The educational gradient in premature cardiovascular mortality; examining mediation by risk factors in cohorts born in the 1930s, 1940s and 1950s

Inger Ariansen MD PhD[1], Bjørn Heine Strand MSc PhD[1,2,3], Marte Karoline Råberg Kjøllesdal PhD[2], Ólöf Anna Steingrímsdóttir MSc PhD[1], Laust Hvas Mortensen PhD[4], Hein Stigum PhD[1,2], Sidsel Graff-Iversen MD PhD[1,5], Øyvind Næss MD PhD[1,2]

Institution where the work was performed: Division for Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

[1]Division for Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

[2]Department of Community Medicine and Global Health, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway

[3]Norwegian National Advisory Unit on Ageing and Health (Ageing and Health), Oslo, Norway

[4]Section of Social Medicine, University of Copenhagen, Copenhagen, Denmark

[5]Department of Community Medicine, the Arctic University of Norway, Tromsø, Norway

Corresponding author: Inger Ariansen

Address: Norwegian Institute of Public Health, PO Box 222 Skøyen, N-0213 Oslo, Norway

Tel: (+47) 22 07 82 62. Fax : (+47) 22 35 36 05. Mobile: (+47) 40 45 52 29

Email: inger.ariansen@fhi.no

Word count: 4763

1   **ABSTRACT**

2

3   **Aims:** Educational inequality in cardiovascular disease (CVD) and in modifiable risk factors

4   change over time and between birth cohorts. We aimed to assess how CVD risk factors

5   mediate educational differences in premature CVD mortality and how this varies over birth

6   cohorts and sex.

7   **Methods:** We followed 360,008 40-45 year olds born in the 1930s, 1940s or 1950s from

8   Norwegian health examination surveys (1974-1997) for premature CVD mortality. Cox

9   proportional hazard and Aalen's additive survival analyses provided hazard ratios and rate

10   differences (RD) of excess deaths in participants with basic versus tertiary education.

11   **Results:** Relative educational differences in premature CVD mortality were stable, whereas

12   absolute differences narrowed from the 1930s to the 1950s cohorts; RD per 100 000 person

13   years declined from 170 (95% confidence interval 117, 224) to 49 (36, 61) in men and from

14   60 (34, 85) to 23 (16, 29) in women. CVD risk factors attenuated RD's by 69% in both

15   cohorts in men, and in women by 102% in 1930s and 61% in 1950s cohorts. Smoking had the

16   single strongest influence on the educational differences for men in all three cohorts, and for

17   women in the two most recent cohorts.

18   **Conclusion:** Smoking appeared to be the driving force behind educational differences in

19   premature CVD mortality in the 1930s to 1950s birth cohorts for men and in the two recent

20   birth cohorts for women. This suggests that strategies for smoking prevention and cessation

21   might have the strongest impact for reducing educational inequality in premature CVD

22   mortality.

23

24   **Keywords:** Cardiovascular diseases, Mortality, Health behaviour, Educational status,

25   Socioeconomic factors, Cohort effect

INTRODUCTION

A substantial proportion of educational differences in cardiovascular disease (CVD) are mediated by CVD risk factors[1-4]. However, risk factors only contribute to educational inequality in disease if they are socially patterned, and this patterning may vary over time periods, cohorts and between sexes[5-7]. In Norway, surveys indicate that absolute educational inequalities in smoking have widened from the mid-1980s and up to 2008[8, 9]. In men, this was due to a faster decline in smoking rates among the highly educated, whereas in women smoking rates increased in the lower educational groups up to the millennium, in line with the smoking epidemic as described by Lopez[8, 10].

Social patterning of CVD mortality has varied over time. Declining CVD mortality in Norway during the last four decades of the twentieth century was initially more rapid in the higher educated population yielding increasing absolute educational differences in CVD mortality up to year 2000 in men and up to 1980 in women[11]. This was followed by a subsequent narrowing, which was also found in other European countries[11, 12]. Studies from England and Scotland suggest evenly improved treatment uptake across all social groups[13, 14]. Changes in social pattering in both CVD risk factors and CVD mortality between birth cohorts and between sexes might be a key to understand changing trends in educational differences in CVD mortality. We are not of aware any study addressing differing impact of risk factors over birth cohorts and sex in cohorts followed over the same life course period.

We aimed to assess to what extent behavioural and biological modifiable CVD risk factors differ in their impact on the educational gradient in premature CVD mortality in cohorts born in the 1930s, 1940s and 1950s, examined at age 40-45; i.e. in the 1970s, 1980s and 1990s.

1

METHODS

3

Study population

From the Norwegian population based health examination surveys we selected health survey participants born in the 1930s, 1940s or 1950s, turning 40-45 years at the year of their health survey participation. Participants with the potential to reach age of 60 years during follow up were selected (Figure S1). The surveys included the Counties Studies (1974-88)[15], the Age 40 Program (1985-1999)[16], and the Cohort of Norway (CONOR) (1994-2003)[17] with overall participation rate of 86%, 70% and 58%, respectively.

Of 364,324 potential participants, we excluded 1.2% with missing risk factor levels and/or missing or no registered educational level, yielding a sample of 360,008 participants included in the analysis (Figure S1). In participants with missing risk factor values the proportion with basic education in the 1930s, 1940s and 1950s birth cohorts was higher (50%, 28% and 26%) than for those with valid values (48%, 24% and 18%).

16

Data linkage

Based on the Norwegian Family Based Life Course Study[18], data from health surveys were linked to national educational data, to the Norwegian Cause of Death Registry, and to the National Registry using the unique national personal identification number. If a participant attended several health surveys between ages 40-45 years, only the first survey was selected.

Permission to be absolved from professional secrecy and linking of data was granted by the Regional Ethics Committee South-East (in May 25th 2012, reference number 2012/872). The study complies with the Declaration of Helsinki.

25

Education

A person's highest attained educational level was classified as either Basic (up to 7 years in the 1960s, up to 9 years from the 1970 and forth), representing compulsory primary and lower secondary school or lower levels, Secondary (10 - 12 years) representing completion of first, second or third year of upper secondary school, or Tertiary (13 years or longer) usually representing completion of a college or university degree. These categories correspond to the International Standard Classification of Education (ISCED) 1997 categories 0-2, 3-4 5-6.

Cardiovascular risk factors

In all health examination surveys self-assessed questionnaires, clinical measures and non-fasting blood sampling were collected with similar methodology and questionnaires[15-17]. Established CVD risk factors available for all birth cohorts were selected. Smoking status and cigarette pack years was collapsed into smoking grade: (1) never smoker, (2, 3) former smoker with < or ≥20 pack years, (4, 5) current daily smoker with < or ≥ 20 pack years. Leisure time physical activity was harmonized into a four graded scale from sedentary (1) to hard physical (4). Self-reported treatment with antihypertensive medications and self-reported diabetes was recorded. Blood pressure was initially measured manually using sphygmomanometers and the second of two measurements defined systolic blood pressure. Later, three automatic oscillometric measures were assessed and the average of the last two available measurements defined systolic blood pressure[19]. Height and weight were measured and body mass index (BMI) was calculated (kg/m^2). Serum total cholesterol and triglycerides were initially measured by non-enzymatic, and later enzymatic method[20].

Cardiovascular mortality

Data on underlying cause of death from CVD was obtained from the Norwegian Cause of Death Registry through 2014 (ICD-8: 390-444.1, 444.3-458, 782.4, ICD-9: 390-459, ICD-10: I00-I99)[21]. CVD mortality before age 60 years was considered premature. The participants were followed prospectively from the time of health examination up to death, emigration or age 60 years.

Statistical methods

Trend in risk factors across educational levels and across birth cohorts was tested. Premature CVD mortality rates per 100 000 person years were age-standardized using the study population as standard. Aalen additive hazard survival model ("timereg" package in R i.386 version 3.4) provided absolute estimates; rate differences (RD) in number of CVD deaths between basic versus tertiary, and basic versus secondary educational level per 100 000 person years with 95% confidence intervals[22]. Cox proportional hazards models (Stata version 14) provided relative estimates; hazard ratio (HR) with 95% confidence intervals. Analysis time was attained age in days. The following models examined risk of premature CVD mortality by education and mediation by risk factors: Educational level adjusted for year of birth (Model 1), educational level adjusted for year of birth and one of the following risk factors; smoking grade, systolic blood pressure and current antihypertensive medication, serum total cholesterol, serum triglycerides, BMI or physical activity (Model 1+ risk factor), and educational level adjusted for year of birth and all the studied risk factors (Model 1 + all risk factors). Validity of self-reported diabetes was considered limited and was included as risk factor in sensitivity analyses only; diabetes was not screened for like the other biological risk factors and did not distinguish between type 1 and type 2 diabetes in which educational gradients may go in opposite directions[23].

5

Proportion of excess premature CVD deaths in basic versus secondary or tertiary educated that is mediated by risk factors (controlled indirect effect) was assessed as the difference in absolute mortality rates (ΔRD) between Model 1(controlled total effect) and Model 1 + risk factor (controlled direct effect); $RD_{Model\ 1}$- $RD_{Model\ 1+\ risk\ factor(s)}$. The mediated proportion was assessed by the ratio of the controlled indirect effect over the controlled total effect in percentage (ΔRD, %); ($RD_{Model\ 1}$- $RD_{Model\ 1+\ risk\ factor(s)}$)/ ($RD_{Model\ 1}$)*100. Year of birth and all risk factor variables were centred on the mean in the RD analyses. Bootstrapping with 1000 replications assessed the precision of the mediated proportion expressed as ΔRD and ΔRD in %.

Similar calculations assessing the relative excess mortality were performed using the β-coefficient (logarithm of hazard ratio (HR)) for education in Cox regression[2]; ($logHR_{Model\ 1}$ $-\ logHR_{Model\ 1\ +\ risk\ factor(s)}$) / ($logHR_{Model\ 1}$)*100.

None of the examined assumptions in Model 1 + all risk factors were violated: In Aalen's additive survival regression, plots of cumulative coefficients with simulated 95% confidence bands of each of the covariates on the outcome over time were inspected for constant or non-constant effect over time[22]. Proportional hazards assumptions were tested and Schoenfeld residuals inspected[24].

Controlled effects assessed by adjustment for mediators provided estimates for mediation analyses, assuming no unmeasured confounding and no exposure-mediator interactions[25]. In case of the latter, natural total and indirect effects were calculated (Supplementary materials).

RESULTS

The distribution of participants across educational groups changed markedly from the 1930s

to the 1950s birth cohorts: the proportion with basic education decreased from 48% to 18%,

and the proportion with tertiary education increased from 10% to 31%. This transition was

similar for men and women (Table S1). The tertiary education groups had more favourable

CVD risk factor profiles compared to those in the lower educational groups in men and

women in all birth cohorts (Table S1).

The level of the CVD risk factors changed from the 1930s to the 1950s cohorts: Serum

total cholesterol levels decreased, serum triglyceride levels increased, and the proportion of

physically inactive had a net increase. The proportions of male current daily smokers

declined, whereas female smoking increased in basic and secondary educated, and levelled off

for tertiary educated. Systolic blood pressure levels increased in men with tertiary education,

whereas the levels decreased in men with basic education and in the basic and secondary

female educational groups. BMI levels increased for all male educational groups and for

women with tertiary education, whereas women with basic education had a decrease in BMI

levels (Table S1).

During the follow-up period of 6,488,891 person years (mean 18 years; range 1 day to

21 years), in all 16,665 persons died prematurely from any causes (4.6 % of the study

population), 3,871 persons died prematurely from CVD (1.1 %), and 0.5 % emigrated.

Premature CVD mortality was lower in women compared to men and declined for both sexes

by more recent birth cohorts (Table S2).

In analyses of absolute educational differences adjusted for year of birth, the rates of

excess premature CVD deaths in basic versus tertiary educated (RDs) decreased by more

recent birth cohorts (Table 1, Figure S2). The relative differences, i.e excess premature CVD

mortality in basic relative to tertiary educated expressed as HRs, were more or less stable over

the three birth cohorts from the 1930s, 1940s and 1950s (Table S3). About two thirds of the

excess premature CVD deaths in the basic versus the tertiary educated were due to their

unfavourable risk factors for all birth cohort groups, except women in the 1930s cohort, where

all of the excess CVD mortality in those with basic education were mediated though the CVD

risk factors (Table 1, Figure S2).

Adjustment for each isolated risk factor indicated that smoking mediated nearly one

third or more of the excess premature CVD deaths in the basic versus the tertiary educated in

all the birth cohort groups for both sexes. Of all CVD risk factors, smoking grade seemed the

single strongest mediator, except in women from the 1930s cohort. Here, systolic blood

pressure, smoking grade and serum total cholesterol, each seemed to mediate about one third

or one fourth of the excess CVD mortality in those with basic education.

From the 1930s to the 1950s cohorts, the influence of systolic blood pressure on the

difference in CVD mortality between basic and tertiary educated was reduced by one half for

both sexes. This was also the case for serum total cholesterol in women and for physical

activity for men, whereas the influence of serum total cholesterol in men and physical activity

in women were stable from the 1930 to the 1950s cohorts. The influence of BMI and serum

triglycerides on the excess CVD mortality on the basic educated was not significant in any of

the cohorts (Table 1).

Highly significant interactions (by $p<0.001$) between education and CVD risk factors

were only observed in the additive analyses. Educational level interacted with serum total

cholesterol levels in women born in the 1940s, and with smoking grade in men born in the

1940s. For these two settings, natural total and indirect effect estimates were similar to the

controlled effects presented in Table 1 (Table S4). Self-reported diabetes (prevalence 0.7%)

mediated a minimal proportion of excess premature CVD mortality by lower education

(Tables S5-S7).

1   The proportion who died prematurely from CVD in the 1930s, 1940s and 1950s

2 cohorts was higher among participants excluded because of missing data for education (4.0%,

3 3.9% and 2.6%) or CVD risk factors (3.1%, 2.5% and 1.9%) than among included participants

4 (2.6%, 1.2% and 0.7% (Figure S1)), respectively.

5

6 **DISCUSSION**

7 Excess absolute number premature CVD deaths per 100 000 person years in the basic versus

8 the tertiary educated group declined in more recent birth cohorts, whereas relative educational

9 differences were stable over cohorts. Over two thirds of this gap in premature CVD deaths

10 between basic and tertiary educated was mediated by the modifiable CVD-risk factors

11 smoking, systolic blood pressure, total cholesterol, BMI, triglycerides and physical activity.

12 The strength of mediation was similar across genders and birth cohorts, except from the oldest

13 birth cohort in women where the CVD-risk factors fully mediated the excess premature CVD

14 deaths in the basic educated. Smoking seemed to be the single strongest mediator in all three

15 birth cohorts for men, and in the two most recent birth cohorts for women.

16

17 The major strengths are that our study is population-based, includes a considerable number of

18 participants examined at the same age born within three decades. Our study has assessed both

19 biologically measured and behavioral risk factors, and includes absolute, relative and sex-

20 specific analyses. Mediation by risk factors may have been stronger if more CVD risk factors

21 than those available for all birth cohort had been included, such as diet, alcohol consumption,

22 objective assessment of physical activity or use of cholesterol lowering medication.

23   To our knowledge only one other study has examined the difference in magnitude of

24 mediation by risk factors on social inequality in disease over birth cohorts[26]. This population-

25 based cohort from West Scotland compared the magnitude of mediation in two birth cohorts

1   with 20 years age-difference examined during the same calendar time. Here, the effect of

2   behavioral risk factors on the occupational gradient in all-cause mortality was numerically

3   stronger for a cohort born in 1952 than for a cohort born in 1932 examined and followed for

4   the same calendar time period. These results were not comparable to our study since we have

5   examined changes over different calendar periods at fixed point in the life course, at age 40-

6   45 years.

7   Our study strongly suggest that smoking is of particular importance in Norway as a

8   modifiable source of educational differences in CVD mortality. European countries have

9   reported similar or weaker impact of smoking on inequality in health: In comparable French

10   and British birth cohorts smoking accounted for 4% and 30%, respectively, of the

11   occupational gradient in all-cause mortality[4], and in a Dutch cohort smoking accounted for

12   28% of educational gradient in incident coronary heart disease[27]. Interestingly, in our cohorts

13   BMI followed a similar but inverse pattern as for smoking habits: By more recent birth cohort

14   mean BMI levels increased in men along with decreasing levels of smoking. In women BMI

15   decreased slightly in basic and secondary educated along with increasing smoking prevalence,

16   and leveled off both for smoking prevalence and BMI development in the tertiary educated.

17   The composite mediating effect of risk factors over birth cohorts has a striking

18   stability for absolute and relative excess premature CVD mortality by lower education, and

19   with smoking as the major mediator. The exception is for women born in the 1930s where all

20   of the excess deaths in the basic educated were due to their unfavorable risk factors, and

21   where blood pressure seems to be of importance. Women with tertiary education seemed to

22   follow the same pattern of change in risk factors by more recent birth cohort, as men. One

23   might speculate that men with tertiary education being at the latest phase of the smoking

24   epidemic, would be the first educational group to experience any new developments in risk

25   factors over time. The increase in mean blood pressure by more recent birth cohorts in tertiary

educated men is somewhat alarming, still, this could be explained by the educational shift

with a higher proportion having higher education in the more recent birth cohorts.

In conclusion, known CVD risk factors have a strong impact on absolute and relative

excess premature CVD mortality by lower educational level in the 1930s, 1940s and 1950s

birth cohorts. In men smoking was the driving force behind educational differences from the

1930s birth cohorts and forth. In women smoking became the single most important CVD risk

factor for educational differences from the 1940s birth cohorts, one decade later than in men.

In Norway and other countries at a late stage of the smoking epidemic, strategies for smoking

cessation and prevention of smoking initiation might have the strongest impact for reducing

educational inequality in premature CVD mortality.

REFERENCES

1. Laaksonen M, Talala K, Martelin T, et al. Health behaviours as explanations for educational level differences in cardiovascular and all-cause mortality: a follow-up of 60 000 men and women over 23 years. *Eur J Public Health*. 2008; 18: 38-43.

2. Stringhini S, Sabia S, Shipley M, et al. Association of socioeconomic position with health behaviors and mortality. *JAMA*. 2010; 303: 1159-66.

3. Strand BH and Tverdal A. Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other heart diseases? 26 year follow up of 50,000 Norwegian men and women. *J Epidemiol Community Health*. 2004; 58: 705-9.

4. Stringhini S, Dugravot A, Shipley M, et al. Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts. *PLoS Med*. 2011; 8: e1000419.

5. Howe LD, Patel R and Galobardes B. Commentary: Tipping the balance: wider waistlines in men but wider inequalities in women. *Int J Epidemiol*. 2010; 39: 404-5.

6. Stringhini S, Spencer B, Marques-Vidal P, et al. Age and gender differences in the social patterning of cardiovascular risk factors in Switzerland: the CoLaus study. *PLoS One*. 2012; 7: e49443.

7. Kanjilal S, Gregg EW, Cheng YJ, et al. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971-2002. *Arch Intern Med*. 2006; 166: 2348-55.

8. Ernstsen L, Strand BH, Nilsen SM, et al. Trends in absolute and relative educational inequalities in four modifiable ischaemic heart disease risk factors: repeated cross-sectional surveys from the Nord-Trondelag Health Study (HUNT) 1984-2008. *BMC Public Health*. 2012; 12: 266.

9. Eggen AE, Mathiesen EB, Wilsgaard T, et al. Trends in cardiovascular risk factors across levels of education in a general population: is the educational gap increasing? The Tromsø study 1994–2008. *J Epidemiol Community Health*. 2014: 721-19.

10. Thun M, Peto R, Boreham J, et al. Stages of the cigarette epidemic on entering its second century. *Tob Control*. 2012; 21: 96-101.

11. Strand BH, Steingrimsdottir OA, Groholt EK, et al. Trends in educational inequalities in cause specific mortality in Norway from 1960 to 2010: a turning point for educational inequalities in cause specific mortality of Norwegian men after the millennium? *BMC Public Health*. 2014; 14: 1208.

12. Mackenbach JP, Kulhanova I, Artnik B, et al. Changes in mortality inequalities over two decades: register based study of European countries. *BMJ*. 2016; 353: i1732.

13. Bajekal M, Scholes S, Love H, et al. Analysing recent socioeconomic trends in coronary heart disease mortality in England, 2000–2007: a population modelling study. *PLoS Med*. 2012; 9: e1001237.

14. Hotchkiss JW, Davies CA, Dundas R, et al. Explaining trends in Scottish coronary heart disease mortality between 2000 and 2010 using IMPACTSEC model: retrospective analysis using routine data. *BMJ: British Medical Journal*. 2014; 348.

15. Bjartveit K, Foss OP, Gjervig T, et al. The cardiovascular disease study in Norwegian counties. Background and organization. *Acta Med Scand Suppl*. 1979; 634: 1-70.

16. Bjartveit K, Stensvold I, Lund-Larsen P, et al. Cardiovascular screenings in Norwegian counties. Background and implementation. Status of risk pattern during the period 1986-90 among persons aged 40-42 years in 14 counties]. *Tidsskr Nor Laegeforen*. 1991; 111: 2063.

17. Naess O, Sogaard AJ, Arnesen E, et al. Cohort profile: cohort of Norway (CONOR). *Int J Epidemiol*. 2008; 37: 481-5.

18. Naess O and Hoff DA. The Norwegian Family Based Life Course (NFLC) study: data structure and potential for public health research. *Int J Public Health*. 2013; 58: 57-64.

19. Lund-Larsen P. Blood pressure measured with a sphygmomanometer and with Dinamap under field conditions–a comparison. *Nor Epidemiol*. 1997; 7: 235-41.

20. Foss OP and Urdal P. Cholesterol for more than 25 years: Could the results be compared throughout all this time? *Nor Epidemiol*. 2003; 13: 85-8.

21. Pedersen AG and Ellingsen CL. Data quality in the Causes of Death Registry. *Tidsskr Nor Laegeforen*. 2015; 135: 768-70.

22. Martinussen T and Scheike TH. *Dynamic regression models for survival data*. Springer, 2006.

23. Olsson L, Ahlbom A, Grill V, et al. High levels of education are associated with an increased risk of latent autoimmune diabetes in adults: results from the Nord-Trondelag health study. *Diabetes Care*. 2011; 34: 102-7.

24. Grambsch PM and Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81: 515-26.

25. Lange T and Hansen JV. Direct and indirect effects in a survival context. *Epidemiology*. 2011; 22: 575-81.

26. Whitley E, Batty GD, Hunt K, et al. The role of health behaviours across the life course in the socioeconomic patterning of all-cause mortality: the west of Scotland twenty-07 prospective cohort study. *Ann Behav Med*. 2014; 47: 148-57.

27. Kershaw KN, Droomers M, Robinson WR, et al. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: the MORGEN study. *Eur J Epidemiol*. 2013; 28: 807-14.