Lost work days in the 6 years leading to premature death from cardiovascular disease in men and women.

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Short title: Disability before cardiovascular death

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ABSTRACT

Background: It is unclear whether individuals experience specific patterns of morbidity prior to premature death from cardiovascular disease (CVD).

Methods: We examined morbidity levels in the 6 years leading up to death from CVD in 37,397 men and 113,198 women under 65 years of age from the Finnish Public Sector study, with a particular focus on gender differences. Morbidity was assessed using lost days from work, extracted from register data on sickness leave and disability pension. Data on cause-specific mortality were obtained from national health registers.

Results: During a median follow-up of 8.5 years, there were 361 CVD deaths (174 from ischemic heart disease (ICD9 410–414, 427.5; ICD10 I21–I25, I46), 91 from stroke (ICD9 430, 431, 434; ICD10 I60–I60, I61, I63), and 96 from other diseases of circulatory system (ICD9 390–459; ICD10 I00–I99). Women had lower morbidity than men over the 6 years preceding stroke deaths (RR for mean annual days=0.33 (95% CI 0.14-0.78). For other causes of CVD mortality, there were no gender differences in morbidity rates prior to death. In men, those who died from CVD had substantially greater morbidity levels than matched controls through the entire 6-year period preceding death (rate ratio=3.59; 95% confidence interval 2.62-4.93). Among women, morbidity days were greater particularly in the year preceding death from stroke.

Conclusion: Our results on working age men and women suggest no gender differences in morbidity prior to death from heart disease and lower morbidity in women prior to death from stroke. These findings challenge the widespread belief that women experience more morbidity symptoms than men.

Cardiovascular diseases (CVD), principally coronary heart disease and stroke, account for 30% of all deaths and are among the leading causes of death globally.[1] CVD is also the main cause of premature mortality in Europe in both men and women, accounting for a third of all deaths before 65 years.[2] Gender differences in CVD incidence, aetiology and disease burden have been widely examined; the most consistent evidence is for the occurrence of CVD at older ages among women than men.[3-5] There is some evidence to suggest that the clinical presentation of CVD might be different in men and women,[6] but the evidence is not consistent due to the retrospective design of many studies.[7] Furthermore, the symptom checklists used in studies or in clinical practice are often based on men's symptoms.[7]

Besides symptoms immediately prior to the event, it is unclear if premature CVD mortality is preceded by a long period of illness. Absence from work, if well documented, is an excellent measure of general morbidity levels over several years. In this study we exploit register data on Finnish public sector working men and women in order to examine morbidity levels in the 6 years leading up to death from CVD. We use 'lost work days' as a marker of morbidity as these data are precise and allow us to calculate annual lost days, working back till 6 years before death in order to address two objectives. First, to examine gender differences in morbidity and mortality patterns associated with CVD. Mortality rates in men are higher[8] alongside greater morbidity rates in women,[9] Thus, we examine the evidence for excess CVD mortality in men and greater morbidity in women for each of the six years prior to death. Second, to compare morbidity levels among those who died to matched controls of the same gender in order to assess whether illness patterns are different in men and women compared to their peers. We examine the broad category of CVD deaths as well as its main components, ischaemic heart disease, stroke and other cardiovascular diseases.

METHODS

The data are drawn from the Finnish Public Sector Study, an ongoing prospective study on the personnel of ten municipalities and 21 hospitals.[10] For this study, we identified the eligible population from the employers' records of 37,397 men and 113,198 women, aged 18 to 64 years, with a full-time employment contract between 1994 and 2005. We obtained information on age, gender, and socioeconomic position, classified as upper-grade non-manual (e.g. physicians, teachers), lower-grade non-manual (e.g. technicians, registered nurses), and manual (e.g. cleaners, maintenance workers). Personal identification numbers, a unique number assigned to each Finnish citizen used for all contacts with the social welfare and health care systems, were used to link the data on mortality, sickness absence and disability pension records from national registers covering the years 1994 to 2005. The ethics committee of the Finnish Institute of Occupational Health approved this study.

Lost work days (sickness absence and disability pension)

The indicator 'lost work days' is composed of sickness absence days and days on disability pension while still of working age.[11] The median retirement age in this population was 63 years. Data on sickness absence days were obtained from the Finnish national sickness insurance scheme which covers the entire population and reimburses loss of income due to periods of sickness absence greater than 9 working days per year on the basis of medical certificates. Data on full- and part-time disability pensions for all study participants were obtained from the Finnish Centre for Pensions, which coordinates all earnings-related pensions for permanent residents in Finland. The annual sum of lost work days, either due to medically certified sickness absences (>9 days) or full- or part-time disability pensions during the 1994–2005 period was calculated for each participant. To avoid an overestimation of

annual lost work days, we removed the weekends from all periods of absenteeism, leading to a 260 maximum possible lost work days per year.

Mortality

Mortality data until 31 December 2005, mean follow-up of the study population of 8.5 years, were drawn from the national mortality register for Finland obtained from Central Statistical Office of Finland. We analysed deaths from ischemic heart disease, IHD, (ICD9 codes 410–414, 427.5; ICD10 I21–I25, I46), stroke (ICD9 codes 430, 431, 434; ICD10 I60, I61, I63), and other diseases of the circulatory system (ICD9 390–459; ICD10 I00–I99, excluding IHD and stroke) and an overall category of all CVD deaths.

Statistical analysis

We first examined gender differences in CVD mortality (1741 deaths) in the entire cohort (37,397 men and 113,198 women) using Cox regression with mortality in women as the reference. Subsequent analysis focussed on the 361 CVD deaths having occurred prior to statutory retirement, in order to examine whether there were gender differences in morbidity levels (lost work days) (objective 1). In order to do this for all the 361 deaths between 1994 and 2005 we extracted data on lost work days for every year until six years before death, resulting in a retrospective observation period from Year -1 to Year -6 in relation to death. We first examined gender differences in the mean annual days lost over 6 years using morbidity levels in men as the reference. Subsequently, gender differences in morbidity levels in each of the six years leading to CVD mortality were assessed using negative binomial regression analyses with the generalized estimating equation (GEE-estimation). GEE estimation was used because annual lost work days were nested within subjects requiring the correlation

between them to be taken into account in the analysis. These analyses were adjusted for age and socioeconomic position.

The analysis for objective 2 was based on a case-control design with the 361 deaths being the cases and the selection of controls based on the following criteria: same year of entry as the case to the eligible population and being of working age in the year preceding the death of the case. We randomly selected five controls for each case, matched for gender, age category (20–39, 40-49 or 50–65), socioeconomic position, type of employment contract (permanent or fixed term), type of employer (hospital district or municipality), and region (the Metropolitan area, South-Western Finland, Middle Finland, Northern Finland), leading to 1800 controls. Annual lost work days for each control were traced backwards for six years. We then compared the annual rates of lost work days between the cases and controls in gender-specific analysis using negative binomial regression analyses with GEE; with the controls as the reference. All analyses were carried out using the software SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Analyses adjusted for age and socioeconomic position showed greater overall CVD mortality in men (Hazard Ratio (HR) = 4.20; 95% Confidence Interval (CI) 3.36-5.25) compared to women, this was true for the sub-categories of death from IHD (HR = 9.00; 95% CI=6.30-13.12), other cardiovascular disease (HR = 4.04; 95% CI = 2.63-6.21) but not stroke (HR = 1.22; 95% CI = 0.77-1.93).

Table 1 presents the sample characteristics of the 361 cases and 1800 controls. The cases and controls did not differ by gender (p =0.97), socioeconomic position (p=0.99) or age (p=0.11). For both cases and the controls, men were marginally older and the socioeconomic distribution was such that men were more likely to be manual workers and women lower

grade non manual workers. Of the 361 deaths, 48.2% were due to IHD, 25.2% to stroke and 26.6% to other diseases of the circulatory system. Table 1 also presents mean annual lost days over 6 years, adjusted for age and socioeconomic position, for CVD and its sub-categories in men and women. For example, death from IHD involved mean annual lost days from work of 36.6 days (95% CI 26.2-51.3) in men and 61.6 days (95% CI 30.1-125.8) in women, with the test for female excess not being significant, Rate Ratio (RR) = 1.68 (95% CI 0.85-3.33). Stroke deaths involved fewer lost work days in women than men (RR=0.33; 95% CI 0.14-0.78) and there was a similar trend for the overall CVD mortality category even though the association was not significant (RR=0.80; 95% CI 0.47-1.34). In the control group, there was no real evidence of excess female morbidity (RR=1.24; 95% CI 0.95-1.60).

Table 2 presents results on gender differences in morbidity trajectories, adjusted for age and socioeconomic position, in each of the six years preceding death, with lost days in men as the reference. IHD deaths were associated with a greater number of lost days in women, although the rate ratios were not significant. For all other deaths and the overall CVD category, morbidity levels in women were lower with those for stroke being significantly lower in all years except the one prior to death where there was no evidence of a difference (RR =0.72; 95% CI 0.31-1.66).

Figure 1 shows the lost days, unadjusted for age or socioeconomic position, in men and women who died of CVD and their matched controls. In men, the controls had lower morbidity levels through all six years of the observation period and cases had an increasing trend in lost days in the years leading up to CVD mortality. While all CVD deaths in men were associated with over 40 days of absence every year starting in the 5^{th} year before death this was the case in women only in the year before death, mostly due to lower number of lost work days associated with stroke deaths in women.

Table 3 presents results on morbidity trajectories by examining lost days in each of the 6 years leading to death, with lost days in the controls as the reference in gender specific analysis. Among men, cases for CVD mortality irrespective of diagnostic category had higher levels of absence than controls over the entire observation window. Among women, this pattern was not observed. The striking result was for stroke deaths where absence days were higher among cases than the controls only in the year prior to death (RR =2.51; 95% CI = 1.46-4.29).

DISCUSSION

This study on morbidity patterns prior to premature cardiovascular mortality presents *two* key findings. *One*, morbidity levels prior to stroke deaths were substantially *lower* in women than men except for the year before death. *Two*, compared to matched controls, CVD mortality, including stroke, was associated with higher morbidity levels in all six years before death in men. In women, the pattern was less clear. For instance, stroke deaths were associated with morbidity level no different to that in matched controls, except in the year before death. Thus, premature CVD mortality is preceded by lower levels of morbidity, as assessed by lost work days, in women. This result is particularly striking for stroke.

There is considerable research on gender differences in the outcome of CVD,[12-18] but less work had been undertaken on the presentation of CVD, particularly at younger ages. There is some evidence to suggest that there are gender differences in the symptoms associated with ischaemic heart disease.[6;19] According to a recent study on the presentation of acute coronary syndromes, men are more likely to present with chest pain, left arm pain, or diaphoresis while nausea is more common in women. In that study, the greater occurrence of diaphoresis in men and of nausea in women remained in multivariably adjusted models.[6] Our data on absence from work is a more global measure of morbidity and the results suggest

somewhat greater morbidity in women, even thought the difference between men and women was not statistically significant. Corresponding to most of the evidence in this field, all CVD deaths were substantially higher in men in our data. This was particularly true for ischaemic heart disease where there was a nine-fold difference between men and women.

Most research on stroke is based on older populations, where women compared to men have been shown to have more pre-stroke disability and hypertension and lower prevalence of smoking, alcohol intake, and heart disease.[5;20] One recent study, using a register-based retrospective case-control design on data from the county of Ostergotland in Sweden examined stroke incidence in the under 65 age-group and reported that men showed greater health care seeking behaviour compared to women in the 3 years leading up to stroke.[21] Health seeking behaviour was assessed via visits to primary health care or hospital, men had an average of 10.6 visits in 3 years compared to 8.1 in women. In our study, the results on morbidity prior to stroke death in women clearly show atypical patterns in that it appears to be "asymptomatic", involving little morbidity until the year before death. It is possible that higher levels of heart disease prior to death from stroke among men explain their higher levels of morbidity prior to death. There is a wide spread belief that women report more symptoms, seek more health care, either as a result of childhood socialization or due to adult role expectation and obligation.[22] Our results show that morbidity levels associated with death due to cardiovascular disease in women certainly do not follow this pattern.

Much research showing greater morbidity in women has used self-reported measures.[23-26] Poorer self reported health in women has been interpreted to imply that men are more stoical and women more willing to use health services and report health problems.[22;25] Our results on men and women, of similar age, suggest no gender differences in morbidity prior to death from heart disease and lower morbidity in women prior to death from stroke. Besides comparing morbidity levels in men and women who die from CVD we also compared

morbidity patterns with controls in sex-specific analysis. These results show that CVD deaths in men are preceded by much greater absence from work compared to other men. This is not the case for women, particularly for stroke where there was little excess morbidity compared to controls till the year before death.

Evidence from the INTERHEART study suggests that similar risk factors explain most of the risk of heart disease in both genders. The impact of smoking, raised lipids, abdominal obesity, psychosocial variables, and vegetable and fruit consumption was similar and that of hypertension, diabetes, and the protective effect of exercise and alcohol greater in women then in men.[27] Further research on stroke, particularly in the under 65 years age-group, is required to understand its silent presentation in women.

There are a few caveats to the interpretation of the results reported here. First, although lost work days are a robust indicator of health,[28] they do not assess morbidity directly. It is possible that health problems other than CVD and reasons not directly related to health could contribute to lost work days. We chose this measure as CVD has multiple risk factors and using specific risk factors might not capture the full extent of morbidity prior to death. Furthermore, as only disability pension and sickness absences longer than 9 days have been included in our definition of lost days it is likely that minor unrelated ailments are not reflected in the measure of morbidity. This is an unlikely source of bias, because it is long- but not short-term absences that predict specific causes of death, such as cardiovascular disease[29] A source of concern is power as the number of CVD deaths in this age group is lower than at older ages. The strengths of the study lie in the comprehensive measure of morbidity, independent of any preconceived ideas on what qualifies as CVD morbidity.

In conclusion, our results suggest no excess morbidity among women in the 6 years leading up to premature death from cardiovascular diseases. In fact, morbidity levels are lower for death from stroke and suggest that further research, preferably using clinical data on

risk factors and morbidity levels, is required to understand gender differences in the disease process.

FUNDING SOURCES

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Table 1. Socio-demographic characteristics, causes of death and lost work days.

		All	Men	Women	Gender difference
CASES		n=361	n=222	n=139	
Age at death (M, SD)		52.9 (7.6)	53.6 (7.1)	51.9 (8.4)	p=0.040
Socioeconomic position (n, %)					
Upper-grade non-manual workers		70 (19.4)	48 (21.6)	22 (15.8)	p<0.0001
Lower-grade non-manual workers		105 (29.1)	42 (18.9)	63 (45.3)	
Manual workers		186 (51.5)	132 (59.5)	54 (38.9)	
CONTROLS		n=1800	n=1105	n=695	
Age at end of follow-up (M, SD)		52.3 (8.1)	53.0 (7.5)	51.3 (8.9)	p<0.0001
Socioeconomic position (n, %)					
Upper-grade non-manual workers		350 (19.4)	240 (21.7)	110 (15.8)	p<0.0001
Lower-grade non-manual workers		520 (28.9)	205 (18.6)	315 (45.3)	
Manual workers		930 (51.7)	660 (59.7)	270 (38.9)	
Annual mean lost days over the six-year observation period[†]					
Cause of death	**(deaths n, %)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**RR (95% CI)***
Ischaemic heart diseases	(174, 48.2%)	39.8 (25.4-62.2)	36.6 (26.2-51.3)	61.6 (30.1-125.8)	1.68 (0.85-3.33)
Strokes	(91, 25.2%)	31.5 (20.2-49.3)	59.0 (26.9-129.4)	19.2 (13.5-27.3)	0.33 (0.14-0.78)
Other diseases of circulatory system	(96, 26.6%)	42.3 (29.1-61.4)	56.4 (34.5-92.1)	28.9 (16.7-50.2)	0.51 (0.25-1.07)
All CVD deaths	(361, 100%)	36.8 (27.7-49.0)	41.3 (31.3-54.4)	32.8 (20.5-52.5)	0.80 (0.47-1.34)
Controls		12.8 (11.1-14.7)	11.5 (9.5-13.9)	14.2 (11.7-17.2)	1.24 (0.95-1.60)

[†] Six consecutive years before the year of death for cases. Analysis adjusted for age and socioeconomic position.

* RR: Rate Ratio; Men are the reference category.

Table 2. Morbidity rates (annual lost work days) in women compared to men in the 6 years leading to death.[†]

	Observation window: time to death					
	Year -6	**Year -5**	**Year -4**	**Year -3**	**Year -2**	**Year -1**
	RR* (95% CI)	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**
Ischaemic heart diseases	1.23 (0.39-3.93)	2.31 (0.86-6.22)	2.59 (0.85-7.90)	1.86 (0.65-5.37)	1.67 (0.70-3.99)	1.70 (0.80-3.60)
Strokes	0.10 (0.03-0.34)	0.23 (0.07-0.75)	0.29 (0.11-0.78)	0.27 (0.11-0.69)	0.30 (0.13-0.67)	0.72 (0.31-1.66)
Other diseases of circulatory system	0.29 (0.06-1.28)	0.61 (0.20-1.89)	0.66 (0.25-1.71)	0.91 (0.44-1.91)	0.76 (0.37-1.55)	0.61 (0.30-1.22)
All CVD deaths	0.40 (0.18-0.88)	0.78 (0.43-1.41)	0.89 (0.49-1.60)	0.79 (0.48-1.32)	0.76 (0.50-1.15)	0.88 (0.62-1.26)

[†] Analysis adjusted for age and socioeconomic position, with men as the reference category within each mortality category.
* Rate Ratio

Table 3. Gender specific analysis comparing morbidity patterns in cases of CVD deaths to matched controls.

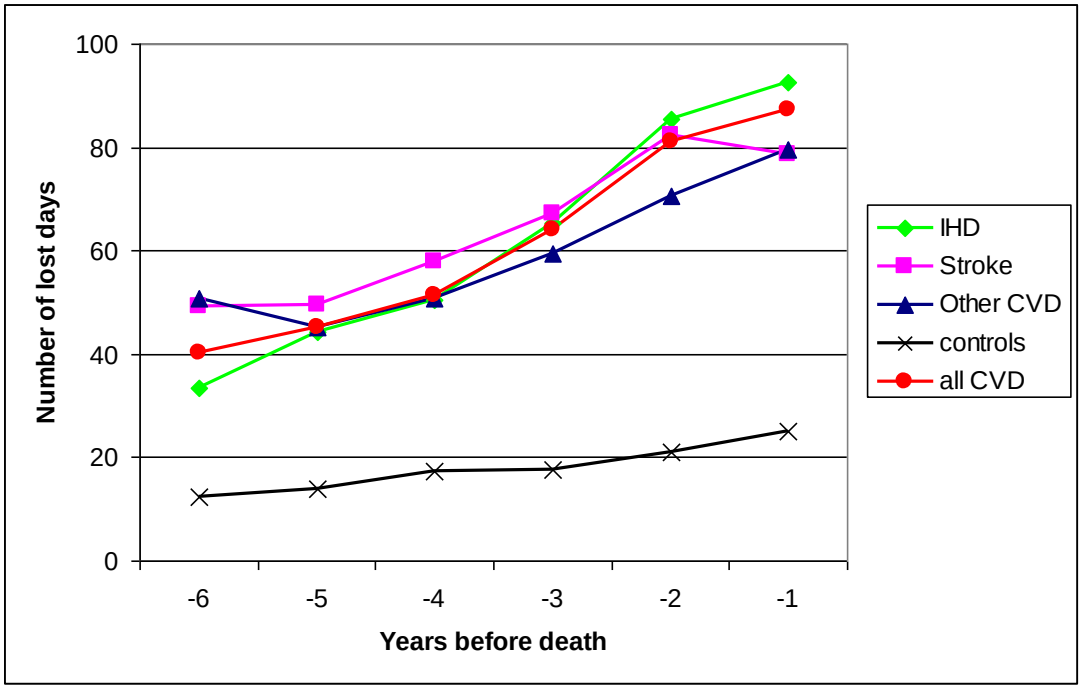
	Time to death					
	Year -6	**Year -5**	**Year -4**	**Year -3**	**Year -2**	**Year -1**
	RR* (95% CI)	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**	**RR* (95% CI)**
MEN						
CONTROLS (lost days) †	ref (12.3 days) †	ref (13.8 days) †	ref (17.4 days) †	ref (17.7 days) †	ref (21.1 days) †	ref (25.1 days) †
Ischaemic heart diseases	2.09 (1.08-4.07)	2.52 (1.50-4.25)	2.56 (1.61-4.05)	3.35 (2.27-4.96)	3.80 (2.69-5.35)	3.50 (2.54-4.83)
Stroke	5.02 (1.74-14.44)	4.74 (1.74-12.94)	5.05 (2.38-10.71)	4.84 (2.31-10.14)	4.72 (2.48-9.00)	3.57 (1.74-7.32)
Other diseases of circulatory system	5.65 (1.74-18.28)	3.65 (1.58-8.45)	2.98 (1.56-5.70)	2.86 (1.64-5.00)	4.25 (2.33-7.77)	4.92 (2.77-8.74)
All CVD mortality	3.52 (1.89-6.57)	3.15 (2.00-4.97)	3.02 (2.08-4.39)	3.43 (2.46-4.78)	4.02 (2.96-5.45)	3.86 (2.86-5.22)
WOMEN						
CONTROLS (lost days) †	ref (16.8 days) †	ref (17.3 days) †	ref (20.6 days) †	ref (23.5 days) †	ref (26.4 days) †	ref (26.7 days) †
Ischaemic heart diseases	1.80 (0.65-5.02)	5.87 (1.75-19.67)	7.34 (1.95-27.61)	5.37 (1.46-19.71)	5.83 (1.94-17.56)	5.83 (2.20-15.44)
Stroke	0.30 (0.13-0.71)	0.82 (0.39-1.70)	1.22 (0.59-2.49)	0.94 (0.51-1.71)	1.07 (0.64-1.81)	2.51 (1.46-4.29)
Other diseases of circulatory system	1.00 (0.31-3.19)	1.78 (0.73-4.33)	1.85 (0.86-3.98)	2.04 (1.13-3.69)	2.55 (1.51-4.33)	2.51 (1.47-4.29)
All CVD mortality	0.90 (0.43-1.89)	2.38 (1.07-5.30)	2.94 (1.24-6.98)	2.37 (1.10-5.14)	2.70 (1.44-5.07)	3.34 (2.00-5.56)

† Unadjusted

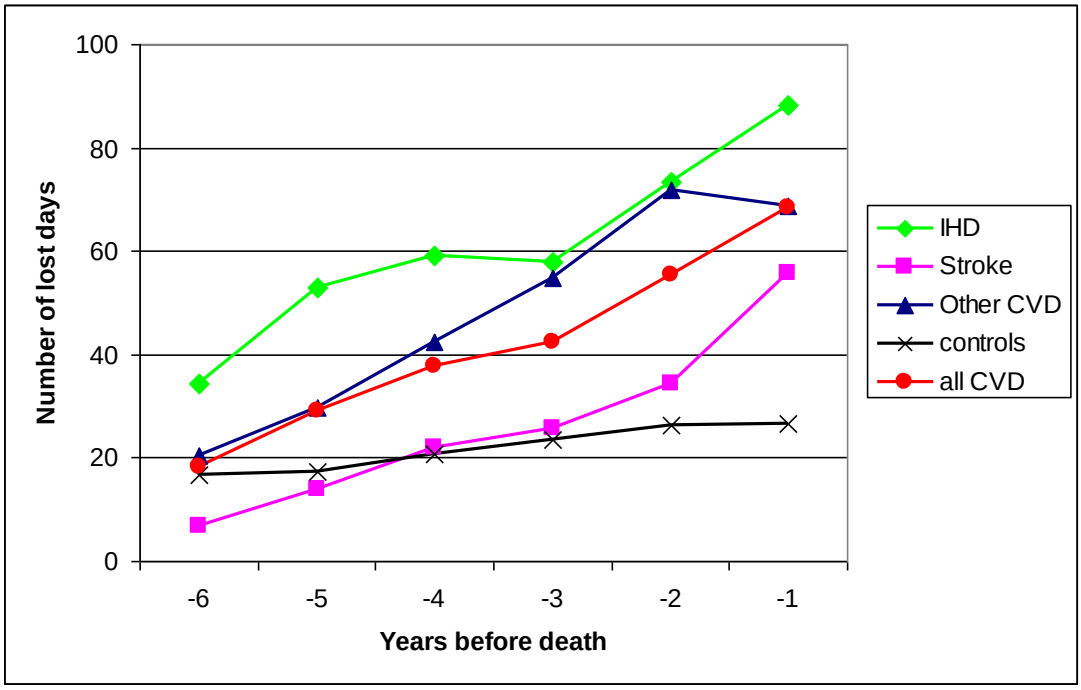
* RR: Rate Ratio, adjusted for age and socioeconomic position, with controls as the reference category within each mortality category.

Figure 1. Lost work days (unadjusted) over 6 years in cases prior to death and in the controls.

MEN



WOMEN



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