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Family burden of cardiovascular mortality: risk implications for offspring in a national register linkage study based upon the Malmö Preventive Project

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Abstract. Nilsson PM, Nilsson J-Å, Berglund G (University Hospital, Malmö, Sweden). Family burden of cardiovascular mortality: risk implications for offspring in a national register linkage study based upon the Malmö Preventive Project. *J Intern Med* 2004; **255**: 229–235.

Objective. To investigate the adjusted relative risk of cardiovascular disease (CVD) events in offspring of parents with cardiovascular mortality before 75 years.

Setting. The city of Malmö, Sweden.

Design. A follow-up study based on register linkage analyses.

Subjects and methods. In the Malmö Preventive Project (MPP), a total of 22 444 men and 10 902 women attended the screening programme between 1974 and 1992. At the screening conventional risk factors for CVD were measured (blood pressure, lipids, glucose, smoking and social class).

Main outcome measures. Parental CVD mortality was determined via register linkage analysis between the Multiple-Generation Register and the National Mortality Register (NMR). CVD events (morbidity and mortality) in offspring were

collected from national registers. The relative risk for CVD events in offspring, in relation to parental CVD mortality, was adjusted for age and risk factors at screening.

Results. The age-adjusted relative risk (RR; 95%CI) for a son to experience a CVD event was increased in relation to a maternal positive family history of CVD mortality before 75 years when compared with no maternal history, RR 1.74 (1.43–2.11). This RR decreased to 1.51 (1.23–1.84; $P < 0.001$) after full adjustment for risk factors. The corresponding fully adjusted RRs for father–son heritage was RR 1.22 (1.02–1.47; $P < 0.05$), mother–daughter RR 0.87 (0.54–1.41), and father–daughter RR 1.20 (0.83–1.73).

Conclusion. The existence of maternal CVD mortality before the age of 75 years implies a substantial risk increase for CVD morbidity and mortality in sons that cannot be explained by social background, lifestyle, or conventional cardiovascular risk factors in the adult offspring.

Keywords: cardiovascular, family history, maternal, mortality, risk factors, social class.

Introduction

The risk factors for cardiovascular disease (CVD) can be subdivided into those risk factors possible to change, and the unchangeable risk factors, e.g. age, gender and family history of CVD [1]. It is well known that a positive family history of CVD implies an increased risk for CVD in offspring, and even more so the earlier the onset of CVD has been in the parents [2–11]. This is the reason why a positive family history (burden) of CVD has been emphasized

in current guidelines for the prevention of CVD in order to target risk individuals, especially for those with CVD in close relatives before the age of 55 years in men and 65 years in women [1]. There are however several limitations to the clinical and research use of a self-reported family history, both to its accuracy and degree of correct details [12, 13], diagnoses, etc. Asking an individual about family history of CVD may be difficult due to biased answers, e.g. as influenced by age of the patient, poor memory, ignorance, misunderstanding, or lack

of correct information about diagnoses and causes of death. Therefore, new methods should be tested to more accurately collect information about family history. One such method could be to use valid registers on parental CVD mortality, based on national register data and certificates of death, in order to link information to registers of offspring and to calculate CVD risk in these offspring.

In Sweden, the introduction of the so called Multiple-Generation Register (MGR) in 1998 has made it possible to use register linkage analyses in order to get more optimal information about an objective family history, e.g. when it has been linked to national registers of cancer [14, 15] or conscript testing for evaluation of family clustering of obesity [16]. This information could also be linked to national registers on mortality, which should be at least as good as the quality of individual death certificates. Traditionally the death certificates in Sweden have been based on diagnostic evaluations by doctors *ante mortem*, or on autopsies. As the autopsy rate has substantially declined in many countries, including Sweden, the quality of death certificates has been questioned. In the majority of cases it is still believed to be accurate enough. Within the MGR it is possible to trace first-degree relatives (parents, siblings) if they had a personal identification number, commonly introduced in Sweden in 1947. It is possible to trace these relatives (parents, siblings) if they were alive as early as 1932 and onwards.

We have had the possibility to use data from the Malmö Preventive Project (MPP) [17–19] to elucidate the role of family history for CVD via a register linkage analysis, thereby using, for the first time, objective register-derived information about the family burden of CVD for prediction of CVD morbidity and mortality in the offspring.

The aim of this observational study was therefore to investigate the predictive power of parental family history of CVD before age 75 years for offspring cardiovascular morbidity and mortality, adjusted for individual social and biological risk factors at screening within the MPP.

Subjects and methods

Subjects

A preventive case-finding programme for cardiovascular risk factors and alcohol abuse, the MPP,

started at the Department of Preventive Medicine, University Hospital Malmö in 1974 [17]. The aim was to screen large strata of the adult population in order to find high-risk individuals for preventive intervention [17–19]. Subjects were invited to participate in a broad health-screening programme, including a physical examination and a panel of laboratory tests. Additionally, every participant filled in a self-administered questionnaire on medical and personal history. Between 1974 and 1992, a total of 22 444 men (mean age 46 years) and 10 902 women (mean age 49 years) attended the screening programme, with an overall attendance rate of 71% (range 64–78%). Men were mostly screened in the first half of the period (1974–82), and women in the latter half (1981–92), implying different follow-up time periods for men and women. Various interventions (lifestyle modification, drug therapy) engaged nearly 25% of the screened subjects [17].

Within the MPP we have identified parents born before 1924 (and alive in 1932) to be at risk of CVD mortality for 75 years until 31 December 1999 (National Mortality Register, Sweden). In all, it was possible to collect information on MPP subjects for paternal history of CVD in 4831 women and 9294 men, and for 5251 women and 9911 men on corresponding maternal history of CVD. The reason we chose 75 years as inclusion limit for paternal CVD mortality was to include all early CVD mortality, but at the same time excluding CVD mortality in the very old. The mean life expectancy in Sweden is currently 76 years for men and 82 years for women. In addition, we could not use the cut-off limits of 55 years in men and 65 years in women for early CVD events in close relatives, as recommended by current guidelines [1], due to lack of statistical power. In a sub-analysis we further subdivided the parents who died of CVD before 75 years, into tertiles (age-groups 50–68, 69–72 and 73–75 years).

Intervention programmes

The Section of Preventive Medicine was an integrated part of The Department of Medicine, Malmö University Hospital, and occupied facilities close to the hospital for screening and for diagnosis and treatment for those subjects with diseases and/or risk factors detected at screening. The intervention programme, thus, was an individually orientated,

high-risk approach with resources set aside for both screening and subsequent treatment. The criteria for intervention and numbers of subjects intervened on have previously been described [17]. Therefore, the current follow-up analysis is not based upon observational data only, but on a study involving some degree of intervention aiming at risk factor control. This did not however influence total mortality in the screened MPP study group when compared with noninvited birth cohorts [19]. No detailed data are available on lifestyle modification or drug treatment in individual patients following screening.

Clinical data and definitions

During the health-screening period, the participants underwent a physical examination, performed by trained nurses, in the morning and the participants were instructed to observe an overnight fast preceding the investigation. A self-administered structured questionnaire was used for the assessment of medical history, smoking habits, physical activity and use of medication. Social class (manual, non-manual occupation) was based on data from national censuses closest to the day of screening.

Physical examination

Weight (kg) and height (m) were measured in light indoor clothing and the body mass (BMI) was calculated (kg m^{-2}). Blood pressure (mm Hg) and heart rate (beats min^{-1}) were measured twice in the supine position after 10 min rest by use of appropriate technical equipment (a sphygmomanometer with a modifiable cuff width and a chronometer), and a mean figure was recorded.

Laboratory investigation

Blood was sampled after an overnight fast. Serum total cholesterol, triglycerides and fasting blood glucose were analysed, using routine laboratory methods at the Department of Clinical Chemistry, Malmö University Hospital.

Follow-up in registers

We used as outcome variable the number of cardiovascular events (morbidity and mortality) in

the MPP subjects. For individuals screened within MPP and who died before 1991 ($n = 1444$; 35%) we partly (approximately 50%) lack information on the parents for technical reasons, which causes some under-reporting. The reason for this is that the MGR did not start until 1998 and did not retrospectively include complete parental data on already deceased offspring. Mortality data on parents and offspring were followed in the National Mortality Register until 31 December 1999. Data on CVD morbidity and mortality (ICD diagnoses I20–25, I61–69, I70–72, I74, 410–414, 431–438, 440–442, 444) were retrieved from national registers, and data on social class from national censuses (National Statistics, Sweden).

Statistical methods

The Cox proportional hazards model was used to test the mortality rates in the group with 'early' family history of CVD compared with the group without such family history of CVD. Results are presented as risk ratios (RR) with 95% confidence interval (CI). All analyses were stratified on gender of participants as well on gender of the parents. $P < 0.05$ was considered to be significant.

Results

Causes of death in 4061 fathers were CVD ($n = 1854$; 47%), cancer ($n = 1231$), and other ($n = 976$). The corresponding numbers for death in 2777 mothers were 989 (36%), 982 and 806, respectively. Cancer deaths in the fathers were mostly caused by cancer in the respiratory tract (25%), prostate (11%), or ventricle (9%). Correspondingly, cancer deaths in the mothers were mostly caused by cancer in the breast (15%), ovary (9%), or colon (9%).

For a positive paternal family history of CVD mortality before age 75 years we noted the following numbers of total CVD events (morbidity and mortality) in the offspring: 41/607 in daughters and 146/1247 in sons. The corresponding numbers for positive maternal family history were 23/351 and 115/638, respectively. This accumulated to a total of 325 CVD events in the offspring with a positive paternal history, when compared with 2352 CVD events in the offspring without a positive paternal history (Table 1). More detailed data on the number

Table 1 CVD events (mortality and morbidity; $n = 327$) for screened subjects (offspring) in relation to parental CVD mortality cases before age of 75 years, within the Malmö Preventive Project 1974–92. Follow-up was done until 31 December 1999

	CVD mortality					
	Fathers			Mothers		
	No	Yes	Σ	No	Yes	Σ
Sons						
<i>n</i>	8047	1247	9294	9273	638	9911
IHD	591 (7.3)	106 (8.5)	697 (7.5)	707 (7.6)	86 (13.5)	793 (8.0)
Stroke	186 (2.3)	26 (2.1)	212 (2.3)	215 (2.3)	19 (3.0)	234 (2.4)
PAD	76 (0.9)	14 (1.1)	90 (1.0)	93 (1.0)	10 (1.6)	103 (1.0)
Total	853 (10.6)	146 (11.7)	999 (10.7)	1015 (10.9)	115 (18.0)	1130 (11.4)
Daughters						
<i>n</i>	4224	607	4831	4900	351	5251
IHD	131 (3.1)	24 (4.0)	155 (3.2)	166 (3.4)	15 (4.3)	181 (3.4)
Stroke	67 (1.6)	11 (1.8)	78 (1.6)	82 (1.7)	7 (2.0)	89 (1.7)
PAD	16 (0.4)	6 (1.0)	22 (0.5)	22 (0.4)	1 (0.3)	23 (0.4)
Total	214 (5.1)	41 (6.8)	255 (5.3)	270 (5.5)	23 (6.6)	293 (5.6)

Values within parenthesis are expressed as percentage. IHD, ischaemic heart disease.

of CHD, stroke and peripheral artery disease (PAD) events are also presented (Table 1).

The age-adjusted relative risk (RR; 95% CI) for a son to experience a CVD event (morbidity or mortality) was increased in relation to a positive maternal family history of CVD mortality before 75 years when compared with no maternal history, RR 1.74 (1.43–2.11). This RR decreased to 1.51 (1.23–1.84; $P < 0.001$) after full adjustment for age, social class, lifestyle, and conventional cardiovascular risk factors at screening of offspring in the MPP (Table 2).

The corresponding fully adjusted RRs for father–son heritage risk was RR 1.22 (1.02–1.47; $P < 0.05$), mother–daughter RR 0.87 (0.54–1.41), and father–daughter RR 1.20 (0.83–1.73) (Table 2).

Subdividing parental age of early death into tertiles (age groups 50–68, 69–72 and 73–75 years) showed a graded association for maternal influence, RR 1.82 (1.35–1.46), 1.55 (1.14–2.10), and 1.50 (1.13–1.98), but not for paternal influence, RR 1.29 (0.99–1.69), 1.08 (0.81–1.44) and 1.40 (1.12–1.76), using surviving parents or mortality after 75 years as the reference group.

Discussion

The most important finding of this observational study was that relatively 'early' CVD mortality in mothers, before 75 years of age, impacted on the

Table 2 Relative risk (RR; 95%CI) of cardiovascular disease (CVD) events (mortality or morbidity) in offspring in relation to a positive family history of parental CVD mortality before 75 years

	CVD events	
	RR age-adjusted	RR full adjustment ^a
Fathers		
Sons	1.24 (1.03–1.48)	1.22 (1.02–1.47)*
Daughters	1.37 (0.97–1.92)	1.20 (0.83–1.73)
Mothers		
Sons	1.74 (1.43–2.11)	1.51 (1.23–1.84)***
Daughters	1.14 (0.75–1.75)	0.87 (0.54–1.41)

* $P < 0.05$; *** $P < 0.001$. ^aFull adjustment for age, social class, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking at baseline screening in the Malmö Preventive Project.

increased relative risk of CVD events (morbidity and mortality) in sons, RR 1.7. This risk was only marginally attenuated (RR 1.5) after adjustment for possible confounders, e.g. social class, lifestyle and cardiovascular risk factors in the adult offspring at screening. A similar but somewhat weaker association was found between paternal early CVD mortality and corresponding outcomes in sons (RR 1.2). The parental influence on CVD events in daughters did not reach statistical significance. A graded association was shown for the maternal influence on offspring CVD risk – the younger the mother died, the higher the offspring risk.

One possible explanation for our findings is that a positive maternal family history of CVD mortality before the age of 75 years is relatively uncommon and relates to a number of other biological cardiovascular risk factors, not measured within this screening study. Examples of such unmeasured risk factors are defects in the fibrinolytic system, increasing the risk of thromboembolism and CVD events, or impaired insulin sensitivity. Genetic factors are often important for risk factor levels causing early CVD manifestations. Another explanation could relate to a more psychological aspect in the way sons may differ from daughters in the emotional reaction pattern after the early death of a mother. Could it be that sons are more susceptible than daughters in this respect, or is this statement too speculative? A third explanation is reversed causality, e.g. that the birth of one or multiple sons will negatively impact on longevity of mothers. This has in fact been shown in preindustrial humans from Northern Finland based on local registers [20]. Finally, fetal programming or genetic factors could be of importance, linking increased cardiovascular risk [21] or insulin resistance [22] in mothers to increased risk of poor fetal growth and cardiovascular disease in the offspring.

Limitations of the study

Several limitations should be pointed out. Even if the MGR represents a unique possibility to achieve a more reliable estimate of the family burden (history) of cardiovascular disease than self-reported data based on memory and biased knowledge, it is still possible that this register is sub-optimal in retrieving data on all cardiovascular events due to diagnostic or reporting failures. Another limitation is that not all parents could be traced. We lack data on parents not alive in 1932, as well as some data on parent-offspring links if the offspring son or daughter died before 1992. It would seem that these data limitations could reduce possible associations, but not inflate them and the corresponding relative risks. We also face the limitation of having access to only a small number of potential cardiovascular risk factors as measured by the baseline screening of index subjects within the MPP. Therefore we lack the important variables plasminogen activator inhibitor-1 and insulin sensitivity, or reliable markers of it (proinsulin). It should also be remembered that the

intervention given to 20–25% of the screened subjects in MPP could potentially dilute any associations. Finally, it should be mentioned that competing causes of mortality could influence our findings, based on the fact that only 47% of all parental deaths before 75 years in males and 36% of all deaths in corresponding females were caused by CVD (see Results). This fact would however tend to dilute our findings, not to exaggerate them.

We could not use the cut-off limits of 55 years in men and 65 years in women for early CVD events in close relatives, as recommended by current guidelines [1], due to lack of statistical power because we did not have any access to data on CVD nonfatal events in the parents.

Interpretation of family history – is it determined by genes or environment?

Most often a positive family history of CVD is interpreted as a proof of genetic influences, e.g. a genetic heritability as shown for mutations in the LDL cholesterol receptor linked to familial hypercholesterolaemia with an increased cardiovascular risk for younger but not older offspring [23]. One classical method to elucidate the genetic influences on CVD risk is to use twin comparisons in concordant or discordant twins [24]. However, family history also encompasses similar lifestyle traits and an aggregation of environmental risk factors within families [25, 26]. Furthermore, some lifestyle factors such as smoking habits could also be influenced by genetic traits [27]. In our study no genetic polymorphisms were measured why this aspect cannot be further explored. We however tried to adjust for social class at screening to decrease the potential bias represented by social stratification of CVD.

Rosengren *et al.* have reported that an increased paternal longevity is associated with decreased risk in middle-aged men [28]. Paternal, but not maternal, longevity thus appears to protect against coronary disease, by mechanisms that are largely unknown. This was however not the scope of our current analysis in the MPP. Correspondingly, we lacked data on individual risk factors in the parents, why correlation analyses, e.g. for cholesterol levels in parents and offspring was not possible, that has been shown for middle-aged men [29].

Based on another Swedish case-control study on survivors of acute myocardial infarction it was

concluded that family history interacted with other cardiovascular risk factors in a synergistic way [30]. Therefore, future prospective studies on the role of family history for CVD should look for both synergistic interactions [30] as well as new intermediary risk factors to explain the findings that conventional risk factors alone are not able to explain the full risk of a positive family history [31]. Most importantly is however that data on family history of CVD can be validated as different definitions have been used in the past [5, 32]. The existence of register-based data will hopefully increase the accuracy of observational epidemiological studies on the risk associated with the true family burden (history) of CVD.

In conclusion, the existence of maternal CVD mortality before the age of 75 years implies a substantial risk increase for CVD morbidity and mortality in sons that cannot be explained by social background, lifestyle, or conventional cardiovascular risk factors in the offspring.

Conflict of interest statement

No conflict of interest was declared.

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