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Causal nature of neighborhood deprivation on individual risk of coronary heart disease or ischemic stroke: A prospective national Swedish co-relative control study in men and women

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ABSTRACT

We studied the association between neighborhood socioeconomic status (SES) and incidence of coronary heart disease (CHD) or ischemic stroke in the total population and in full- and half-siblings to determine whether these associations are causal or a result from familial confounding. Data were retrieved from nationwide Swedish registers containing individual clinical data linked to neighborhood of residence. After adjustment for individual SES, the association between neighborhood SES and CHD showed no decrease with increasing genetic resemblance, particularly in women. This indicates that the association between neighborhood SES and CHD incidence is partially causal among women, which represents a novel finding.

1. Introduction

Coronary heart disease (CHD) and ischemic stroke are associated with increased mortality rates and disability as well as substantial costs for health care systems worldwide (Mozaffarian et al., 2016). Strong correlations to socioeconomic factors have been established, both at the individual- and neighborhood level (Winkleby et al., 2007; Sundquist et al., 2004b, 2004a; Diez Roux et al., 2001; Hamano et al., 2013; Calling et al., 2016).

However, appropriate preventive efforts and interventions, particularly at the neighborhood level, have been hampered because causality in the associations between neighborhood socioeconomic factors and CHD and ischemic stroke has been difficult to prove. Establishing causality is often a challenge in observational studies, including those examining neighborhood effects (Oakes, 2004). This is because it is nearly impossible to perform randomized controlled trials where large numbers of individuals are randomly assigned and adhere to move to different types of neighborhoods (Diez Roux, 2004). However, novel analytic strategies, like quasi-experimental co-relative designs (Lahey and D'onofrio, 2010; Merlo et al., 2013; Kendler et al., 2014), provide new opportunities for investigating the causal effect of neighborhood exposure on health-related outcomes in individuals who share similar genes and similar family environmental background but differ in exposure. In co-relative designs, the association between a certain exposure and an outcome is examined in the general population as well as in relatives (Kendler et al., 1993).

Previous studies have used co-relative designs to examine the causal nature of neighborhood effects on individual CHD in full brothers (Chaix, 2009; Merlo et al., 2013). However, to the best of our knowledge, no previous study has included both women and men or examined the causal nature of neighborhood effects on individual CHD as well as ischemic stroke in both full-siblings and half-siblings and in different age groups. These knowledge gaps will be addressed in the present study.

The aim of the present study was to examine the association between neighborhood socioeconomic status (SES) and incidence of CHD or ischemic stroke in the total population and in full- and half-siblings in order to determine whether these potential associations are causal or result from familial confounding factors. These associations were examined in men and women and in different age groups separately.

2. Method

The data used in the present study were retrieved from nationwide registers provided by the National Board of Health and Welfare (health care data) and Statistics Sweden, the Swedish Government-owned statistics bureau (population and family data). All data were linked by

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the personal Swedish identification number, which was replaced by a serial number in the dataset in order to maintain anonymity for all individuals. Ethical approval was granted by the Ethics Committee of Lund University, Sweden, and was conducted in accordance with the 1975 Declaration of Helsinki. Health care data was retrieved from two nationwide Swedish medical registers: the Hospital Discharge Register containing in-patient data from 1987 and onwards, and the Outpatient Register containing outpatient specialist care data from 2001 and onwards. The Swedish Multi-generation Register (2011), which includes all individuals born in 1932 and onwards , was used to identify all full-sibling and half-sibling pairs.

2.1. Outcome variables

The outcome variables were incidence of CHD and ischemic stroke during follow-up (until 2013). Incidence was defined as the first registered diagnosis of CHD or ischemic stroke during the study period. The CHD outcome diagnoses were collected from the Hospital Discharge Register or Outpatient Register using the International Classification of Diseases (ICD) codes from the following different ICD versions: ICD-8 codes 410–414, ICD-9 codes 410–414 or ICD-10 codes I20-25, which is in accordance with previous studies (Calling et al., 2013). The ischemic stroke outcome diagnoses were collected from the Hospital Discharge Register or Outpatient Register using ICD-8 codes 432–438, ICD-9 codes 433, 434, 435, 437.0, 437.1 or ICD-10 codes I63 (not I63.6), I65, I66, I67.2, I67.8, and G45. For the Hospital Discharge Register we used main and secondary discharge diagnoses encoded in the ICD format (Ludvigsson et al., 2011). The diagnoses in this register have a positive predictive value between 85–95%, and the diagnostic validity of many diseases are even higher; e.g., myocardial infarction (MI) and stroke have a positive predictive value of > 95% (Ingelsson et al., 2005; Ludvigsson et al., 2011; Nilsson et al., 1994).

2.2. Neighborhood-level socioeconomic status (SES)

The home addresses of all Swedish individuals have been geocoded to small geographical units that have boundaries defined by homogeneous types of buildings. These neighborhood areas, developed by Statistics Sweden, are called small areas for market statistics (SAMS) and have an average of 1000 people each. SAMS were used as proxies for neighborhoods (Sundquist et al., 2006a; Cubbin et al., 2006). A summary index was calculated to characterize neighborhood-level SES (Winkleby et al., 2007). The neighborhood SES index was based on four items: low education level, low income, unemployment and receipt of social welfare. Neighborhood SES was approximately normally distributed with a mean value of 0 and a standard deviation (SD) of 1. Neighborhood SES was used as a continuous variable in the models with the score ranging between − 3.2 and 12 with higher values indicating higher levels of neighborhood deprivation. SES was measured at inclusion in the study.

2.3. Individual-level variables

2.3.1. Marital status

Individuals were classified as married/cohabitating or widowed/divorced/never married.

2.3.2. Family income

Individualized disposable family income was defined as combined family income minus current taxes divided by the number of people in the family. In order to be able to use the income variable to categorize SES over time, we standardized the variable (mean 0 and SD 1) by sex and year.

2.3.3. Educational attainment

The education variable was primarily based on the number of years of education: less than 9 years; 9 years; 10–11 years; 12 years; 13–15 years; 16 years or more; and having a Ph.D./licentiate degree. The education variable was also standardized (mean 0 and SD 1) by sex and year.

2.4. Sample, time of inclusion, and follow-up

The dataset included all men and women born in Sweden between 1932 and 1966. Time for inclusion in the study of the men and women was between 1990 and 2006. For the variables neighborhood SES, educational attainment, family income and marital status we had access to yearly information during the entire inclusion period, i.e., 1990–2006 for all individuals residing in Sweden. We assessed these variables at time for inclusion in the study in the three different groups, i.e., those who became 40 years (N_{40y} = 1,702,541), 50 years (N_{50y} = 1,741,835) or 60 years (N_{60y} = 1,276,705) somewhere during the inclusion period. The relatively lower number of individuals aged 60 years was because one of the inclusion criteria in this study was to have a registered sibling in the Multi-Generation Register (i.e., brother for the men in the study population or sister for the women in the study population). “Wash-out” was performed in order to secure that all cases were incident cases. For this purpose, we excluded all patients with a CHD diagnosis between 1987 and study start for the CHD analyses and all patients with an ischemic stroke diagnosis between 1987 and study start for the ischemic stroke analyses. The total number of individuals with a CHD registration prior to study start were 97,827 in the three age groups (N_{40y} = 3618, N_{50y} = 25,514 and N_{60y} = 68,695). Individuals with less than five years of residence in their neighborhood at inclusion were also excluded (N_{40y} = 434,337, N_{50y} = 320,012 and N_{60y} = 175,733). Exclusion of individuals with less than five years of residence was done because these individuals would have had a limited exposure to their current neighborhoods, and, as CHD or stroke most likely develops after longer time exposures. Additionally, all individuals who had lived abroad at some time point (N_{40y} = 23,089, N_{50y} = 19,366 and N_{60y} = 6408) during the study period were excluded. The follow-up started at time of inclusion and ended at the time of a possible event, death, emigration or at the end of 2013, whichever came first.

3. Statistical methods

We used Cox proportional hazards models to assess the risk of CHD as a function of neighborhood SES. In the first model, we estimated hazard ratios (HRs) to assess the risk of CHD from age at inclusion (40, 50 or 60 years) until end of follow-up, death, possible event, or emigration, as a function of neighborhood SES at age at inclusion while controlling for family income, educational attainment, and marital status at inclusion. We then replicated the models for ischemic stroke. All models were stratified by sex. In all models, the proportionality assumption was checked. If not fulfilled, we conducted two additional analyses; in the first, we added a time-dependent variable and, in the second, we divided the follow-up period in three time intervals and modeled each time interval separately.

Next, we sought to assess the degree to which the association between neighborhood SES and our cardiovascular outcomes is a result from confounding by familial risk factors (genetic and/or shared environmental) using a co-relative design for the full- and half-sibling pairs. We used a stratified Cox regression model, in which we refitted all analyses within strata of the defined relative sets (full-sibling pairs and half-sibling pairs). Only pairs in which the members differed in their exposure to neighborhood SES would contribute to the regression estimates.

Within each stratum, the hazard ratio (HR) is adjusted for the familial cluster, and, therefore, accounts for an array of unmeasured genetic and environmental factors shared within the relative set. All statistical analyses were performed using SAS 9.4.