Gender differences in the association between education and the incidence of cardiovascular events in Northern Italy

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Background: The educational differences in the incidence of major cardiovascular events are understudied in Southern Europe and among women. **Methods**: The study sample includes $n = 5084$ participants to 4 population-based Northern Italian cohorts, aged 35–74 at baseline and with no previous cardiovascular events. The follow-up to ascertain the first onset of coronary heart disease (CHD) or ischaemic stroke ended in 2002. At baseline, major cardiovascular risk factors were investigated adopting the standardized MONICA procedures. Two educational classes were obtained from years of schooling. Age- and risk factors-adjusted hazard ratios of first CHD or ischaemic stroke were estimated through sex-specific separate Cox models (high education as reference). **Results:** Median follow-up time was 12 years. Event rates were 6.38 (CHD) and 2.12 (ischaemic stroke) per 1000 person-years in men; and 1.59 and 0.94 in women. In men, low education was associated with higher mean Body Mass Index and prevalence of diabetes and cigarette smokers; but also with higher HDL cholesterol and a more favourable alcohol intake pattern. Less-educated women had higher mean systolic blood pressure, Body Mass Index and HDL cholesterol and were more likely to have diabetes. Men and women in the low educational class had a 2-fold increase in ischaemic stroke and CHD incidence, respectively, after controlling for major risk factors. Education was not associated with CHD incidence in men. Higher ischaemic stroke rates were observed among more educated women. **Conclusion**: In this northern Italian population, the association between education and cardiovascular risk seems to vary by gender.

Keywords: Social inequalities, women, education, coronary heart disease, ischaemic stroke

Introduction

Socio-economic inequalities in cardiovascular and coronary heart disease (CHD) mortality have been described across several European populations during the 1990s[1,2] and the early 2000s,[3] both in men and in women. Social disparities have also been reported for stroke mortality.[4] The magnitude of social inequalities varies across Europe,[3] being smaller in the southern countries, including Italy.

As a possible cause of the observed inequalities in cardiovascular deaths, the association between incidence of events and socio-economic status has been studied.

We identified 14 prospective cohort studies,[5–18] published from 1995 to 2007, that investigated the association between individually assessed measures of socio-economic status (either occupation or education) and the incidence of coronary events or stroke. Separate social gradients for men and women were reported by three studies for CHD[5,7,15] and by four for stroke.[8–10,18] All of these were conducted in USA, UK or North European countries. Therefore, in spite of the large number of studies investigating socio-economic disparities in cardiovascular mortality, the educational gradient in the incidence of major cardiovascular events is relatively under-reported, in particular for women and for South European countries.

The aim of the present report is to assess, in men and women, the relationships between years of schooling and 12-year incidence of CHD and ischaemic stroke. The contribution of major risk factors in explaining the association between education and cardiovascular disease incidence is also explored.

Methods

Study design and recruited cohorts

The design is a pooled-cohort study, including the MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Brianza population surveys and the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) sample. As part of the MONICA Project, in each of the periods 1986–87, 1989–90 and 1993–94, a population survey was carried out to assess coronary risk factor changes over time.[19] In every survey, a 10-year age- and gender-stratified random sample was selected from the municipality rolls among 25- to 64-year-old residents of five representative towns. People enrolled in one survey were not included in subsequent ones. The participation rates were 70.1, 67.2 and 70.8% for the three surveys, respectively, with no differences between men and women.

The PAMELA Study was carried out in 1991–92 to investigate the relationship between clinic and ambulatory blood pressure measurements at the population level.[20] Subjects were sampled with the same sampling procedures from 25- to 74-year-old residents of the city of Monza, the largest town in Brianza. The participation rate was 64%. Both the baseline screening and the follow-up were approved by the ethical committee of the Monza Hospital.

Due to the low number of events in the age range 25–34 years, the analysis focused on men and women aged 35–74 years at baseline.

Measurements of risk factors at baseline

Cardiovascular risk factors were collected at baseline strictly adhering to the standardized procedures and quality standards of the MONICA Project.[21] Trained technicians collected blood pressure on sitting subjects at rest for at least 10 min, using a standard mercury sphygmomanometer equipped with two side cuff bladders (13 and 17 cm). Systolic and diastolic blood pressure (BP) were assessed twice, at 5 min apart and taken at the first and fifth phase of the Korotkoff sounds. The study variable for systolic BP is the average of the two measurements. Venous blood specimens were taken from the ante-cubital vein on fasting subjects (≥ 12 h). Serum total cholesterol, High Density Lipoprotein (HDL) cholesterol and blood glucose were determined using the enzymatic methods; HDL cholesterol fraction was separated using the Phosphotungstate-Mg^{++} method.[21] Height and weight were measured on subjects without shoes and wearing light clothing. Body mass index (BMI) was computed as weight in kilograms divided by squared height in metres.

A standardized interview was administered to participants by trained interviewers. Information on cigarette smoking habit was dichotomized in current vs. past/never smokers. Average daily consumption of wine, beer and spirits was also investigated and categorized as teetotaller, up to 50 g per day, and >50 g per day. Due to the very small prevalence of women in the last class, the variable was dichotomized as 'teetotallers', 'any alcohol intake' for that gender. Diabetes mellitus was defined using self-reported diagnoses, information on insulin and oral hypoglycemic treatments and fasting blood glucose exceeding $7 \, \text{mmol} \, l^{-1}$. Self-reported information on hospitalization for myocardial infarction (MI), unstable angina pectoris, cardiac revascularization or stroke defined the history of acute cardiovascular event.

Classification of education

Information on the educational attainment and on full-time years of schooling was assessed via questionnaire. We derived a two-group classification of education (ED; High and Low) from years of schooling: a subject was classified into the 'High' ED if his number of years of schooling was greater than a cut-off value derived from the sample median of the distribution of years of schooling of all the study subjects with the same sex and birth cohort. More details on the method have been published previously.[22]

Ascertainment of incident coronary events and ischaemic stroke

The follow-up for fatal and non-fatal events ended on 31 December 2002 for all cohorts. Subjects' vital status was actively investigated by the municipality of residence, including those who moved to different towns. Death certificates were obtained from Local Health Districts and coded according to the International Classification of Diseases and Causes of Deaths—IX Revision (ICD-IX).

Suspected fatal and non-fatal events, identified on the basis of selected underlying causes of deaths or hospital discharge codes, were investigated and validated according to the MONICA diagnostic criteria.[23] The list of investigated codes is reported in table 1, while full details on follow-up procedures are available online.[24] The stroke subtype (ischaemic or haemorrhagic) was attributed after review of the clinical material. Suspected events were identified through deterministic and probabilistic record linkage.[25] The CHD endpoint for the current analysis is defined as the first MONICA validated fatal or non-fatal MI (definite or possible) or coronary revascularization. The ischaemic stroke endpoint comprises MONICA validated fatal or non-fatal ischaemic strokes and endarterectomies.

Statistical analysis

We calculated sex-specific age-adjusted mean (prevalence) of major cardiovascular risk factors, stratified by educational class, through standard linear or logistic regression models, respectively.

Sex-specific age-adjusted incidence rates by education were obtained from Poisson regression models. The same analysis was repeated for fatal and non-fatal events separately. The main survival analysis was carried out using sex-specific Cox proportional hazards models, with the 'High' educational group as reference. We also considered a model including sex and a sex*education interaction term, to test whether the association between education and CVD outcome differed by gender. Proportionality of hazards over time was tested formally by adding a time*education interaction term to the age-adjusted Cox model; the null hypothesis of proportionality was not rejected at a 0.05 significance level. Multivariate adjustment included established risk factors for CHD and ischaemic stroke and alcohol intake. The selection of risk factors was based both on previous knowledge and on the estimation of the age adjusted, univariate association between each risk factor and the study outcomes in the investigated cohorts.

Results

In the age range 35–74 years, 2792 men and 2803 women were originally enrolled. Of these, 101 men (3.6%) and 111 women (4%) were excluded due to missing data. A specific analysis (results not shown) revealed that the distribution of CVD risk factors was not different in subjects with missing data respect to those with complete information; and that the observed

Table 1 Definition of suspected coronary and stroke events, according to the ICD-IX° revision, for fatal and non-fatal events

	CHD	Cerebrovascular event
Death Certificate	Underlying cause of death: ICD-IX 410–414, 798, 799; or 250, 428, 440 in association with 410–414 in any other cause	Underlying cause of death: ICD-IX 430–432, 434, 436–437; or 250, 401–404, 427, 440 in association with 430–432, 434, 436–437 in any other cause
Hospital Discharge Codes	ICD-IX 410 or 411 and ICD-IX CM 36.0-9 codes for coronary surgery revascularization	ICD-IX 430–432, 434, 436; ICD-IX CM 38.01–39.22 or 39.50–39.52 with at least one 430–438 as discharge code, for carotid endarterectomy

social differences in CHD and ischaemic stroke incidence were not substantially modified by our selection.

In addition, 186 men (44 CHD, 10 ischaemic strokes) and 113 women (5 CHD) who reported at baseline a previous coronary event or stroke were also excluded, reducing the sample size to 2505 and 2579 for men and women, respectively.

In 12-year median follow-up time, we observed 180 incident CHD and 61 ischaemic strokes among men (incidence rates: 6.38 and 2.12 per 1000 person-years, respectively); 49 incident CHD and 29 ischaemic strokes (incidence rates: 1.59 and 0.94 per 1000 person-years) among women.

Sample characteristics and socio-economic differences in cardiovascular risk factors are reported in table 2. Men stayed at school 1.4 years more than women did. On average, subjects in the low ED completed the primary education cycle (5 years in Italy), while those in the high ED had some years of schooling less than the requirement for the high school degree (13 years).

Among men, total cholesterol did not differ between the ED groups, while HDL cholesterol was on average higher among less-educated subjects (average difference $0.04\,\text{mmol}\,l^{-1}$). No difference in mean Systolic BP between education groups was detected, the average difference being 1.0 mmHg (P-value = 0.17). Finally, men in the low ED were more likely to smoke, to have Type II diabetes, to consume more grams of alcohol per day and to have a greater BMI.

We observed higher mean values of systolic BP and BMI, as well as higher prevalence of diabetes, among less-educated women. However, opposite to men, they were 5% less likely to smoke and had on average $0.07\,\text{mmol}\,l^{-1}$ HDL cholesterol less than their more educated counterparts had. No social differences in alcohol consumption were observed.

The last two columns of table 2 report the age-adjusted association between each risk factor and the study outcomes. Systolic BP, blood lipids, diabetes and cigarette smoking were associated with CHD in both men and women, while BMI was a predictor of CHD in women only. A 30% CHD risk reduction was observed for any alcohol intake with respect to teetotallers, in men (P-value: 0.12) and in women (P-value: 0.22). Blood lipids were not predictors of ischaemic strokes in men, while a protective effect of HDL cholesterol was present in women.

Age- and multiple-risk factor-adjusted CHD event rates and hazard ratios, with relative 95% confidence intervals, are reported in table 3. In men, there was no evidence of any educational disparity in CHD incidence. On the other hand, less-educated women were at 2-fold risk of CHD than more educated ones: the age-adjusted hazard ratio was 2.86 (P-value: 0.01). The sex*education interaction was significant (P-value: 0.007). Most of the risk excess was attributable to fatal events, but it was evident for non-fatal events as well (see Supplementary figure S1, left panel). Adjustment for major risk factors, including alcohol intake, accounted for only a small portion of the reported excess risk.

We observed a 2-fold increase in ischaemic stroke incidence for less-educated men as compared with their more educated counterparts (age-adjusted hazard ratio: 2.14, P-value: 0.01; table 4), mostly due to non-fatal ischaemic stroke and

Table 2 Age-adjusted mean and prevalence of major CVD risk factors at baseline, in the entire sample and by ED classes; and age-adjusted hazard rate ratio between each risk factor and the study outcomes

	Mean/Prevalence			Age-adjusted HR[a]	
	Entire sample (SD)	High ED	Low ED[b]	CHD event	IS event
Men					
Number of subjects	2505	1296	1209	–	–
Age	51.3 (9.7)	50.6	52.1[†]	1.77[§]	2.29[§]
Years of schooling	8.7 (4.1)	11.6	5.5[§]	0.93	0.47[†]
Systolic BP (mmHg)	134.2 (19.7)	133.7	134.7	1.25[†]	1.51[†]
Total Cholesterol (mmol l^{-1})	5.75 (1.1)	5.75	5.74	1.53[§]	1.11
HDL Cholesterol (mmol l^{-1})	1.31 (0.3)	1.29	1.33[†]	0.84[‡]	0.90
BMI[c]	26.1 (3.5)	25.9	26.3[†]	1.07	0.99
Diabetes (%)	6.5	5.4	7.5[‡]	2.41[§]	2.27[‡]
Current cigarette smokers (%)	36.7	33.0	40.2[†]	1.78[†]	2.03[†]
Alcohol Intake (%)					
Teetotallers	22.0	25.6	18.1[§]	Ref.	Ref.
Up to 50 g per day	48.8	52.3	45.0	0.69	0.67
≥50 g per day	29.2	22.1	36.9	0.71	0.94
Women					
Number of subjects	2579	1128	1451	–	–
Age	50.8 (9.5)	48.6	52.5[§]	2.54[§]	3.52[§]
Years of schooling	7.3 (3.4)	10.2	5.1[§]	0.57[‡]	1.36
Systolic BP (mmHg)	131.2 (20.5)	128.9	133.0[§]	1.48[†]	1.62[†]
Total cholesterol (mmol l^{-1})	5.74 (1.1)	5.75	5.73	1.53[†]	1.05
HDL cholesterol (mmol l^{-1})	1.59 (0.4)	1.63	1.56[§]	0.64[†]	0.54[†]
BMI	25.5 (4.7)	24.7	26.2[§]	1.28[‡]	0.96
Diabetes (%)	4.1	3.2	5.3[‡]	3.77[†]	4.22[†]
Current cigarette smokers (%)	19.3	21.4	16.5[†]	2.35[†]	2.77[‡]
Alcohol intake (%)					
Teetotallers	56.4	56.7	56.1	Ref.	Ref.
Up to 50 g per day	40.2	40.0	40.4	0.70	0.78
≥50 g per day	3.4	3.3	3.4		

Men and women, without any previous CHD or ischaemic stroke at baseline

SD, Standard Deviation; BP, Blood Pressure; HR, Hazard Ratio; IS, Ischaemic Stroke

a: The reported HRs are for 1SD increase (continuous risk factor), or relative to the reference level (discrete risk factors). *P*-values are to test the null hypothesis of HR = 1 (1 df test): [§]<0.0001; [†]<0.01; [‡]<0.05

b: Reported *P*-values are for heterogeneity test among educational classes. The test has 1df except for alcohol intake (2df). *P*-values: [§]<0.0001; [†]<0.01; [‡]<0.05

c: Data available for 2470 subjects only

Table 3 Age- and multiple-risk factors (MRF)-adjusted CHD incidence rates and hazard rate ratios (HR) among educational classes

	No. of events	Age adjusted		MRF-Adjustment[a]	MRF-Adjustment[b]
		Rate[c]	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men					
High ED	88	6.2	Ref. (–)	Ref. (–)	Ref. (–)
Low ED	92	6.5	1.03 (0.77–1.39)	1.01 (0.75–1.36)	1.07 (0.79–1.44)
P-value	–	–	0.83	0.95	0.68
Women					
High ED	8	0.75	Ref. (–)	Ref. (–)	Ref. (–)
Low ED	41	2.23	2.86 (1.33–6.12)	2.80 (1.29–6.07)	2.83 (1.30–6.12)
P-value	–	–	0.01	0.01	0.01

Men and women aged 35–74 years without any previous CHD or ischaemic stroke at baseline
a: MRF-adjustment: men: age + systolic BP, diabetes mellitus, cigarette smoking, total cholesterol, HDL cholesterol. Women: age + systolic BP, diabetes mellitus, cigarette smoking, total cholesterol, HDL cholesterol and BMI
b: MRF-adjustment: men: age + systolic BP, diabetes mellitus, cigarette smoking, total cholesterol, HDL cholesterol. Women: age + systolic BP, diabetes mellitus, cigarette smoking, total cholesterol, HDL cholesterol and BMI plus alcohol intake
c: per 1000 person-years

Table 4 Age- and multiple-risk factors (MRF)-adjusted Ischaemic Stroke incidence rates and hazard rate ratios (HR) among educational classes

	No. of events	Age adjusted		MRF-adjustment[a]	MRF-adjustment[b]
		Rate[c]	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men					
High ED	19	1.3	Ref. (–)	Ref. (–)	Ref. (–)
Low ED	42	2.9	2.14 (1.25–3.69)	2.04 (1.18–3.51)	2.18 (1.26–3.78)
P-value	–	–	0.01	0.01	0.01
Women					
High ED	14	1.2	Ref. (–)	Ref. (–)	Ref. (–)
Low ED	15	0.7	0.54 (0.26–1.12)	0.47 (0.22–0.99)	0.40 (0.20–0.85)
P-value	–	–	0.10	0.05	0.02

Men and women aged 35–74 years without any previous CHD or ischaemic stroke at baseline
a: MRF-adjustment: Men: age + systolic BP, diabetes mellitus, cigarette smoking. Women: age + systolic BP, diabetes mellitus, cigarette smoking and HDL cholesterol
b: MRF-adjustment: Men: age + systolic BP, diabetes mellitus, cigarette smoking. Women: age + systolic BP, diabetes mellitus, cigarette smoking and HDL cholesterol plus alcohol intake
c: Per 1000 person-years

endarterectomies (Supplementary figure S1, right panel). Adjustment for traditional risk factors and alcohol intake slightly modified the risk excess. Conversely, the direction of the association was reversed among women; the sex*education interaction was significant (*P*-value: 0.006). The risk reduction among less-educated women was more evident for fatal events and endarterectomies (Supplementary figure S1).

Discussion

In this North Italian population-based pooled-cohort study, the association between the incidence of major CVD events and educational classes seems to vary by gender and different endpoints. Among less educated men, we observed a 2-fold increase in ischaemic stroke incidence, but education was not associated with CHD incidence. Women in the low ED showed a 2-fold increase in CHD incidence. Finally, higher ischaemic stroke rates have been observed among more educated women.

Higher CHD incidence rates in less-educated adult men were found by two studies in Finland, Ireland and France,[12,16] but neither investigated women. Cohort studies that considered occupational classes reported consistent results for men[5–7,11,14,15] but not for women.[5,7,15] One cohort study in USA[10] did not find any association between education and stroke in men, while a relative risk of 1.67 was reported for

women. An increased risk of stroke in less-educated women was reported by another Swedish study[17] and by a cohort of Dutch elderly women.[8]

Less-educated men had higher prevalence of diabetes and cigarette smokers. Higher values of BMI were also detected, although the role of BMI as CHD predictor in this population is marginal.[25] We could not find any education class difference in total cholesterol and systolic BP, in contrast to other studies, which also did report social disparities in CHD outcome.[5,6,11,12,15,17] At the same time, less-educated men are characterized by higher HDL cholesterol mean levels and by a more favourable alcohol consumption. The former is a strong protective factor for CHD in this population[26] and in other European ones.[27] The protective effect of alcohol intake on CHD events in our cohorts is similar to what already reported for Mediterranean Countries.[28] Moreover, the pattern of alcohol intake in this population is likely to be characterized by a small daily amount of wine (74% of men who declared any alcohol intake drank wine only), thus resulting in an even more favourable effect.[29,30] On the other hand, in literature the association between ischaemic stroke and blood lipid levels, HDL cholesterol in particular, in men is controversial,[31–34] as is also the association with alcohol consumption.[35] Therefore, these composite social differences in the cardiovascular risk

profile are consistent with our finding on the absence of inequalities in CHD incidence, as well as with the higher incidence of ischaemic stroke observed among less-educated subjects.

The more favourable profile in HDL cholesterol and alcohol intake that was observed among less-educated men either reversed or disappeared when considering less-educated women. Furthermore, less-educated women showed higher values of systolic BP. An exploratory analysis of hypertensive subjects (BP $\geq$140/90 mmHg or under current anti-hypertensive medication) showed the existence of social disparities in hypertension control in women (22% vs. 14% in the high and low ED, respectively; *P*-value 0.03) but not in men. The increased prevalence of cigarette smoking among more educated women is consistent both with other Southern European data from the same period[36] and with more recent data in Italy.[37] All considered, the social differences in cardiovascular risk factors, therefore, support the increased CHD incidence that we detected among less-educated women. More unusual[38] was the higher ischaemic stroke incidence among more educated women. Although cigarette smoking is a strong risk factor for ischaemic stroke in middle-aged women,[39] we cannot rule out an under-recognition of the number of strokes in the lowest educational classes, as in our data nuclear magnetic resonance of the brain, a highly reliable exam for diagnosis of stroke, was more prevalent in more educated women. If we exclude endarterectomies from the endpoint definition, the age-adjusted hazard ratio increased to 0.70.

The present study has several methodological strengths: the standardization of risk factors measurements at baseline, the validation of CHD and ischaemic stroke diagnoses, both fatal and non-fatal; and the high coverage in the detection of the events in the follow-up, due to the high percentage of censoring for vital status (99% of the subjects) and the adoption of a probabilistic record linkage that was documented to be efficient for the identification of non-fatal events.[25]

Study limitations include the lack of information on other risk factors potentially involved in the social gradient in CVD risk, such as physical activity, work-related factors or environmental exposures. The underlying population is prevalently urban, with high levels of industrialization and one of the highest income of the country; generalizations of our results to other populations must carefully evaluate these factors as well.

In spite of a median 12-year follow-up, the documented low event rate in this population[23] resulted in a low number of events. Therefore, caution is required when interpreting the reported hazard ratios, in particular for CHD among women and ischaemic stroke among men.

However, the most conservative estimates based on our data, i.e. the lower bounds of the 95% confidence interval for the hazard ratio, still indicate an excess risk due to social class of ~30% (CHD, women) and 25% (ischaemic stroke, men). The observed association between education and CHD was consistent through all the considered event subtypes: fatal, definite and possible non-fatal MI, thus reducing the possibility of artefact due to event selection or validation. Finally, selection bias could have occurred if non-response probability in one social class was associated with risk factors levels. Participation rates in our sample did not differ between men and women, and were consistent across 10-year age groups. Although we do not have information on participation rates by education and therefore cannot completely rule out selection bias, it is unlikely that the same bias could explain opposite findings among women, and both a positive and a null result among men.

In conclusion, our analysis suggests that in this northern Italian population the association between education and cardiovascular risk seems to vary by gender. In particular, women might be experiencing the social inequalities in CHD risk factors and incidence documented in men in the last decades. Our findings call for further research on other southern European populations and women.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Key points

- Previous studies assessing the association between socio-economic position and CHD or stroke incidence focused mainly on men from northern European populations.
- In this Italian population, women might be experiencing the social inequalities in CHD risk factors and incidence documented in men in the past decades.
- Among men, the protective effect of HDL cholesterol and alcohol intake might have contributed to mitigate the social difference in CHD incidence. However, less-educated men are at higher risk of ischaemic stroke than their more educated counterparts are.
- Our results need to be confirmed and call for further research focusing on southern European populations and women.

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