SUPPLEMENTAL MATERIAL

Material and methods

Study Design
The study is a cohort study of persons with FH identified from the Unit for Cardiac and Cardiovascular Genetics (UCCG) Registry linked to the Norwegian Cause of Death Registry and the Cardiovascular Disease in Norway (CVDNOR) project database.[1, 2] The three data sources were linked by means of the 11-digit personal identification number, unique to each Norwegian resident.

The UCCG Registry
The UCCG Registry, after written informed consent, includes all genetically confirmed FH cases in Norway since 1992. The registry is described in detail elsewhere.[3–7] A total of 4273 persons with FH were included in the registry during 1992-2009.

Cerebrovascular outcomes and study cohorts
Information on cerebrovascular disease including ischemic stroke among persons with FH and in the total Norwegian population was obtained from the CVDNOR database and the Norwegian Cause of Death Registry. The main and supplementary diagnoses were coded according to the International Classification of Diseases (ICD), version 9 until 1998 and version 10 from 1999 and onwards. Causes of death were coded according to ICD-9 until 1995 and ICD-10 from 1996 and onwards.

The study cohort was defined separately for analyses of the two endpoints cerebrovascular disease (ICD-9 430-438, ICD-10 160-I69 and G45) and ischemic stroke (ICD-9 433-434, ICD-10 I63). A flow-chart for inclusion and exclusion of patients is given in Figure 1. CHD was defined as the ICD9 codes 410-414 or ICD10 codes I20-I25.

For cerebrovascular disease, the study cohort was defined as all persons with FH registered in the UCCG Registry before December 31st 2009 and without any known prior hospitalization with cerebrovascular disease. In order to reduce the risk of including patients who already had cerebrovascular disease at baseline we used the period 1994-2000 as a seven year washout period to search for previous events and restricted the analyses of incidence rates and standardized incidence ratios (SIRs) to the period 2001-2009, excluding persons with FH with the first occurrence of cerebrovascular disease before 2001. A seven year washout period has previously been used to identify incident myocardial infarction events in Norway and has been found to result in approximately 4% overestimation of incident events.[8] A seven year washout period is also applied by the Swedish National Board of Health and Welfare in order to define first-ever strokes.[9] In addition we excluded patients who were <25 years old throughout the study period since the risk of cerebrovascular disease is considered to be low in children and young adults.[10]

An incident event of cerebrovascular disease was defined as a hospitalization with cerebrovascular disease, or ischemic stroke, as main or secondary diagnosis or death with cerebrovascular disease as the underlying cause, without any prior hospitalizations with cerebrovascular disease during the past seven years. Persons were followed from inclusion in the FH registry until the first occurrence of cerebrovascular disease, death or 31st December 2009, whichever came first.

Statistical analyses

Unadjusted incidence rates per 1000 person-years of follow-up were calculated for each endpoint for the time period 2001-2009 stratified by sex and age groups. SIRs were calculated for each endpoint using indirect standardization,[11] with incidence rates for the total Norwegian population as reference rates. Incidence rates for the total Norwegian population during 2001-2009 in one-year sex- and age strata were obtained from CVDNOR. We calculated the expected number of incident events for men and women for each combination of 1-year age group and calendar year in the UCCG Registry as time spent in the cohort multiplied by the incidence rate for the same combination of birth year and calendar year in the total Norwegian population.

The follow-up time for each individual was split over calendar years and the attained age for each individual was updated for each calendar year. SIRs were calculated as the observed number of events divided by the expected number of events and 95% confidence intervals (CIs) were obtained using the normal approximation to the Poisson distribution. SIRs were calculated for the total study cohorts with men and women combined and separately for men and women. A test for difference in SIRs between men and women was obtained using Poisson regression with observed events as dependent variable, the logarithm of expected events as offset and sex as a covariate.

Because we also wanted to investigated whether a previous occurrence of CHD increased the risk of cerebrovascular disease we searched through CVDNOR-data during 1994-2009 to look for hospitalizations for CHD. The association between CHD and risk of cerebrovascular disease was analyzed by including CHD as a time-dependent covariate in a Cox proportional hazard regression model and reported as hazard ratios (HRs) with 95% CIs. Follow-up time in the Cox model was calculated in the same manner as for calculation of SIRs. Age was included in the model as a continuous covariate. A test for difference in association between men and women was done by including an interaction term between sex and the time-varying CHD covariate in the model. Because of a significant interaction effect we report the results of the Cox analysis stratified by sex.

All analyses were performed using Stata version 14.

References

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