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Educational differences in cardiovascular mortality - the role of shared family factors and cardiovascular risk factors.

Kjøllestad MKR¹, Ariansen I², Mortensen LH³, Davey Smith G⁴, Næss Ø^{1,2}

- 1) Institute of Health and Society, University of Oslo, Norway.
- 2) Norwegian Institute of Public Health
- 3) University of Copenhagen, Denmark
- 4) MRC Integrative Epidemiology Unit (IEU), at the University of Bristol, UK

Corresponding author:

Marte Kjøllestad, Institute of Health and Society, Faculty of Medicine, University of Oslo.

Postbox 1130 Blindern, 0318 Oslo, Norway. E-mail: m.k.kjollesdal@medisin.uio.no. Phone: 0047

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Abstract

Aims

To explore the confounding effects of early family factors shared by siblings and cardiovascular risk factors in midlife on the educational differences in CVD mortality.

Methods

Data from national and regional health surveys in Norway (1974-2003) was linked with data from the Norwegian Family Based Life Course Study, the National Educational Registry and the Cause of Death Registry. The study population consisted of participants with at least one full sibling among health survey participants (n=271.310). Data were available on CVD risk factors; weight, height, blood pressure, total cholesterol and smoking.

Results

Hazard Ratio (HR) of CVD mortality was 3.44 (95 % CI 2.98, 3.96) in the lowest educational group relative to the highest. In within sibship analyses, the HRs were little altered. Adjusted for risk factors, HR for CVD mortality in cohort analyses was 2.05 (1.77, 2.37) in the lowest educational group, relative to the highest. The respective HR in within sibship analyses was 2.46 (1.48, 2.24).

Conclusion

Using a sibling design, we did not find the association between education and CVD mortality to be considerably confounded by early life factors shared by siblings, but to a large extent explained by CVD risk factors. Results suggest that reducing levels of CVD risk factors could have the greatest effect on mortality risk in less-well educated individuals.

Key words: early life, sibling, social inequalities, cardiovascular mortality, cardiovascular risk factors.

Word count: 216

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide [1]. Conventional risk factors in adult life, such as smoking, hypertension and high cholesterol have been shown to account for a large proportion of the cases within a population [2]. Early life factors have also been suggested to be important contributors to later CVD risk. In the 1970s, based on Norwegian data analyses, Forsdahl suggested that poor living conditions during childhood was associated with adult coronary heart disease [3]. In the 1980s, Barker proposed that suboptimal nutrition during early life was associated with increased risk of chronic diseases, including CVDs [4]. Since then, the importance of early life factors has been under considerable scrutiny.

Socioeconomic position (SEP) in early life is a key indicator of living conditions during childhood and has been suggested as a driver of the types of findings reported by Forsdahl and Barker. SEP, both in adulthood and childhood, has repeatedly been associated with both cardiovascular disease (CVD) and its risk factors [5-6]. While Barker emphasized a critical period in early life determining later health [4], others have suggested an accumulated risk of low SEP in more periods during life [7]. SEP is commonly captured using education, occupation or income. Education represents knowledge-related assets, as well as being a predictor of occupation and income [8]. Income reflects material circumstances, possibly connected to health-promoting environments [8]. Occupation is a predictor of social relations and norms regarding health and health behaviour [8]. It is also related to various privileges and facilities, as well as material and psychosocial working conditions [8]. Education is stable over time, which is an advantage when looking at associations between SEP and health.

Own adult and childhood SEP are considerably inter-related, and the effects of each may be difficult to separate. Adult CVD may be influenced by childhood SEP through its impact on future adult SEP of the child, and through adult CVD risk factors. Furthermore, parents' lifestyle and behaviors may influence the same behaviors in the next generation [9-11]. Childhood SEP could also influence adult CVD directly, through, for instance, unfavorable conditions during pregnancy or infancy, such as malnutrition [4]. Thus, the association between adulthood SEP

and CVD may be confounded by early life factors, and these factors may also be related to adult risk factors which mediate the association between SEP and CVD. Moreover, social mobility over generations varies with welfare systems [12], and is also related to health, making the associations even more complex.

Recently, data from population registers with possibilities to link siblings has been used to study the importance of factors in early life shared by siblings on socioeconomic differences in morbidity and mortality. Early life factors shared by siblings include parental SEP, housing, schooling, neighborhood and parenting style. In studies from Norway and Denmark, educational differences in all- and cause specific mortality, including CVD, were partly explained by factors shared by siblings [13;14]. In Finland, mortality differences between income groups were not explained by such factors [15].

The aim of the current study was to explore the extent of confounding by factors shared by siblings in early life on the association between education and CVD mortality among Norwegian adults, and further, the role of modifiable risk factors in this. Ultimately this will shed light on the inter-linked role of cultural and biological mechanisms on adulthood CVD risk. CVD serves as a model disease for the impact of important risk factors used in our study and shows the mechanisms we were interested in studying more clearly than with all-cause mortality.

Methods

Study population

Data from national and regional Norwegian health surveys were linked with data from the Norwegian Population Registry, generational data from the Norwegian Family Based Life Course Study (NFLC) [16], the National Educational Registry and the Cause of Death Registry using the unique national personal identification numbers. In the Counties Study (1974-88), all men and women aged 35-49 years, living in three different counties in Norway were invited to cardiovascular health surveys [17]. In the Age 40 Program, inhabitants aged 40-44 years from all counties in Norway, except for Oslo, were invited to health surveys (1985-99) [18]. Some places

also those aged 39-45 years were invited. The Cohort Norway (CONOR) (1994-2003) is based on data from several regional health surveys with participants aged 20-103 years [19]. The attendance rate of the three surveys was 86 %, 70 % and 58 % respectively.

For the current study, participants from the health studies born in 1940 or after were included. If participants attended more than one health survey, data from the first survey attended was used. The study population consisted of participants with at least one full sibling (sharing mother and father) among the health survey participants. The index person's mother and father were identified by linkage in the NFLC study [16]. Parental identification has proven to be reliable for persons born in 1940 and after [16]. Participants with missing information on one or both parent (n=52397), educational attainment (n=344, 0.1% of those with a full sibling) or cardiovascular risk factors (Total Cholesterol (TC) n= 316, 0.1%, Blood Pressure (BP) n=1250, 0.5%, smoking n=1357, 0.5%, Current treatment for hypertension n= 543, 0.2%, Body Mass Index (BMI) n=862, 0.3%) were excluded. The study population consisted of 271.310 participants (Figure 1).

Education

Education was registered in the National Educational Registry and reported in National Population and Housing Censuses every 10th year from 1970 to 2011. A person's highest attained educational level was classified as "≤ 9 years", "10-12 years/started or completed upper secondary school", "≥13 years/university college or university education".

Cardiovascular risk factors

In all health survey screenings self-assessed questionnaires, clinical measurements and blood sampling were collected. Self-reported smoking ("daily smoker" vs "not daily smoker") and current treatment of hypertension was recorded. BP was initially measured manually by sphygmomanometers and later by automatic oscillometric measures. Height and weight were measured and BMI (kilogram/meter²) calculated. Non-fasting serum TC was initially measured

by non-enzymatic, and later enzymatic, method. Non-enzymatic values were converted by a correction factor.

Cardiovascular mortality

Data on underlying causes of death from CVD were obtained from the Norwegian Cause of Death Registry (ICD-9: 390-459, ICD-10: I00-I99). Participants were followed from time of survey to death or end of follow-up (31.12.2012), with a mean follow-up time of 19.0 (5.2) years.

Statistical analyses

Cox proportional hazards regression with age (years) as underlying time was used to estimate Hazard Ratios (HR) of cardiovascular mortality in educational groups “<10 years” and “10-12 years” relative to “≥13 years”. In the cohort analyses, analyzing all participants with no regard to sibships, we used sandwich estimator corrected standard errors to take account of familiar clustering. The cohort analyses should produce results similar to those found in studies of unrelated individuals. For the within sibship analyses, where each sibship had a group specific baseline hazard, we used the stratified Cox regression model of Holt and Prentice [20]. This model is similar to so-called fixed effects model, where the association is estimated within sibships. The stratified Cox regression model makes no extra distributional assumptions when compared to the Cox model. The proportional hazards assumption was examined by first plotting the scaled Schoenfeld residual against age, supplemented by a global test of a zero slope in the association between age and the scaled Schoenfeld residuals. The cohort- and within sibship analyses included one model adjusted for sex and birth year, and one model adjusted for sex, birth year and cardiovascular risk factors. We compared the cohort and sibship analyses to assess the importance of shared environment. This strategy is known to have some limitations. First, in a Cox regression the inclusion of any variable that is associated with the outcome may cause the estimates of other variables to inflate even in the absence of confounding [21]. This might counteract the attenuation of confounding from early life factors. Secondly, confounders could be the cause of discordance in education and thus inflate estimates [22]. Examples of such confounders include intelligence and health in early life. This

may cause the estimates for education to become stronger in the sibship analyses. The variation in CVD risk factors within sibships and between individuals in the cohort has previously been reported (among 40-45 year olds in a sample overlapping ours) (Ariansen I. In press). Interaction between education and sex and education and birth year was checked for, and there were no interactions. Sensitivity analyses were carried out including only those with a sibling discordant in education in the cohort analyses, and also adjusting for the different health surveys as source of data on risk factors. The intraclass correlation for educational groups within sibships was estimated using random effect models. All analyses were performed in Stata 14.

The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK) (2012/827).

Results

The characteristics of the population are given in table 1. Participants were screened between 1974 and 2003. Mean age was 41 years, and 84 % of the sample was between 40 and 45 years. At the end of the follow-up, 2508 participants were dead from CVD. The number of CVD deaths during follow-up was lowest in the highest educational groups (table II). Of those with one sibling in the sample, 42 % had a sibling with discordant educational level, and among those with four or more siblings in the sample, 86 % had a sibling with a discordant educational level (table III). The intraclass correlation for education was 36 %, indicating a reasonably high resemblance of educational level in sibships.

In cohort analyses, HR of CVD mortality was 3.44 in the lowest and 2.20 in the middle educational group relative to the highest educated (table IV). The inverse educational per step gradient was not meaningfully changed in the within sibship analyses, indicating that early life factors shared by siblings are not a major contribution to educational differences in CVD mortality. Additional adjustment for CVD risk factors in the cohort analyses substantially

attenuated the per step gradient between CVD mortality and education. After adjustment for CVD risk factors, HR for CVD mortality was 2.05 in the lowest and 1.61 in the middle educational group, relative to the highest educated. In the within sibship analyses of the corresponding model, the gradient was attenuated to a smaller extent when adjusted for risk factors, and the respective HRs in within sibship analyses were 2.46 and 1.82. The per step risk factor adjusted HR was numerically slightly higher in the within sibship than in the cohort analyses. CVD risk factors appeared more important for explaining educational differences in CVD mortality than early life factors shared by siblings.

In sensitivity analyses, adjustment for health survey did not introduce meaningful changes (results not shown). When including only siblings with discordant educational level in cohort analyses, the per step HR was about the same in the cohort (1.73) and in the within sibship analyses (1.72) (supplementary table A).

Discussion

Family factors shared by siblings did not explain much of educational differences in CVD, while a substantial part was explained by CVD risk factors.

Strengths and limitations

This population based study had a large sample size and the ability to study impact of early life environment on educational differences in CVD mortality with within sibship analysis and at the same time adjust for cardiovascular risk factors. Use of register data eliminates problems related to loss to follow-up, except for emigration, which is very limited. Data on risk factors originated from surveys with a reasonable response rate. However, the response rate in CONOR was only 58 %. This may have affected the results, but the low response rate was especially low among those aged younger than 30. Further, only 18 % of the participants had data from CONOR. The majority of the sample was in their forties at screening, and many subjects did not

reach a high age during follow-up, where CVD mortality is more probable. Mean age at CVD death was 55 years, and our results apply particularly to premature CVD death.

The health surveys were carried out during a 30 years period, and secular trends in CVD mortality may have changed. To account for this, we adjusted the analyses for birth year. Furthermore, CVD mortality may vary with age. In Cox regressions, age was used as underlying time, and thus adjusted for. We did not stratify on sex, in order to preserve the power of the analyses, as few women died from CVD in higher educational groups, and as stratification on sex would give fewer sibship comparisons. Stratification would also mean that we would work on a potentially selected fraction of the sample. We did, however adjust for sex in order to account for possible sex differences in CVD trajectories and their association with early life factors. How much of early life factors that are shared between siblings is an open question, and same sex and different sex siblings might not share these factors to the same extent.

Assumptions in sibling design

Only siblings discordant for education contribute to the estimation of the impact of early life factors. Differences in characteristics between the participants contributing to the cohort and sibship analyses may introduce bias, and statistical power is lower in sibship analyses. In our sample, 1099 of 2508 cardiovascular deaths occurred among participants with no sibling discordant on educational level. Measurement errors in education are unlikely in our sample, as it is register based [22]. In families where all siblings have a high education, many factors facilitating both education and health may be in place. An individual from such a family may be at lower risk of CVD than another person with the same education, but with siblings in lower educational categories. Siblings discordant in education may also differ more regarding non-shared factors than other persons discordant in education, as despite many shared factors in early life, they have attained different educational levels. In analyses including only those with siblings discordant for education, cohort estimates were not attenuated in within sibship analyses. This supports our main findings, that factors in early life shared by siblings do not account for much of the educational differences in CVD mortality.

We do not know whether some parents were separated during early life, which could possibly influence the extent of shared factors in early life, and also discordancy in educational attainment. Until the sixties, the divorce rate was low and constant at 4 per 1000 marriages, raising to about 7 per 1000 marriages during the beginning of the eighties [23]. Defining siblings as sharing both mother and father will define siblings generally sharing early life environment, as well as being partially matched on germ line genetic variation, more than siblings defined as having the same mother only. We rely on this shared part of the family context, and shared proportion of germline, to estimate the impact of early life on educational differences in CVD mortality. Family factors not shared between siblings include birth order, birth year, and events such as sibling-sibling interactions, differential parental treatment and peer groups [24]. There might also be genetic differences between siblings, predicting both educational attainment and mortality risk [25].

Explanations of results

The results indicated that early life factors shared by siblings were not important in explaining the educational gradient in CVD mortality, resembling findings by Tarkiainen et al [15]. Previous studies have suggested that early life circumstances influence CVD mortality through risk factors. A recent study (Ariansen I, In press) carried out in a population overlapping the present found that one third of educational differences in CVD risk factors could be explained by early life factors shared by siblings. Lawlor et al [26] reported an attenuation of the association between BMI and education in within sibship analyses. Kamphuis et al [27] found that childhood circumstances more or less completely influenced cardiovascular mortality through known CVD risk factors. Childhood SEP is not exactly the same as early life factors shared by siblings, however, they are likely to be strongly connected. Further, van de Mheen et al [28] reported that parts of the association between childhood SEP and adult health went through health behavior. In our study, estimates of educational differences in CVD mortality in cohort analyses were not substantially attenuated in within sibship analyses, however, considerably attenuated when adjusted for risk factors. This suggests that any confounding effect of early life factors on the association between CVD and education goes through established adult CVD risk factors.

As most of the risk factors adjusted for in our study are linked to health behavior, such confounding will represent cultural factors, as well as biological. Health behavior have been shown to track from parents to the next generation [9-10] and are thus plausible ways in which early life circumstances can confound the association between SEP and CVD mortality. Madsen et al [14], reported a somewhat stronger attenuation of the association between education and CVD in within sibship analyses among monozygotic than dizygotic twins, indicating that genetic differences are at play. Possibly, both perspectives may be at work, both separately and interacting. Height is an indicator of, in addition to early life health and nutrition, IQ and education, and genetic overlap has been shown in these factors [29]. Thus, as we adjust for height in our study, shared genetics and general ability is partly controlled for. However a substantial component of unaccounted for genetic influences may exist.

There may be various reasons to why CVD risk factors explained more of the educational differences in cohort analyses than in sibship analyses. When factors shared by siblings are taken into account, CVD risk factor may already have been partly adjusted for as well. (Ariansen I, in press). Further, the importance of non-shared factors may be more important in within sibling than in cohort analyses. The somewhat steeper educational gradient in adjusted sibship than cohort analyses could be attributed to inflation of the parameters due to the conditioning on sibship [20]. Finally, a stronger within than between sibship association may indicate that unmeasured factors have obscured the association. Being siblings is used as a measure of shared factors in early life. If sibship does not capture much of these factors, it could as well explain why risk factors, which are a fairly precise measure of biological risk, explain more than shared family factors in the analyses.

Conclusion and implications

In this study, using a sibling design, we did not find the association between education and CVD mortality to be considerably confounded by factors in early life shared by siblings. It seems that any effect of these factors is mostly transmitted through conventional risk factors related to

adult health behavior. As previously recognized by others [30], reduction of CVD risk factor levels, could have the largest absolute effect in less economically advantaged individuals.

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ON conceived the idea for the article. MKRK did the statistical analyses and the drafting of the article. All authors contributed in the final stage of the writing.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Table I. Sample characteristics

N=271310	
	N (%)
Sex	
Male	132037 (48.7)
Female	139273 (51.3)
Year of screening, mean (SD) range	1992 (4.9) 1974-2003
Year of birth, mean (SD) range	1952 (5.4) 1940-1982
Age at examination, mean (SD) (min max)	40.6 (4.7) (15-62)
Education, in years	
7-9	46293 (17.1)
10-12	161626 (59.6)
≥ 13	63391 (23.3)
Systolic blood pressure, mean (SD)	130.2 (14.4)
Current treatment hypertension	5790 (2.1)
Total cholesterol, mean (SD)	5.6 (1.1)
Body mass index, mean (SD)	25.0 (3.7)
Smoking	108055 (39.8)
Deaths during follow up	13756 (5.1)
CVD deaths	2508 (0.9)
Age at death, mean (SD) (min max)	55.0 (7.2) (18 72)
Age at CVD death, mean (SD) (min max)	55.0 (7.1) (28 72)

Table II. Cardiovascular mortality according to educational level. Number of CVD deaths, and as proportions of educational groups.

Educational level	7-9 years	10-12 years	>13 years
CVD deaths, n (%)			
Total	797 (32)	1457 (58)	254 (10)
Men	576 (30)	1136 (60)	194 (11)
Women	221 (37)	321 (53)	60 (10)

Table III: Educational levels according to size of sibling groups in the sample, and number of individual with discordant educational level than their siblings.

	Two siblings	Three siblings	Four siblings	Five siblings
n (%)	162768 (60)	71717 (26)	25223 (9)	11602 (4)
Educational level, n (%)				
Level 1: 7-9 years	25235 (16)	12845 (18)	5219 (21)	2994 (26)
Level 2: 10-12 years	96323 (59)	43014 (60)	15403 (61)	6886 (59)
Level 5: > 13 years	41210 (25)	15858 (22)	4601 (18)	1722 (15)
Mean educational level (SD)	2.1 (0.6)	2.0 (0.6)	2.0 (0.6)	1.9 (0.6)
Individuals in sibling groups with discordant educational level, n (%)	68948 (42)	45117 (63)	18795 (75)	9966 (86)

Table IV. CVD mortality in relation to educational level, crude and adjusted for risk factors, at the cohort level and within sibship groups. Cox Proportional Hazard regression analyses, all adjusted for sex and birth year.

Educational level (years)	<i>Hazard Ratio of cardiovascular mortality (95 % CI)</i>			
			Adjusted for risk factors*	Adjusted for risk factors*
	Cohort	Within sibship	Cohort	Within sibship
7-9	3.44 (2.98, 3.96)	3.23 (2.58, 4.04)	2.02 (1.74, 2.33)	2.44 (1.91, 3.11)
10-12	2.20 (1.93, 2.52)	2.17 (1.80, 2.62)	1.59 (1.39, 1.82)	1.81 (1.47, 2.23)
≥ 13	1	1	1	1
Per one step	1.76 (1.65, 1.87)	1.71 (1.54, 1.90)	1.37 (1.28, 1.46)	1.50 (1.34, 1.68)

*systolic blood pressure, smoking, cholesterol, body mass index, height, current treatment for hypertension

Figure 1. Flow chart