



Original Contribution

Does Educational Status Impact Adult Mortality in Denmark? A Twin Approach

Mia Madsen*, Anne-Marie Nybo Andersen, Kaare Christensen, Per Kragh Andersen, and Merete Osler

* Correspondence to Mia Madsen, Unit of Epidemiology, J. B. Winsløvsvej 9B, DK-5000 Odense C, Denmark (e-mail: mimadsen@health.sdu.dk).

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To disentangle an independent effect of educational status on mortality risk from direct and indirect selection mechanisms, the authors used a discordant twin pair design, which allowed them to isolate the effect of education by means of adjustment for genetic and environmental confounding per design. The study is based on data from the Danish Twin Registry and Statistics Denmark. Using Cox regression, they estimated hazard ratios for mortality according to the highest attained education among 5,260 monozygotic and 11,088 dizygotic same-sex twin pairs born during 1921–1950 and followed during 1980–2008. Both standard cohort and intrapair analyses were conducted separately for zygosity, gender, and birth cohort. Educational differences in mortality were demonstrated in the standard cohort analyses but attenuated in the intrapair analyses in all subgroups but men born during 1921–1935, and no effect modification by zygosity was observed. Hence, the results are most compatible with an effect of early family environment in explaining the educational inequality in mortality. However, large educational differences were still reflected in mortality risk differences within twin pairs, thus supporting some degree of independent effect of education. In addition, the effect of education may be more pronounced in older cohorts of Danish men.

education; mortality; social class; twin study

Abbreviations: CI, confidence interval; DZ, dizygotic; DZSS, dizygotic same-sex; HR, hazard ratio; ICD, *International Classification of Diseases*; MZ, monozygotic; SEP, socioeconomic position.

Consistent evidence has shown that socioeconomically advantaged individuals, whether expressed in terms of education, income, or occupation, tend to have better health than disadvantaged individuals (1). In many cases, these socioeconomic health differentials are not confined to a small marginalized group of society but are expressed as a gradient over the full spectrum of social stratification (2).

The mechanisms underlying the social patterning of disease and the way contributing factors are interrelated are still poorly understood, but among the most common explanations are those emphasizing 1) material conditions (e.g., lack of basic amenities and access to services), 2) lifestyle and behavioral factors, and 3) psychological interpretations that emphasize direct and indirect effects of stress due to being lower in the socioeconomic hierarchy (3). However, the association between socioeconomic position (SEP) and health need not reflect a causal relation. Instead, it could be

due to selection processes, working either directly by selection of healthier individuals into higher socioeconomic positions or indirectly via genetic or other background factors influencing both SEP and health (4).

Although the different hypotheses that seek to explain the social inequality in health (i.e., causality or selection mechanisms) are not mutually exclusive, controversies exist about their relative importance, and it is difficult to disentangle their respective contributions. One way that previous studies have addressed this issue of causality is by means of instrumental variables. This approach has typically relied on “natural policy experiments,” such as modifications of compulsory schooling laws, which entail differences in educational attainment that are not attributable to innate characteristics. In these cases, selection or unmeasured confounding can be excluded, and the potential effects of education can be attributed to causal mechanisms (5, 6). The

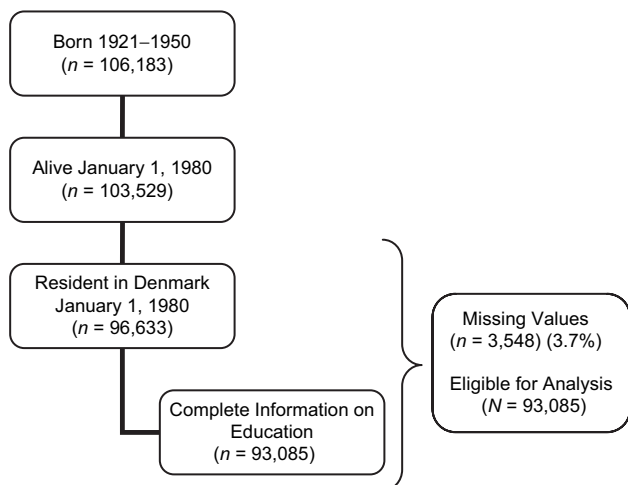


Figure 1. Definition of a 5% sample of the Danish population born during 1921–1950 with data from Statistics Denmark.

body of literature on these types of studies is incoherent, although there seems to be an overweight of studies in favor of an independent effect of education (7). However, many instrumental variables studies face problems of instruments only weakly correlated to the endogenous variable, which may lead to bias or inconsistent estimates (6).

An alternative approach to address causality is the discordant twin-pair design (co-twin control study) (8), where health or mortality status is compared within twin pairs who are discordant on SEP, but are matched fully or partly on genetic setup and rearing environment. This makes it possible to account for unobserved genetic and early environmental confounders to get a more valid estimate of the health effect of SEP. Furthermore, differences in genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twins can be exploited to make inferences about the nature of potential confounding (i.e., genetic factors or shared environment). A number of previous studies have used this approach to address social inequality in health (9–14), but many suffer from small sample sizes.

The aim of this study was to investigate whether SEP, indicated by educational status, has an additional impact on all-cause mortality above and beyond the influence of childhood environment and genetic constitution in a large sample of unselected twins.

MATERIALS AND METHODS

Study population

The study is based on data from the Danish Twin Registry and Statistics Denmark. A population-based 5% sample of the Danish population born during 1921–1950 ($N = 93,085$) was analyzed to evaluate the representativeness of the results from the unpaired twin analyses (Figure 1). A total of 5,260 MZ and 11,088 dizygotic same-sex (DZSS) twins

born during the same period of time were included in the study and followed from 1980 to 2008 (Figure 2).

Education

Information on educational status was drawn from the Demographic Database in Statistics Denmark and was defined according to the *standard* number of years of schooling in 1980 (i.e., the number of years a given education is supposed to take, irrespective of the actual time spent on the study by an individual). In 1980, study participants were at least 30 years of age and were assumed to have reached their highest level of education. Length of education was categorized into a binary variable of 7 years or less and more than 7 years, allowing sufficient power for stratified analyses. For supplementary analyses, a more detailed exposure measure was introduced (≤ 7 , >7 – <10 , 10 – <13 , 13 – <15 , ≥ 15 years).

Mortality

Data on mortality came from the Causes of Death Registry, covering the period from 1980 to 2008. We analyzed data from all-cause and cardiovascular mortality (*International Classification of Diseases* (ICD), Eighth Revision, codes 390–458/ICD, Tenth Revision, codes I00–I99 and G45) and cancer mortality (ICD, Eighth Revision, codes 140–209/ICD, Tenth Revision, codes C00–C97). However, despite the large sample size, statistical power allowed meaningful intrapair analyses only on all-cause mortality, so the reported results are restricted to all-cause mortality.

Other covariates

Additional variables included were sex (male/female), zygosity (MZ/DZSS), and birth cohort (1921–1935/1936–1950).

Data analysis

Cox regression analyses were performed by using age as the underlying time variable. Person-years of follow-up were accumulated from age at the beginning of the study (January 1, 1980), and follow up was terminated at the age at death, emigration, or the end of follow up (December 31, 2008), whichever came first. Initially, standard analyses were performed by treating the population of twins as individuals, while still taking the interdependence of observations within twin pairs into account by including a cluster term. In the intrapair analyses, the variable “twin pair” was included as a stratum variable, fixing the baseline hazard within a twin pair, while at the same time allowing it to vary freely between pairs. The hazard function for twin pair i is then written $\lambda_i(t, z) = \lambda_{0i}(t) \exp(\beta z)$, where $\lambda_{0i}(t)$ is the pair-specific baseline hazard and βz is the common effect of education (15).

As such, the effect parameter for educational status could be estimated, adjusted for the genetic and background factors shared by a pair of twins, exploiting the fact that MZ

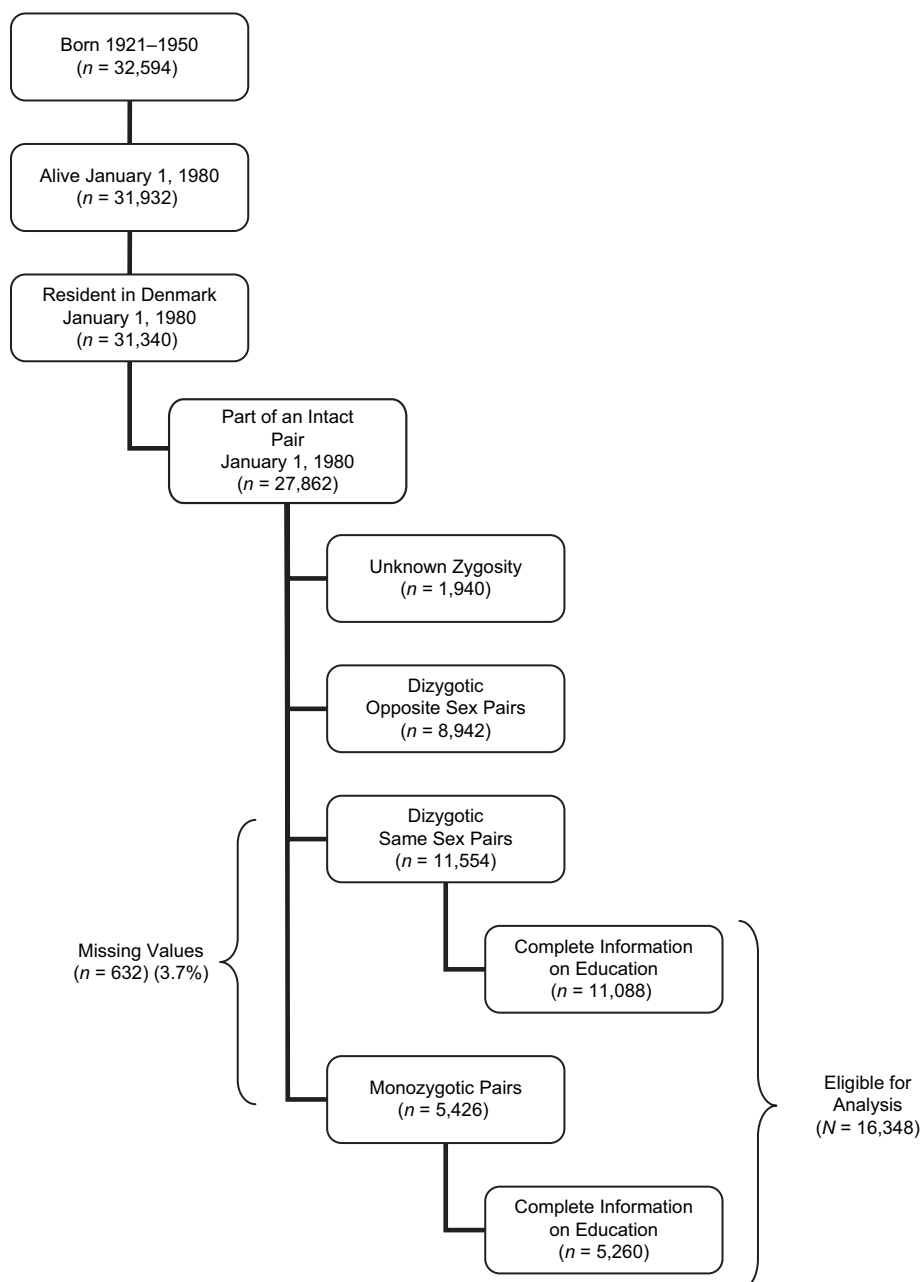


Figure 2. Definition of twin population born during 1921–1950 with data from the Danish Twin Registry and Statistics Denmark.

twins share 100% of their genes and DZ twins, like siblings, share only 50% of the genes on average. In the intrapair analysis, the following scenarios and interpretations are possible, if we assume educational differences in mortality in the standard analyses.

Scenario 1. Persistence of a social gradient in the intrapair analyses within both DZ and MZ twin pairs suggests an independent effect of educational status in adulthood; that is, the twin with the highest educational status tends to have the lowest mortality risk within both DZ and MZ pairs.

Scenario 2. No social gradient in the intrapair analyses for both DZ and MZ twins suggests that family environmental factors shared by the twins explain the association.

Scenario 3. Persistence of a social gradient in the intrapair analyses within DZ twin pairs, but not MZ twin pairs, suggests that genetic factors account for the association.

It should be noted that these scenarios reflect only unambiguous situations, where one type of factors explains the whole association. More realistically, an attenuation of the social gradient in the twin analyses would indicate that

Table 1. Descriptives of Educational Status in 1980 According to Zygosity, Birth Cohort, and Gender in a 5% Population Sample ($N = 96,633$) and a Population of Danish Twins ($N = 16,980$)

Cohort, Gender, and Educational Status, years	5% Population Sample			Dizygotic Same-sexed Twin Pairs			Monozygotic Twin Pairs		
	No.	% ^a	Mean, years (SD)	No.	% ^a	Mean, years (SD)	No.	% ^a	Mean, years (SD)
1921–1935									
Male			10.5 (3.57)			10.0 (3.54)			10.7 (3.67)
≤7	9,312	45.0		1,103	50.9		436	44.1	
>7	10,556	51.0		949	43.8		514	52.0	
Missing	812	3.9		114	5.6		38	3.9	
Female			9.2 (3.03)			9.0 (2.98)			9.3 (3.13)
≤7	11,966	57.5		1,368	62.3		644	58.3	
>7	8,368	40.2		756	34.4		438	39.7	
Missing	490	2.4		72	3.3		22	2.0	
1936–1950									
Male			11.8 (3.38)			11.4 (3.45)			11.8 (3.34)
≤7	7,121	25.2		1,224	30.3		443	25.3	
>7	19,803	69.9		2,602	64.4		1,239	70.9	
Missing	1,392	4.9		212	5.3		66	3.8	
Female			10.8 (3.25)			10.6 (3.24)			10.8 (3.21)
≤7	8,366	31.2		1,117	35.4		490	30.9	
>7	17,593	65.6		1,969	62.4		1,056	66.6	
Missing	854	3.2		68	2.2		40	2.5	
Total cohort									
≤7	36,765	38.1	7.0 (0.07)	4,812	41.7	7 (0.01)	2,213	37.1	7 (0.02)
>7	56,320	58.3	13.1 (2.19)	6,276	54.3	13.1 (2.14)	3,247	59.8	13.2 (2.15)
Missing	3,548	3.7		466	4.0		166	3.1	
Total	96,633	100	10.7 (3.44)	11,088	100	10.5 (3.44)	5,426	100	10.8 (3.45)

Abbreviation: SD, standard deviation.

^a May not sum to 100 because of rounding.

several factors contribute to the association between education and mortality.

In all analyses, we calculated hazard ratio estimates together with 95% confidence intervals using the STATA command *stcox* (STATA, release 10, statistical software; StataCorp LP, College Station, Texas).

For zygosity (MZ/DZSS), sex (male/female), and birth cohorts (1921–1935/1936–1950), we evaluated their potential interaction with education by including an interaction term in the model one at a time and testing statistical significance levels by means of a Wald test. The variables were further used for stratification of analyses.

Finally, in the oldest birth cohorts (1921–1935), for whom we had information on early and late death, we investigated whether the association between educational status and mortality differed for early (<65 years) and late (≥65 years) death, as these outcomes are likely to reflect different underlying causes of death.

RESULTS

A total of 31,340 twins were alive and resident in Denmark at the start of follow-up (Figure 1), and 27,862 were

part of an intact pair (i.e., both twins alive in 1980). Of these, 16,980 were MZ or DZSS twins and included in the study. Among those, 16,348 had complete information on education and were thus eligible for analysis. In the eligible population, a total of 2,168 twin pairs (MZ ($n = 675$)/DZSS ($n = 1,493$)) were actually informative, as only twin pairs discordant on educational status with at least one event before censoring contributed with statistical information to the intrapair analyses. In the twin population, a total of 4,362 deaths occurred during the follow-up period (26.8%).

The level of education was similar in the twin population and the population-based sample (Table 1). However, more people had a lower educational level among DZSS twins compared with the population sample, while MZ twins had a slightly longer education than the population sample. Consistently, men had a longer education than women, especially in the oldest cohorts. In addition, younger birth cohorts had longer education than did older birth cohorts.

Among twin pairs, intrapair differences in educational status were generally smaller among MZ than DZSS twins (i.e., 17.4% vs. 25.8% and 3.5 years vs. 3.9 years of education), when discordance was defined as 7 years or less

Table 2. Descriptives of Intrapair Discordance on Educational Status in 1980 According to Zygosity, Birth Cohort, and Gender in a Population of Danish Twins ($N = 16,348$)

Years of Education	Dizygotic Same-sexed Twin Pairs			Monozygotic Twin Pairs		
	No.	%	Mean, years (SD)	No.	%	Mean, years (SD)
<i>Distribution of Discordant Twin Pairs as Defined in Main Analysis^a</i>						
≤7 vs. >7						
1921–1935						
Males	606	29.5	4.5 (2.78)	188	19.8	3.9 (2.77)
Females	488	23.0	4.2 (2.39)	196	18.1	3.8 (2.39)
1936–1950						
Males	972	25.4	3.7 (2.68)	270	16.1	3.2 (2.64)
Females	794	25.7	3.7 (2.16)	260	16.8	3.5 (2.07)
Total	2,860	25.8	3.9 (2.54)	914	17.4	3.5 (2.49)
<i>Distribution of Discordant Twin Pairs as Defined in Supplementary Analysis^b</i>						
≤7 vs. <10	326	2.9	1.3 (0.46)	148	2.8	1.4 (0.49)
≤7 vs. 10–<13	558	5.0	4.6 (0.85)	190	3.6	4.7 (0.71)
≤7 vs. 13–<15	1,670	15.1	6.5 (0.47)	496	9.4	6.5 (0.42)
≤7 vs. ≥15	306	2.8	8.6 (0.88)	80	1.5	8.6 (0.75)
7–<10 vs. 10–<13	136	1.2	2.8 (1.18)	52	1.0	2.8 (1.11)
>7–<10 vs. 13–<15	382	3.5	5.0 (0.68)	170	3.2	4.9 (0.76)
>7–<10 vs. ≥15	64	0.6	7.3 (1.17)	22	0.4	7.6 (0.48)
10–<13 vs. 13–<15	626	5.7	2.1 (1.05)	284	5.4	2.3 (1.01)
10–<13 vs. ≥15	312	2.8	4.5 (1.36)	108	2.1	4.7 (1.25)
13–<15 vs. ≥15	732	6.6	2.4 (0.99)	214	4.1	2.2 (1.12)
Total	5,112	46.1	4.6 (2.27)	1,764	33.5	4.4 (2.24)

Abbreviation: SD, standard deviation.

^a Definition of discordant twin pairs in main analysis is shown in Table 3.

^b Definition of discordant twin pairs in supplementary analysis is shown in Table 5.

vs. >7 years (Table 2). Older birth cohorts, particularly men, displayed the largest intrapair differences. A more detailed categorization of educational status showed more discordant twin pairs (46.1% among DZSS twins and 33.5% of the MZ twins). An education contrast of ≤7 years versus 13–<15 years was the most prevalent (15.1% in DZSS and 9.4% in MZ twins), and the mean difference in this group was 6.5 years.

Results from the Cox regression analyses of mortality according to educational status showed a significantly increased risk of death associated with low compared with high educational status in the standard analyses in both the twin cohort and the population sample (Table 3). Risk estimates were of a similar magnitude in the 2 populations. There seemed to be a stronger association between educational status and mortality in the younger cohorts (population sample: hazard ratio (HR) = 1.46, 95% confidence interval (CI): 1.37, 1.55; HR = 1.47, 95% CI: 1.37, 1.58) compared with in the older cohorts (HR = 1.18, 95% CI: 1.14, 1.23; HR = 1.24, 95% CI: 1.19, 1.30), and the test for interaction showed a significant interaction between educational status and birth cohort in the standard analyses ($P = 0.02$). There was no strong evidence for an interaction between educational status and sex and zygosity, respec-

tively. In the intrapair analyses, the combined estimates in the standard analyses (HR = 1.14, 95% CI: 0.99, 1.31; HR = 1.24, 95% CI: 1.21, 1.26) were comparable. However, for the stratum-specific estimates, there was an attenuation of the association between education and mortality in the intrapair analyses in all strata but males born during 1921–1935 for whom the association was actually slightly stronger and displayed borderline significance (HR = 1.25, 95% CI: 0.99, 1.57 compared with HR = 1.17, 95% CI: 1.06, 1.30). As in the standard analyses, there was no evidence of a significant difference in the effect of education in the MZ and DZSS twin population ($P = 0.59$). However, the statistical power in the intrapair analyses was limited, despite the large sample size, and all estimates had wide confidence intervals.

From Table 4, showing results from an analysis based on a more detailed measure of educational status, the expected social gradient in mortality can be observed ($P_{\text{trend}} < 0.001$). In addition, the pattern from Table 3 is replicated, showing an absence of attenuation for males born during 1921–1935. For other subgroups, attenuation does seem to occur in the intrapair analyses, but for the largest contrasts, education still has a strong independent effect on mortality risk, except for females born during 1921–1935. In addition, a social gradient seems to exist in the intrapair analyses in most

Table 3. The Hazard Ratio of Death (1980–2008) According to Low Educational Status (≤ 7 Years of Education) in a 5% Population Sample ($N = 96,633$) and a Population of Danish Twins ($N = 16,348$), Showing Results From Standard Analyses and Intrapair Analyses Stratified on Zygosity, Birth Cohort, and Gender

Birth Cohort and Gender	5% Population Sample ($N = 96,633$)		Standard, Twins, cluster ^a						Intrapair Analysis, strata ^b					
			All ^c ($N = 16,348$)		Dizygotic Same-sexed Twin Pairs ($N = 11,088$)		Monozygotic Twin Pairs ($N = 5,260$)		All		Dizygotic Same-sexed Twin Pairs		Monozygotic Twin Pairs	
	HR ^d	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
1921–1935														
Males	1.18 ^e	1.14, 1.23	1.17 ^e	1.06, 1.30	1.15 ^e	1.02, 1.30	1.17	0.96, 1.44	1.25	0.99, 1.57	1.23	0.95, 1.59	1.32	0.81, 2.16
Females	1.24 ^e	1.19, 1.30	1.28 ^e	1.13, 1.44	1.21 ^e	1.05, 1.40	1.41 ^e	1.14, 1.74	1.02	0.77, 1.36	1.06	0.76, 1.47	0.92	0.52, 1.62
1936–1950														
Males	1.46 ^e	1.37, 1.55	1.54 ^e	1.34, 1.77	1.59 ^e	1.36, 1.87	1.36 ^e	1.02, 1.81	1.11	0.85, 1.45	1.13	0.83, 1.52	1.05	0.57, 1.94
Females	1.47 ^e	1.37, 1.58	1.32 ^e	1.10, 1.58	1.24	1.00, 1.53	1.51 ^e	1.09, 2.08	1.12	0.77, 1.62	1.19	0.77, 1.86	0.94	0.46, 1.90
Total	1.24 ^e	1.21, 1.26	1.25 ^e	1.17, 1.33	1.24 ^e	1.15, 1.33	1.26 ^e	1.12, 1.42	1.14	0.99, 1.31	1.15	0.99, 1.35	1.08	0.81, 1.44

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Standard analysis treating twins as individuals taking interdependence of observations into account by including a cluster term. The interpretation of hazard ratio is the risk of death for an individual with an educational length of 7 years or less compared with a random individual with an educational length of >7 years.

^b Intrapair analysis of twins by inclusion of a stratum statement. The interpretation of hazard ratio is the risk of death for a twin with an educational length of 7 years or less compared with its co-twin with an educational length of >7 years.

^c All = dizygotic same-sexed twin pairs + monozygotic twin pairs.

^d Reference value: >7 years of education.

^e Statistically significant at the 5% level.

subgroups, although it is significant only in the total cohort ($P_{\text{trend}} = 0.007$).

Table 5 shows the results from a Cox regression analysis among the oldest cohorts (1921–1935), in which we analyzed the association between educational status and early (<65 years) and late (≥ 65 years) death. Although not entirely clear, the results from the standard cohort analyses do not appear markedly different for early and late death, respectively. Worth noticing, however, are the results from the intrapair analyses, where an attenuation of the association can be observed for the late deaths, while the association between educational status and early deaths actually appears to become stronger. A likelihood ratio test comparing the models treating early and late death separately with the general model showed a significant, better goodness of fit of the models differentiating early and late death. This suggests a violation of the proportional hazards assumption in the intrapair analyses, which implies that the estimates from Tables 3 and 4 combining early and late deaths are somewhat reductive, compared with Table 5.

DISCUSSION

In this study, the expected educational differentials in mortality were demonstrated in the cohort analyses of a 5% population sample and a population of 16,348 MZ and DZSS twins. In the intrapair analyses, where genetic and early environmental factors were controlled for per design, the associations were attenuated for all but one subgroup with estimates close to 1 in both MZ and DZSS twins. However, for large educational contrasts, there still seemed to be a considerable difference in mortality risk within twin

pairs. Because no moderation of effect by zygosity was demonstrated, the overall results of the study seem most compatible with an effect of early environmental factors in explaining the educational inequality in mortality, although the effect of education did not disappear entirely in the intrapair analyses. Particularly, the association persisted for men born during 1921–1935, which might suggest a greater effect of educational status in those cohorts. If the effect of education on mortality risk to a large extent were mediated by occupational exposures, an explanation for this finding could be that the work environment associated with low educational status in earlier days was more health detrimental than later on, thus affecting primarily the older birth cohorts. In order to investigate a potential explanation for the lack of association in women in older birth cohorts, we carried out a post-hoc analysis, where education was included as the highest *household* educational attainment. (This was identified via a marital link in Statistics Denmark linking the study population to their potential spouses in 1980. The one in the couple with the highest educational attainment would contribute with years of education to the household measure.) Our hypothesis was that educational differentials in mortality risk in the women might be obscured by a higher educational status of their partner. This proved not to be the case, as only small differences in the results were seen for the oldest cohorts, when highest household education was introduced as a binary measure analogous the one in Table 3 (HR = 1.24, 95% CI: 0.99, 1.54 and HR = 1.04, 95% CI: 0.83, 1.31 compared with HR = 1.25, 95% CI: 0.99, 1.57 and HR = 1.02, 95% CI: 0.77, 1.36). Rejecting the post-hoc hypothesis, an alternative explanation for the observed gender differences could be that a large proportion of women in the older birth cohorts, regardless of

Table 4. The Hazard Ratio of Death (1980–2008) According to Educational Length in a 5% Population Sample ($N = 96,633$) and a Population of Danish Twins ($N = 16,348$), Showing Results From Standard Analyses and Intrapair Analyses Stratified on Birth Cohort and Gender

Birth Cohort, Gender, and Years of Education	Standard, Twins, cluster ^a ($N = 16,348$)			Intrapair Analysis, strata ^b ($N = 16,348$)		
	HR	95% CI	P_{trend}^c	HR	95% CI	P_{trend}^c
1921–1935						
Males						
≤7	1	Referent		1	Referent	
>7–<10	1.01	0.74, 1.41		0.70	0.39, 1.24	
10–<13	0.77	0.60, 1.00		0.71	0.43, 1.16	
13–<15	0.93	0.83, 1.05		0.84	0.66, 1.07	
≥15	0.63 ^d	0.50, 0.75	<0.001	0.69	0.45, 1.05	0.088
Females						
≤7	1	Referent		1	Referent	
>7–<10	0.82	0.62, 1.08		1.08	0.63, 1.84	
10–<13	0.74 ^d	0.60, 0.91		1.09	0.74, 1.60	
13–<15	0.86	0.73, 1.01		0.85	0.60, 1.22	
≥15	0.67 ^d	0.52, 0.86	<0.001	1.03	0.63, 1.67	0.708
1936–1950						
Males						
≤7	1	Referent		1	Referent	
>7–<10	0.87	0.64, 1.20		1.21	0.68, 2.17	
10–<13	0.64 ^d	0.48, 0.87		1.30	0.79, 2.14	
13–<15	0.69 ^d	0.59, 0.80		0.86	0.64, 1.15	
≥15	0.44 ^d	0.34, 0.57	<0.001	0.62	0.37, 1.04	0.081
Females						
≤7	1	Referent		1	Referent	
>7–<10	0.88	0.63, 1.23		1.28	0.72, 2.27	
10–<13	0.80	0.60, 1.06		0.72	0.44, 1.16	
13–<15	0.79 ^d	0.64, 0.98		0.88	0.56, 1.36	
≥15	0.54 ^d	0.37, 0.79	<0.001	0.52	0.22, 1.22	0.120
Total						
≤7	1	Referent		1	Referent	
>7–<10	0.86	0.74, 1.00		1.05	0.80, 1.39	
10–<13	0.70 ^d	0.62, 0.79		0.93	0.74, 1.16	
13–<15	0.89 ^d	0.83, 0.96		0.86	0.78, 1.00	
≥15	0.60 ^d	0.53, 0.68	<0.001	0.73 ^d	0.56, 0.94	0.007

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Standard analysis treating twins as individuals taking interdependence of observations into account by including a cluster term. The interpretation of hazard ratio is the risk of death for an individual with an educational length from greater than 7 years to 15 years or more compared with a random individual with a low educational length (7 years or less).

^b Intrapair analysis of twins by inclusion of a stratum statement. The interpretation of hazard ratio is the risk of death of a twin with an educational length from greater than 7 years to 15 years or more compared with its co-twin with a low educational length (7 years or less).

^c Derived from inclusion of a continuous variable consisting of the median values for each educational category.

^d Statistically significant at the 5% level.

household educational status, tended to be housewives (16). This would explain the lack of effect in women in older birth cohorts, when genetics and background factors are controlled for.

No clear pattern was seen for the analyses of early and late death, but the finding of an attenuation of association for late but not early deaths in the intrapair analyses and a significant, better goodness of fit for these models may imply

Table 5. The Hazard Ratio of Death (1980–2008) Before Age 65 Years and at Age 65 Years or Above According to Low Educational Status (≤ 7 Years of Education) in the 1921–1935 Birth Cohort in a 5% Population Sample and a Population of Danish Twins, Showing Results From Standard Analyses and Intrapair Analyses Stratified on Birth Cohort and Gender

Age at Death and Gender	5% Population Sample		Standard, Twins, cluster ^a		Intrapair Analysis, strata ^b	
	HR ^c	95% CI	HR ^c	95% CI	HR ^c	95% CI
Death at age <65 years ^d						
Males	1.09 ^e	1.02, 1.17	1.26 ^e	1.03, 1.53	1.40	0.95, 2.05
Females	1.20 ^e	1.09, 1.31	1.53 ^e	1.17, 2.00	1.47	0.82, 2.64
Total	1.07 ^e	1.01, 1.13	1.25 ^e	1.07, 1.47	1.42 ^e	1.03, 1.96
Death at age ≥ 65 years ^f						
Males	1.25 ^e	1.20, 1.31	1.18 ^e	1.04, 1.34	1.13	0.84, 1.52
Females	1.29 ^e	1.23, 1.37	1.20 ^e	1.04, 1.39	0.92	0.64, 1.32
Total	1.20 ^e	1.16, 1.24	1.13 ^e	1.03, 1.24	1.04	0.83, 1.31

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Standard analysis treating twins as individuals taking interdependence of observations into account by including a cluster term. The interpretation of hazard ratio is the risk of death for an individual with an educational length of 7 years or less compared with a random individual with an educational length of >7 years.

^b Intrapair analysis of twins by inclusion of a stratum statement. The interpretation of hazard ratio is the risk of death for a twin with an educational length of 7 years or less compared with its co-twin with an educational length of >7 years.

^c Reference value: >7 years of education.

^d For 5% population sample, $n = 41,405$; for standard twins, cluster, $n = 6,208$.

^e Statistically significant at the 5% level.

^f For 5% population sample, $n = 35,529$; for standard twins, cluster, $n = 5,066$.

that early and late mortality reflect different underlying causes of death that display different educational patterns. For instance, we know that a greater proportion of early deaths are due to external causes (results not shown). This might explain a part of this finding. However, even this large data set did not allow for analyses of cause-specific death.

This study is register based and one of the first to use a classical twin design to explore the causality of educational patterning of mortality in a large and unselected twin population. The population size allows us to investigate a hard endpoint such as mortality, and the prospective and almost complete nature of the registers ensures valid information about educational status and mortality.

A number of other studies have used twin data to address the social patterning of health and disease, but the majority are based on small twin populations, focusing on continuous outcomes, such as self-rated health, body mass index, or physical activity (10–14). In another Danish register-based study of Behrman et al. (9), the authors did not find any effect of education on hospitalizations in the intrapair analyses among MZ and DZSS twins. Mortality was also touched upon in this study, but only as a dichotomous measure without taking the time of death into account. The results were similar to those reported in this study. Other studies with similar designs have looked at different social indicators (e.g., occupation-based measures and marital status) (11, 13, 14, 17). The previous studies show inconsistent results: Several lend support to an effect of SEP on health-

related outcomes, while just as many studies draw opposite conclusions. However, studies have been carried out in different societal contexts, mainly in Denmark and the United States, and there seems to be a greater independent effect of adult SEP in the American data (10–12) than in the Danish data (9, 13, 14), and it is conceivable that adult SEP has a different impact in different societal contexts. The Danish welfare system with a more even distribution of wealth, as well as a more equal access to health care services, might explain the different findings in the 2 countries. However, the choice of social indicator also seems to influence the results. For instance, Krieger et al. (11) did not find a health effect, when using education as a social indicator in a female twin population, while they did find an effect of social position when they used an occupation-based measure. Thus, the lack of educational effect in their study is in accordance with the study of Behrman et al. but stands in contrast to the 2 studies by Osler et al. (13, 14) based on Danish survey data, which reported an attenuation of effect when using an occupation-based measure of social status. Another factor that might contribute to the blurred picture of evidence is imprecise estimation of effects, which makes it difficult to determine whether loss of statistical significance in the intrapair analyses is in fact true or due to type II errors. Consequently, only cautious interpretations can be made.

A key assumption in the discordant twin-pair design is that twins have been reared together. In our data, we expect that this is the case for more than 98% of the study

population, on the basis of information from a survey among middle-aged Danish twins ($n = 4,311$), which showed that only 2% of twin pairs had lived together to less than 14 years of age. However, an inherent problem in the discordant twin-pair design is the selection issue: Twins discordant on educational status may be a selected group, who are special in the sense that, in spite of identical genes and rearing environment, they differ in their educational accomplishments. As such, it may be a crude assumption that twins are perfectly matched. Lundborg (12) investigated this assumption in more detail and found that the majority of all twins went to the same school and class and shared the same friends. In addition, 85% of all parents stated that they had “never” tried to treat their twins differently. So even though twins are not perfectly matched on childhood environment, a shared early environment does seem like a fairly reasonable assumption to make, and the discordant twin-pair design is probably the closest one can get to the counterfactual ideal.

One potential explanation for an association between SEP and health is “health selection” (i.e., that child health determines the obtainment of education and not the other way around). With these data, it was not possible to rule out this explanation, as we did not have any health information before 1980. However, it has previously been investigated in the study of Lundborg (12), where he concludes that all intratwin-pair differences in education were uncorrelated with all measures of early life differences in health and birth weight. These findings lend credibility to the results of this paper and to the discordant twin-pair design in general.

Only MZ and DZSS twin pairs were included in this study, as dizygotic opposite-sex twin pairs may involve great challenges in handling complex gender interactions, which was not the focus of this study. Furthermore, twin pairs with unknown zygosity (7%) are known not to be representative for the twin population at large. However, an analysis of robustness including all twins of unknown zygosity ($n = 18,182$) changed the risk estimates only marginally (results not shown).

In this study, 2 measures of education were applied. For the dichotomous measure, a cutoff point of 7 years was chosen primarily because 7 years of education has been mandatory in Denmark for many years, thus reflecting the basic education in the population. In order to allow for more detailed analyses, a categorical exposure measure of 5 categories of educational attainment was also applied. In addition, we tried to operationalize education in various different ways, including International Standard Classification of Education codes and length of education as a continuous variable using both a linear specification and various transformations since a linear relation was not supported by the data. Ultimately, all specifications of education rendered similar results.

Educational status was measured in 1980 to ensure that exposure preceded outcome. However, especially the younger cohorts may be misclassified because of the fact that they had not yet obtained their final educational attainment in 1980. As such, we compared the length of education in 1980 with the length of education in 1990 and found that 1% of the twins were misclassified according to the educational

status in 1990. The mean age of the misclassified group was 35 years, confirming that the misclassification was most prevalent in younger cohorts. However, considering the few cases of misclassification, the issue is negligible.

Education is only one aspect of socioeconomic position and possibly the social indicator that is most closely related to the early stage of the life course (18). It would also be of interest to investigate the health effect of other social indicators, such as occupational status and income, which may reflect adult socioeconomic conditions more exclusively. However, education has some practical advantages to the other indicators because it is the most valid and constant measure displaying no fluctuations over time.

In conclusion, the extraordinary data resource of the Danish Twin Registry linked to Statistics Denmark offers a unique possibility to investigate the effect of educational status controlled for genetic make-up and early environmental factors. The findings of an attenuation of educational effect in the intrapair analyses for all subgroups but men from older birth cohorts suggest that increasing welfare in Denmark over time has made the independent effect of education in adulthood less pronounced, and social inequality in health among younger cohorts seems mainly to be traceable back to early environment. However, health differentials still exist if educational differences are large, even after control for confounding by genetic and shared environmental factors.

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Author affiliations: Unit of Epidemiology, Institute of Public Health, University of Southern Denmark, Odense, Denmark (Mia Madsen, Anne-Marie Nybo Andersen, Kaare Christensen); The Danish Aging Research Centre, Odense, Denmark (Mia Madsen, Kaare Christensen, Merete Osler); The Danish Twin Registry, Institute of Public Health, Odense, Denmark (Mia Madsen, Kaare Christensen); Department of Biostatistics, Institute of Public Health, University of Copenhagen, Copenhagen, Denmark (Per Kragh Andersen); and Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark (Merete Osler).

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