bias, the two twins in a pair were never interviewed by the same interviewer, not even in cases where the twins lived together. A pilot study performed in November 1994 and comprising 100 twins from the study population was included in the analysis, because it was made just a few months before the main survey using the same procedure and an interview that differed minimally from that used in the main survey. All surviving participants are reassessed during 1997.

The questionnaire included questions on self-rated health, diseases, medicine, activities of daily living (ADLs), cognitive abilities, depression, and life circumstances and events. Self-rated health was the first health-related question of the interview, and it was assessed by the question: "How would you rate your health in general?" (very good, good, fair, poor, very poor were the possible responses).

REGISTER LINKAGE

The National Danish Discharge Registry comprises information on practically all discharges from somatic hospitals in Denmark since 1977 (including deaths in hospital) (Jürgensen et al., 1984). Diagnoses are coded according to the International Classification of Disease (ICD) system, and the registry allows up to 20 diagnoses for each discharge. Register data could be obtained for all but 123 (4%) of the twins. Hospital information was obtained for all nonresponders. Due to time lag in the registry, the present study was based on hospitalization of the twins in the period January 1, 1977, through December 31, 1994.

TWIN ANALYSIS

In humans, two types of twinning occur: monozygotic (MZ) twins, who share all their genetic material, and dizygotic (DZ) twins, who, on average, share 50% of their genes like nontwin siblings. In the classical twin study, MZ and DZ correlations for a trait are compared. A significantly higher correlation rate in MZ twins indicates that genetic factors play a role in the etiology. In the case of ordinal traits like self-rated health or a categorization of the number of hospital discharges (none, one to two, or three or more), polychoric correlations are used in the analysis (Kendler, Heath, Neale, Kessler, & Eaves, 1992). It is assumed in this statistic that underlying the observed ranking of self-rated health, a latent, normal distribution of liability to self-reported health exists with thresholds that separate the different levels. If the trait has a multifactorial etiology involving many genetic and environmental factors, which is likely for self-rated health and the number of hospitalizations, the distribution of liability in a large population will be approximately normal. If more than two levels are present in an ordinal scale, then it is possible to use a goodness-of-fit test to assess whether the multifactorial liability threshold model provides a good fit to the observed data. These analyses were performed with the computer program PRELIS-2 (Jöreskog & Sörbom, 1988). To estimate the

heritability of the liability to the general health measurements, the twin data were analyzed using standard structural equation modeling (Neale, 1994; Neale & Cardon, 1992).

Results

STUDY POPULATION AND NONRESPONSE

The ascertainment of twins stratified by zygosity and type of interview (twin/proxy) is shown in the flow chart in Figure 1. Some health information was obtained on 100% of the sample. A total of 2,401 interviews were conducted, corresponding to a participation rate of 77% (1% constituted partial interviews due to inability to complete). In addition, general health information was obtained on 279 twins (9% of the study population) who were willing to provide information but did not wish to participate in the full interview. No interview information was obtained on 398 (13%). Of the twins interviewed, 60% were single twins—that is, twins whose co-twin was either dead or a nonresponder.

Table 1 contains the sex, age, and zygosity distributions for the responders and nonresponders, together with data on hospital admissions. The response rate was significantly higher in males (81%) than in females (76%) ($p < .01$). Furthermore, it was observed that the response rate in the metropolitan Copenhagen area was lower compared to the rest of the country (72% vs. 79%), a finding common to virtually all nationwide Danish surveys.

The responders and nonresponders were similar in terms of age-distribution, MZ:DZ ratio, and earlier hospitalizations. The mean age for responders and nonresponders in both sexes was within 0.6 year of 81 years. More twins of unknown zygosity were found among the nonresponders (12%) than among the responders (1%), reflecting that these nonresponders had not participated in earlier studies where zygosity was determined. The small number of opposite-sex DZ twins is due to the fact that the Danish Twin Registry only includes these twins if they were born before 1911. The previous 18 years of hospital admission patterns were nearly identical for female responders and nonresponders, whereas the male nonresponders tended to have

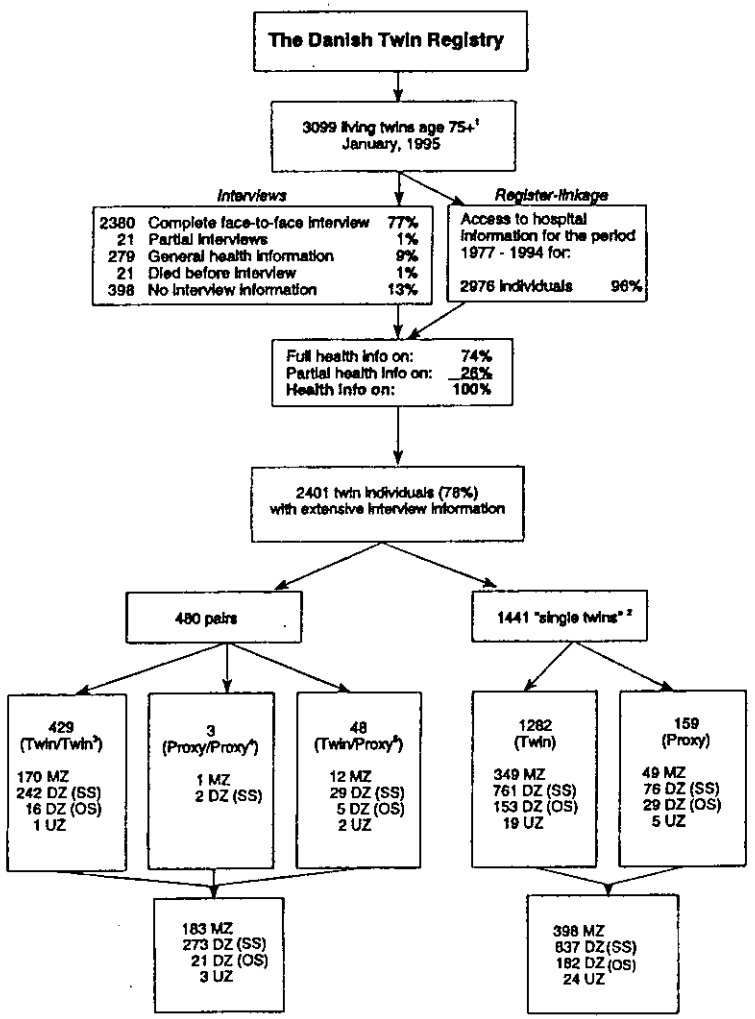

Figure 1. **The ascertainment of twins stratified for zygosity and interview-type.**
Note. MZ = Monozygotic, DZ = Dizygotic, UZ = Zygosity unknown, SS = Same-sex, OS = Opposite-sex.
1. A pilot-study performed in November 1994 comprising 100 twins from the study population was included in the analysis.
2. Twins whose co-twin was either dead, non-traced, or a non-responder.
3. Both twins participated in an interview.
4. Both twins participated in the study by proxy-responder.
5. One twin participated in the study and the other twin participated by proxy.

Table 1
Danish Twins Ages 75 Years and Older Stratified According to Response Status

	Responders		*Responders by Proxy*		*All Responders*		*Nonresponders*		*Total*	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*
N (%)	789 (74)	1,399 (69)	70 (7)	143 (7)	859 (81)	1,542 (76)	205 (19)	493 (24)	1,064 (100)	2,035 (100)
Sex ratio (M:F)	.56		.49		.56		.42		.52	
Age (years)										
Mean	81.0	81.1	82.7	85.3	81.1	81.6	80.6	81.5	81.0	81.6
SD	4.5	4.7	5.5	5.3	4.6	4.8	4.2	4.9	4.6	4.8
Median	80.0	81.0	81.5	86.0	81.0	81.0	80.0	81.0	80.0	81.0
Maximum	102	96	98	100	102	100	96	99	102	100
Zygosity (*N*, %)										
MZ	260 (33)	441 (32)	16 (23)	47 (33)	276 (32)	488 (32)	63 (31)	131 (27)	339 (32)	619 (30)
DZ-SS	445 (56)	829 (59)	41 (58)	68 (48)	486 (57)	897 (58)	93 (45)	256 (52)	579 (54)	1,153 (57)
DS-OS	71 (9)	119 (9)	9 (13)	25 (17)	80 (9)	144 (9)	17 (8)	52 (11)	97 (9)	196 (10)
UZ	13 (2)	10 (1)	4 (6)	3 (2)	17 (2)	13 (1)	32 (16)	54 (11)	49 (5)	67 (3)
Number of hospital admissions, 1977-1994[a]										
Number of individuals	755	1,325	66	132	821	1,457	205	493	1,021	1,934
Mean	4.0	3.3	4.6	4.2	4.0	3.4	3.3	3.1	3.8	3.3
SD	5.2	4.4	4.4	4.2	5.1	4.4	4.1	3.9	4.9	4.2
Median	3.0	2.0	3.5	3.0	3.0	2.0	2.0	2.0	3.0	2.0
Never hospitalized (%)	17.4	25.0	8.0	17.0	16.6	24.3	23.9	24.5	18.0	24.5
Maximum	51	44	22	30	51	44	39	28	51	44

Note. MZ = Monozygotic; DZ = Dizygotic; DZ-SS = Dizygotic same sex; DZ-OS = Dizygotic opposite sex; UZ = Zygosity unknown.
a.No hospital information was available for 108 among the responders and 15 among responders by proxy.

slightly fewer hospitalizations than the male responders. The nonresponse for the various questions in the interview was very low. For self-rated health there were no missing values or "don't know" answers among the 2,188 responders.

ANALYSIS OF TWIN RESEMBLANCE FOR GENERAL HEALTH

The distribution of answers to the question, "How would you rate your health in general?" was 584 very good (27%), 822 good (38%), 539 fair (25%), 179 poor (8%), and 64 very poor (3%). In the twin analysis, the numbers are divided according to sex and zygosity, and to avoid cells with zeros, the three last categories were grouped into "less than good health."

Self-reported health is influenced by age. For the group ages 75 to 84 years, the distribution in self-reported health was 27 very good, 34 good, and 38 less than good, whereas the corresponding distribution for 85 years and older was 16, 34, and 50 ($p < .01$), respectively. A similar trend was seen for number of hospitalizations, where the distribution was 23 (0), 32 (1 to 2), and 45 (3 or more) for the 74 to 84 years old group and, correspondingly, 16, 30, and 54 for the 85 years and older twins ($p < .001$).

Self-reported health and hospital categorization were only moderately correlated (Spearman correlation = .29, $p < .001$). Among individuals reporting very good health, 27% had three or more hospitalizations during the previous 18 years, whereas 24% of individuals with no hospitalizations during the previous 18 years reported less than good health.

The distributions of self-reported health and number of hospitalizations were nearly identical for MZ and DZ twins. The only difference between MZ and DZ was found when the comparison was restricted to intact pairs. In this subgroup, there were fewer MZ twins with less than good health (38%) than DZ twins (46%), $p < .05$.

Tables 2 and 3 contain the within-pair distribution of self-rated health and hospitalizations, and Table 4 lists the corresponding polychoric correlations. The MZ correlations are consistently greater than the DZ correlations for both males and females, but the differences are not statistically significant. Inclusion of nonresponders and proxy responders reduced the DZ correlation for hospitalization pattern in

Table 2
The Within-Pair Distribution of Self-Rated Health Stratified for Zygosity (males and females combined)

	Monozygotic Twin 1 (N = 170)			*Dizygotic (same sex) Twin 1 (N = 242)*		
	Very Good	*Good*	*Less Than Good*	*Very Good*	*Good*	*Less Than Good*
Twin 2						
Very good	18	18	15	25	22	23
Good	13	33	19	24	39	29
Less than good	11	18	25	18	30	32

Note. The sample sizes correspond to responders only.

Table 3
The Within-Pair Distribution of Number of Hospitalizations During the Last 18 Years Stratified for Zygosity (males and females combined)

	Monozygotic Twin 1 (N = 157)			*Dizygotic (same sex) Twin 1 (N = 227)*		
	0	*1 to 2*	*3 or More*	*0*	*1 to 2*	*3 or More*
Twin 2						
0	17 (28)	7 (19)	9 (15)	15 (25)	18 (32)	16 (33)
1 to 2	15 (19)	27 (40)	25 (33)	17 (25)	24 (39)	39 (63)
3 or more	9 (16)	22 (33)	26 (45)	17 (40)	28 (51)	53 (90)

Note. The sample sizes correspond to responders only. Values in parentheses show the sample sizes when the nonresponders and proxy responders were also included (monozygotic $N = 248$, dizygotic $N = 398$). Information on hospitalization was obtained for all nonresponders as well as 96% of all responders.

females markedly but had no impact on the MZ estimate. In the male sample, the difference between MZ and DZ correlations also increased when proxy responders and nonresponders were included, although the pattern and the effect were less clear than in the female sample—maybe due to the small size of the male sample.

Table 3 shows that the probability of a twin having 3 or more hospitalizations, given that the co-twin had no hospitalizations, was 25% for MZ twins and 41% for DZ twins corresponding to a probability difference of 16% (95% CI = 5.4%-26.2%). The probability of a twin having no hospitalizations, given that the co-twin had no hospitalizations, was 45% for MZ twins and 28% for DZ twins corresponding to a probability difference of 17% (95% CI = 6.1%-27.9%).

Structural equation modeling revealed that a model including genetic factors and nonshared environment with no sex difference

Table 4
Twin Pair Polychoric Correlations in Liability to Self-Rated Health and Number of Hospitalizations During the Last 18 Years

	Monozygotic			*Dizygotic*		
	Males	*Females*	*Total*	*Males*	*Females*	*Total*
Responders only						
Self-reported health						
Number of pairs	53	117	170	66	176	242
Correlation[a] (*SE*)	.39 (.16)	.16 (.12)	.21 (.10)	.18 (.15)	.11 (.10)	.13 (.08)
Hospitalizations						
Number of pairs	49	108	157	63	164	227
Correlation[a] (*SE*)	−.03 (.18)	.35 (.11)	.30 (.10)	−.18 (.15)	.32 (.09)	.20 (.08)
Including nonresponders and proxy responders						
Hospitalizations						
Number of pairs	74	174	248	109	289	398
Correlation[a] (*SE*)	.25 (.15)	.33 (.09)	.31 (.07)	−.16 (.12)	.19 (.07)	.10 (.06)

a. The correlations are polychoric correlations assuming bivariate normal distribution of liability. In all cases, the model test was nonsignificant, indicating no violation of this assumption.

provided the most parsimonious fit to both self-reported health and hospitalization pattern (lowest Akaike Information Criteria; Akaike, 1987). In this model, genetic factors were estimated to account for 25% of the variation in self-reported health. For hospitalization pattern, the corresponding estimate was 31% when nonresponders and proxy responders were included. Excluding genetic factors from the model resulted in significantly worse fits for both measures (increase in goodness-of-fit 9.3, $df = 1$, $p < .01$ for self-reported health and 18.2, $df = 1$, $p < .001$ for hospitalization pattern). When proxy responders and nonresponders were excluded from the analyses of hospitalization pattern, the estimate of the genetic component to hospitalization pattern decreased and became statistically insignificant.

Discussion

The two measurements in our study, self-reported health and number of hospitalizations, reflect complex processes involving health, disposition, and social factors. The consistently higher correlations in MZ twins compared to DZ twins suggest an influence of genetic factors, as does the significant difference between MZ and DZ

twins in the predictive value of the hospitalization pattern of the co-twin (e.g., the probability of a twin having no hospitalizations, given that the co-twin has no hospitalizations, is 45% for MZ twins and 28% for DZ twins, $p < .01$). Structural equation modeling showed that genetic factors could not be omitted from the best-fitting model without a significant increase in the goodness-of-fit statistic. Genetic factors were estimated to account for approximately one fourth of the variation in the liability of these measurements of general health.

An advantage of the study was the possibility of evaluating the influence of nonresponders through data on hospitalization pattern for all nonresponders. Twin studies are particularly vulnerable to nonresponse, because both twins in a pair have to participate to obtain an informative pair in twin analysis. The hospitalization information is of particular value in this connection. As mentioned, the free, nationwide health care system minimizes the influence of socioeconomic status on the hospitalization pattern and enables information to be obtained on all nonresponders. However, the Danish National Discharge Registry had one limitation: Hospitalizations, beginning in 1994 and extending into 1995, could not, for technical reasons, be included. This limitation is, however, probably of little importance compared to the 18-year time span covered by the register.

The methods used for analyzing twin data are well validated for time constant traits, but when the methods are applied to traits that change over time (like general health measurements), they can become vulnerable to selection induced by survival. Methods that try to address this problem are currently being developed (Yashin & Iachine, 1997). Furthermore, it will be possible to study the impact of selection through the follow-up of the present study population.

Inclusion of nonresponders and proxy responders increased the MZ-DZ difference in correlations for hospitalization pattern. In the large female sample, inclusion of nonresponders and proxy responders decreased the DZ correlations but left the MZ correlations nearly unchanged. Participating DZ twins seem to have a more concordant hospitalization pattern than DZ pairs of which neither or only one twin participated in the study. This phenomenon has also been observed in studies of obesity, where DZ co-twins with big difference in body-mass-index tend not to be concordant for participation in the study

(Lykken, McGue, & Tellegen, 1987). The structural equation modeling confirmed that, for both males and females, exclusion of proxy responders and nonresponders decreased the estimate of the genetic component to hospitalization pattern. This suggests that estimates of the genetic influence on health in the study tend to be conservative.

Although the twin method has been applied to numerous phenotypes in a wide age range, there are, with good reason, very few studies comprising a substantial number of elderly twins. Twinning is a relatively rare event (1 in approximately 80 to 100 births), and most classic twin studies only include twin pairs in which both twins survive to the age of interest. Furthermore, elderly and sick persons are reluctant to participate in studies, the combined effect of which makes it difficult to obtain reasonable sample sizes in studies of elderly twins. Previous studies (Harris, Pedersen, McClearn et al., 1992; Harris, Pedersen, Stacey, McClearn, & Nesselroade, 1992) examined age differences in genetic and environmental influences for overall health status among participants in the Swedish Adoption/Twin Study of Aging (SATSA). This sample is younger ($M = 59$ years, range = 26-86 years) and includes 145 70 years and older twin pairs. The studies used an index of chronic health problems and a self-rated health scale consisting of four questions. For self-rated health, a genetic component could not be detected before age 60, whereas approximately a quarter of the variation in the self-rated health score could be explained by genetic factors for the groups 60 to 69 years and 70 years and older. However, for the group 70 and older, the correlation in self-rated health was not consistently higher in MZ twins than in DZ twins when the twin pairs were stratified for rearing conditions (reared together or apart), probably a result of the small sample size.

Diseases and disorders and psychological factors are genetically influenced to varying degrees (Plomin et al., 1994). Because general health is associated with diseases and sociopsychological factors to some degree, a genetic influence on self-rated health could be mediated by genetic influences on these diseases or other factors. Multivariate twin analyses could be used to test whether there are common genetic influences on self-rated health and other health measurements. The Swedish study (Harris, Pedersen, Stacey et al., 1992) has shown that, for a group of 65 and older twins, both genetic and

environmental effects contribute substantially to the association between life satisfaction and self-reported health.

It has been suggested that MZ twins have an increased incidence of certain diseases, such as cardiovascular and Alzheimer's diseases, which could pose a potential threat to the validity of the twin method (Phillips, 1993; Räihä et al., 1996). In this study, we found nearly identical patterns of general health for MZ and DZ twins; the only difference was found in the subgroup of intact pairs, where a slight tendency toward better health among MZ twins and an increased MZ:DZ ratio was observed. The finding of similar health patterns in MZ and DZ agrees with our earlier observations of similar mortality trajectories throughout adult life and similar dementia frequency in the two groups (Christensen, Holm, & Vaupel, 1996; Christensen, Vaupel, Holm, & Yashin, 1995).

Through various approaches, the present study indicates the presence of a genetic component to self-rated health and hospitalization patterns among the elderly. However, the study also indicates that the factors contributing most to variation in these measurements are to be found in individuals' nonfamilial environments. Analyses of the hospitalization pattern of proxy responders and nonresponders suggest that the estimates of the genetic influence on health outcomes in the study are conservative.

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