Handedness and Mortality: A Follow-Up Study of Danish Twins Born between 1900 and 1910

Olga Basso,[1] Jørn Olsen,[1] Niels V. Holm,[2] Axel Skytthe,[2] James W. Vaupel,[2] and Kaare Christensen[2]

The declining prevalence of left-handed individuals with increasing age has led to two main avenues of hypotheses; the association is due either (1) to a birth cohort effect and/or an age effect caused by a switch to right-handedness with advancing age or (2) to mortality selection that reduces survival in left-handed individuals, or both. It is uncertain whether a cohort or age effect can explain the decline in age-related prevalence, and conflicting evidence exists in favor of the mortality hypothesis. We compared mortality in a subgroup of 118 opposite-handed twin pairs by counting in how many instances the right-handed twin died first. There was no evidence of differential survival between right-handed and non-right-handed individuals in the entire 1900–1910 cohort. With respect to the number of right-handed twins who died first, there was no material disadvantage among those who were not right-handed. In 60% (95% confidence interval = 49.0–71.5%) of dizygotic pairs, the right-handed twins died first. In 50% of monozygotic pairs, right-handed twins died first. The prevalence of not being right-handed was higher among males (9.2%) than females (6.5%); there was a similar frequency of non-right-handedness in monozygotic (8.0%) and dizygotic (7.8%) twins. We did not find evidence of excess mortality among non-right-handed adult twins in this follow-up study. (Epidemiology 2000;11:576–580)

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The determinants of handedness are still largely unknown, but lateralization is probably determined during fetal life. The brain undergoes major development between the 16th and 22nd weeks of gestation, which may be the time when lateralization is determined.[1] Exposure of the developing brain to toxic agents or insults in this time window may interfere with this process, and handedness has been examined as a sensitive marker of neurotoxic exposures.[2] Newborns may be at higher risk of being left-handed as a result of hypoxia at birth.[3] Indicators of pregnancies at risk such as advanced age or parity of the mother have also been associated with left-handedness,[4,5] and left-handedness was more common among children who were born very premature or small.[6] Because twin pregnancies are often high risk, one might expect a higher prevalence of left-handedness among twins, as has been reported by some,[4,7,8] but not all,[9–11] researchers studying the issue.

It is well known that prevalence of left-handedness decreases with increasing age in cross-sectional samples,[12–15] a finding that may be explained in at least two different ways. It may be due to the diminishing social pressure against left-handedness during this century, which may produce a cohort effect, and it may be due to an age effect. Alternatively, it may be due to mortality selection; left-handed individuals may have a shorter life span compared with right-handed individuals, not only because they are more accident prone in a world constructed for right-handed individuals, but because of correlates of left-handedness, such as covert neuropathologic features or immune system dysfunction, which are associated with reduced life expectancy.[14,16,17] Some observations suggest that the first hypothesis fails to explain the decline of left-handedness in old age[12,13] and a shorter survival of left-handed individuals has been reported,[13,14] but the methodology of these studies was prone to bias, and the issue is not yet settled. Larger longitudinal studies tend to show that survival in left-handed individuals is comparable with that of those who are right-handed,[18–20] but these studies had short follow-up and few deaths.

In this investigation, we focused on survival of adult non-right-handed individuals compared with that of right-handed individuals in a sample of Danish twins

From the [1]The Danish Epidemiology Science Centre at the Department of Epidemiology and Social Medicine, Aarhus University, and [2]The Danish Twin Registry, Epidemiology, Institute of Public Health, and the Danish Center for Demographic Research, Odense University, Denmark.

Address correspondence to: Olga Basso, The Danish Epidemiology Science Centre at the Department of Epidemiology and Social Medicine, Aarhus University, Vennelyst Boulevard 6, DK 8000 Aarhus C, DK.

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TABLE 1. Survival According to Gender and Zygosity Group for Same-Sex Twins Born in Denmark from 1900 to 1910

Gender	Zygosity	Handedness	N	Mean Age on 1/1/64	SD	Median Survival from 1/1/64	95% CI
Males	MZ	RH	431	57.7	3.1	19.2	18.2–20.2
Males	MZ	NRH	46	57.5	3.2	18.7	14.0–23.5
Males	DZ	RH	743	58.0	3.1	18.0	17.0–19.0
Males	DZ	NRH	73	57.7	3.1	22.0	20.3–23.8
Females	MZ	RH	426	57.8	3.0	24.1	23.1–25.2
Females	MZ	NRH	29	57.4	3.5	24.5	19.1–29.8
Females	DZ	RH	711	58.0	3.2	24.4	23.2–25.6
Females	DZ	NRH	50	57.4	3.2	23.0	14.1–31.9

MZ = monozygotic; DZ = dizygotic; RH = right handed; NRH = non-right handed.

born from 1900 to 1910. Because recording of handedness in twins in Denmark started in 1954, this dataset offers the opportunity of a virtually complete follow-up after the information on handedness was collected. The data also provided survival information on a group of opposite-handed pairs of twins. This design has the advantage of reducing confounding for environmental conditions in fetal life and early childhood.

Subjects and Methods

DATA

The Danish Twin Registry was established in 1954.[21–23] 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 (operative since 1924) and other public sources, a search was made for the twins. As soon as a twin was traced, he or she received a questionnaire. 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 like-sexed twins. For twins who died or emigrated 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. Nearly all of the twins surviving past age 15 have been traced; untraced twins are almost entirely those who died or emigrated in childhood, although the date of death or emigration is unknown. The zygosity classification based on answers to mailed questionnaires has been evaluated, comparing it with blood group determinations, and the misclassification rate was found to be less than 5%.[22] The Danish Twin Registry includes twin pairs born in Denmark between 1870 and 1910 and same-sex pairs born between 1911 and 1930. However, information on handedness was only available for same-sex twins.

The information on handedness was obtained through questionnaires sent out in the period 1953–1963 to twins born before 1911 including the question "Are you left-handed?" The answering options included "yes," "no," and "using both hands." In this analysis, we grouped left-handed individuals with those who reported using both hands.

To reduce selection related to survival, we only included in the analysis the cohort of twins born from 1900 to 1910. They were 53–64 years of age at the beginning of follow-up. Therefore, the analysis comprises twins who were alive on January 1, 1964. Follow-up started from that date and ended on December 31, 1998.

ANALYSIS

1. Survival

We analyzed survival using the entire cohort of same-sex twins born from 1900 to 1910 for whom information on handedness was present. Of the 3,849 twins born from 1900 to 1910 who survived to 1964 and who were registered in the Danish Twin Registry, 2,527 had provided information on handedness between 1953 and 1963. In 18 cases (0.7%), no zygosity information was available, so 2,504 subjects remained. In males there were 46 (9.6%) non-right-handed twins among the 477 monozygotic and 73 (8.9%) among the 816 dizygotic pairs. In females, 29 (6.4%) were non-right-handed twins out of 455 monozygotic and 50 (6.6%) among the

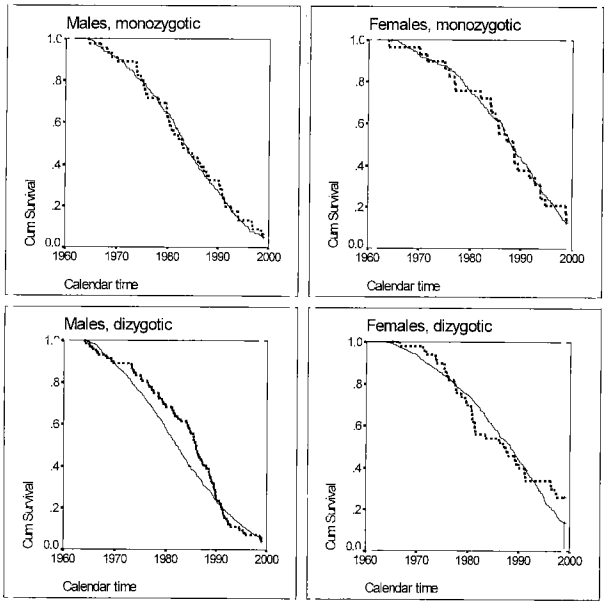

FIGURE 1. Survival according to handedness in same-sex Danish twins born from 1900 to 1910.

TABLE 2. Survival According to Handedness in Opposite-Handed Pairs of Twins

	N	%	95% CI
Male pairs	77	64.6	
Female pairs	44	36.4	
Monozygotic pairs	47	38.8	
Dizygotic pairs	74	61.2	
Still alive at the end of follow-up (121 pairs)			
Non-right handed*	17	14.1	
Right handed*	7	5.8	
Pairs in which right-handed twin died first			
All informative (118 pairs)	67	56.8	34.3–52.2
Monozygotic (45 pairs)	23	51.1	36.5–65.7
Dizygotic (73 pairs)	44	60.3	49.0–71.5

* The median survival time from January 1, 1964, was 23.5 (95% CI = 21.1–25.9) for non-right-handed and 19.6 (95% CI = 18.4–20.8) for right-handed twins.

761 dizygotic pairs. Among the 198 non-right-handed individuals, 33 (16.7%) reported that they used both hands.

We estimated survival curves using the Kaplan-Meier method and stratified by gender and zygosity. We also analyzed survival among opposite-handed pairs of twins. In this subgroup we selected pairs in which both twins were alive as of January 1, 1964. The opposite-handed pairs were 15.2% of monozygotic and 16.2% of dizygotic twins in males and 9.6% and 9.0%, respectively, in females. There was a total of 121 pairs of eligible opposite-handed twins, but in three pairs, both twins were still alive at the end of follow-up and were thus excluded from this analysis as noninformative. We counted the pairs in which the right-handed twin died before the non-right-handed twin, and we compared this proportion with the expected fraction under the null hypothesis of no differential survival (50%). As the analysis was done within same-sex pairs, no adjustment for gender was needed.

2. Cause of Death

We had information on cause of death until December 31, 1993. Causes of death were grouped in four categories: cancer, cardiovascular diseases, violent causes, and others. We compared the occurrence of these causes in right- and non-right-handed individuals.

Results

The prevalence of non-right-handed twins in the cohort born from 1900 to 1910 (N = 2,509) was 7.9%. There were more non-right-handed twins among males than females (9.2% *vs* 6.5%), but a similar fraction among monozygotic and dizygotic twins (8.0% *vs* 7.8%, respectively).

Table 1 and Figure 1 illustrate survival according to handedness for the 2,509 twins stratified by gender and zygosity. In dizygotic males, there was a median survival from January 1, 1964, of 21.2 years in non-right-handed twins compared with 18.6 years in right-handed twins. In females, the median survival was 23.2 years in non-right-handed twins and 24.2 years in right-handed twins.

Table 2 describes the findings for the 118 opposite-handed pairs. There was little difference in survival according to handedness between the groups, with slightly more right-handed individuals dying before their respective twins. Results differed between the outcomes in monozygotic and dizygotic pairs: in the latter group a much higher proportion of right-handed individuals died before their twins.

Tables 3 and 4 illustrate the distribution by cause of death in the 1900–1910 birth cohort of twins and the opposite-handed pairs, respectively. Cause of death did not differ much between right-handed and non-right-handed individuals according to our grouping, but data were too sparse for more specific analyses. When we examined the cohort of twins born from 1900 to 1910 after stratifying by sex and zygosity, the only tendency to deviate from the expected result was among dizygotic males, in whom we found slightly more deaths from accidents than expected in non-right-handed individuals, as well as fewer deaths from cancer.

Discussion

Our data showed that twins who survived to an age between 53 and 64 years as non-right-handed individuals had roughly the same life expectancy as was seen in right-handed individuals. If anything, non-right-handed twins had a slightly longer survival. It is possible that left-handed twins who resisted social pressure to change handedness were better suited to resist to the hazards of

TABLE 3. Mortality by Grouped Causes According to Handedness and Gender in Same-Sex Twins

	Males*				Females†				All‡			
	NRH		RH		NRH		RH		NRH		RH	
Grouped Causes	N	%	N	%	N	%	N	%	N	%	N	%
Cancer	22	21.2	268	27.1	14	25.5	183	23.2	36	22.6	451	25.4
CHD	43	41.3	381	38.6	24	43.6	292	37.0	67	42.1	673	37.9
Violent causes	7	6.7	37	3.7	2	3.6	43	5.4	9	5.7	80	4.5
Other causes	32	30.8	302	30.6	15	27.3	272	34.4	47	29.6	574	32.3
Total	104	9.5	988	90.5	55	6.5	790	93.5	159	8.2	1778	91.8

NRH = non-right handed; RH = right handed; CHD = coronary heart disease.
* Males who died after 1993 were 9 (7.6%) among NRH and 122 (10.4%) among RH. Still alive in 1998 were 6 (5%) among NRH and 64 (5.5%) among RH.
† Females who died after 1993 were 7 (8.9%) among NRH and 196 (17.2%) among RH. Still alive in 1998 were 17 (21.5%) among NRH and 151 (13.3%) among RH.
‡ Those who died after 1993 were 16 (8.1%) among NRH and 318 (13.8%) among RH. Still alive in 1998 were 23 (11.6%) NRH and 215 (9.3%) RH.

TABLE 4. Mortality by Grouped Causes According to Handedness and Gender in Opposite-Handed Pairs

	Males*				Females†				All‡			
	NRH		RH		NRH		RH		NRH		RH	
Grouped Causes	N	%	N	%	N	%	N	%	N	%	N	%
Cancer	17	27.0	14	21.5	6	21.4	10	32.3	23	25.3	24	25.0
CHD	26	41.3	31	47.7	13	46.4	13	41.9	39	42.9	44	45.8
Violent causes	2	3.2	1	1.5	2	7.1			4	4.4	1	1.0
Other causes	18	28.6	19	29.2	7	25.0	8	25.8	25	27.5	27	28.1
Total	63	49.2	65	50.8	28	47.4	31	52.6	91	48.7	96	51.3

NRH = non-right handed; RH = right handed; CHD = coronary heart disease.
* Males who died after 1993 were 8 (7.8%) among NRH and 10 (13.0%) among RH. Still alive in 1998 were 6 (7.8%) among NRH and 2 (2.6%) among RH.
† Females who died after 1993 were 5 (11.4%) among NRH and 8 (18.2%) among RH. Still alive in 1998 were 11 (25.0%) among NRH and 5 (11.4%) among RH.
‡ Those who died after 1993 were 13 (10.7%) among NRH and 18 (14.9%) among RH. Still alive in 1998 were 17 (4.0%) NRH and 7 (5.8%) RH.

life. Marks and Williamson[19] also reported that non-right-handed individuals (entering the study between 25 and 74 years of age) had a 30% lower mortality during follow-up compared with right-handed individuals.

The reduction in mortality of non-right-handed twins we observed was, however, only seen in opposite-handed dizygotic twins (both genders) and, marginally, in the entire cohort of dizygotic males. It may be a chance finding, because it occurred in dizygotic twins, who are supposed to be closer to singletons regarding intrauterine conditions.[24,25] In monozygotic pairs, the prevalence of "dying first within the pair" was equally split between right-handed and non-right-handed individuals.

Ascertainment of handedness in our data was based on a single question, and we most likely included a number of left-handed individuals among self-reported right-handed individuals. We do not, however, expect that the misclassification affected our results substantially.

We only addressed the hypothesis of differential survival in this paper, as we have no data to study the cohort effect or modification of handedness during lifetime. Information obtained in 1998 from a population-based sample of 2,262 individuals born in 1905 showed that, at the age of 93 years, 5.8% males and 4.0% females were left-handed (K Christensen, unpublished data, 1999), thus challenging the findings by Coren and Halpern,[13] who reported virtually no left-handed individuals at this age. Despite the similar year of birth in these subjects, however, this figure is not directly comparable with our findings because the twin questionnaire was administered at age 53–64 years.

The analysis among opposite-handed pairs of twins should be free of confounding, as fetal life and early social conditions must be similar in this group. The number of eligible pairs was small, however, and the results are thus susceptible to random variation. It is, however, reassuring that results were similar when we analyzed the entire 1900–1910 cohort of same-sex twins. If any disadvantage in survival in non-right-handed individuals exists, then the phenomenon must occur earlier in life than at the age at which our follow-up started. Even so, it would be highly unlikely that higher mortality in left-handed individuals would explain the cohort differences in the prevalence of left-handedness. Mortality in young non-right-handed individuals would have to be alarmingly high to explain the decreasing prevalence of non-right-handedness with age,[15] a situation that is not supported by the available evidence.[18–20,26,27] Although severe diseases associated with left-handedness could reduce life expectancy in this group, the group affected is most likely very small, especially in our population of adult twins.

There was no excess of opposite-handed twins in monozygotic pairs, as the proportion of non-right-handed individuals was the same between monozygotic and dizygotic twins,[8] although it was more frequent in males, as is normally,[7,13] although not universally[10] seen.

It could be argued that non-right-handedness in twins has a different etiology than in singletons. Nevertheless, the prevalence of non-right-handed twins that we observed was similar to what has been reported by others for general population samples of adults,[15,20,28] but lower than what others found for younger twins.[4,7,8,29] It has, moreover, been observed that mortality after age 6 in twins does not consistently differ from that of singletons.[30] There is no reason to believe that our findings would not apply to singletons if handedness has the same determinants.

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