Familial [corrected] transmission of coronary heart disease: a cohort study of 80,214 Swedish adoptees linked to their biological and adoptive parents.

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Abstract

Background Studies of adoptees have the potential to disentangle the contributions of genetic versus family environmental factors in the familiar transmission of coronary heart disease (CHD) because adoptees do not share the same family environment as their biological parents. The aim of this study was: 1) To examine the risk of CHD in adopted men and women with at least one biological parent with CHD, and 2) to examine the risk of CHD in adopted men and women with at least one adoptive parent with CHD.

Methods The Swedish Multigenerational register was used to follow all Swedish-born adoptees (born in or after 1932, n = 80,214) between January, 1, 1973 and December 31, 2008 for CHD. The risk of CHD was estimated in adopted men and women with at least one biological parent with CHD, and adopted men and women with at least one adoptive parent with CHD. The control groups consisted of adopted men or women without a biological parent with CHD or adopted men or women without an adoptive parent with CHD.

Results Adopted men and women with at least one biological parent with CHD (n = 749) were 1.4 to 1.6 times (statistically significant, 95% CI) more likely to have CHD than adoptees without a biological parent with CHD. In contrast, men and women with at least one adoptive parent with CHD (n = 1,009) were not at increased risk of the disease.

Conclusions These findings (based on validated hospital diagnoses unbiased by recall) suggest that the familiar transmission of CHD from parents to offspring is more related to genetic factors than to family environmental factors.

Introduction

A family history of CHD has been firmly established as a potent risk factor for CHD. Previous studies have shown that siblings, including twins, have an increased risk of CHD if the sibling/twin has the disease and that parents transmit the disease to their offspring [1-11]. This transmission is likely to be through genetic factors [12-16] but may also be through family environmental factors that are shared by siblings/twins or "transmitted" from parents to their children via the adoption of unhealthy behaviors such as smoking, physical inactivity and a poor diet [17,18]. In addition, familial networks are an important part of social networks, which can contribute to obesity, an established risk factor for CHD [19]. Family environmental factors may also include a transmission of infectious agents related to the development of CHD, as suggested by recent studies showing an association between chronic inflammation and cardiovascular risk [20].

Knowledge of the contributions of genetic versus family environmental factors is important for a better understanding of possible mechanisms underlying CHD. It has, however, been difficult to disentangle the contributions of genetic versus family environmental factors in family studies of CHD because most children, including dizygotic and monozygotic twins, grow up in their biological families.

One of the most promising avenues to study whether genetic versus family environmental factors have differential influences on the transmission of CHD is through a follow-up study of a large sample of adoptees. Studies of adoptees offer the unique opportunity to study the genetic transmission of CHD because adoptees do not grow up in their biological families. Transmission of CHD from biological parents to offspring would therefore be explained by genetic rather than by family environmental factors. In addition, transmission of CHD from adoptive parents to offspring would be explained by family environmental rather than genetic factors.

In studies of adoptees, it is essential to have information that allows one to link adoptees to both their biological and adoptive parents, and identify a control group of adoptees with biological or adoptee parents without CHD. This is possible in Sweden through the nearly complete registration of all residents in a national healthcare system and recent linkages of demographic and health outcome data bases. An additional key strength with health care register data is that they are unbiased by individual patient self-report or recall as all registered diagnoses are established by physicians.

To the best of our knowledge, there has been no large-scale population-based follow-up study of familiar transmission of CHD with a particular focus on adoptees. This study uses the Swedish Multigenerational register that includes all adoptees born in Sweden from 1932 or after, linked to their biological as well as their adoptive parents. The large size of the study population allows for a robust calculation of risk estimates. The study had two aims: 1) to examine the risk of CHD in adopted men and women with at least one biological parent affected by CHD, and 2) to examine the risk of CHD in adopted men and women with at least one adoptive parent affected by CHD. The comparative control groups consisted of adopted men or women without a biological parent affected by CHD (first aim), and adopted men or women without an adoptive parent affected by CHD (second aim).

METHODS

MigMed Research Database

Data used in this study were retrieved from the MigMed Database, located at the Center for Primary Health Care Research at Lund University. MigMed is a single, comprehensive database that has been constructed using several national Swedish data registers, including the Total Population Register, the Multigeneration Register, and the Swedish Hospital Discharge Register (1973 through 2008) [21-23].

Information from the various registers in the database is linked at the individual level via the national 10-digit civic registration number assigned to each person in Sweden for his or her lifetime. Prior to inclusion in the MigMed Database, civic registration numbers were replaced by serial numbers to ensure the anonymity of all individuals.

Because the database contains information from the Multigeneration Register, it is possible to link more than 10 million index persons (persons born in or after 1932) with their parents. From these linked databases, we were able to identify our study population of 80,214 Swedish born adoptees who were linked to their biological parents as well as to their adoptive parents. It was possible to link 84% of the total population of adoptees to their biological as well as their adoptive parents. The analyses were limited to Swedish-born individuals because first-generation immigrants cannot be linked to their biological parents outside Sweden.

CHD Predictor and Outcome Variables

The predictor variable was first hospitalization for non-fatal CHD during the study period (1973 through 2008) for either the biological or adoptee parents. The outcome variable was first hospitalization for non-fatal CHD during the same time period for adoptees. The 8th, 9th,

and 10th revision of the *International Classification of Diseases* (ICD-8, ICD-9 and ICD-10) were used to identify these cases. The following ICD codes were included: 410 to 414 (ICD-8 and ICD-9) and I20 to I25 (ICD-10).

ICD 8 and 9

410: acute cardiac infarction

411: other acute and subacute forms of CHD

412: old cardiac infarction

413: angina pectoris

414: other forms of chronic CHD

ICD 10

I20: angina pectoris

I21: acute cardiac infarction

I22: reinfarction (within 4 weeks)

I23: complications due to acute cardiac infarction

I24: other acute forms of CHD

I25: chronic CHD

We also performed an additional analysis of fatal CHD only as an outcome variable.

Explanatory variables

Adoptee's age at first hospital admission for CHD (<50, 50-59, or ≥ 60 years) was included as one of the explanatory variables in the analysis. Income was used as the indicator of socioeconomic status (divided into three groups based on the income level registered by the taxation authorities), and included as socioeconomic factors are strongly related to CHD [24-28]. Study time period was divided into five-year intervals (from 1973-2008) and Geographic region of residence was divided into large cities (with a population of more than 200 000, i.e.,

Stockholm, Gothenburg, and Malmö), Southern Sweden, and Northern Sweden. Time period and region were included in the analysis to adjust for possible differences in hospitalization rates over time and across regions. We also adjusted for hospitalization for the following conditions that represent established CHD risk factors: Hospitalization for hypertension (ICD-8 and ICD-9: codes 401–404; ICD-10: codes I10–I14); hospitalization for hyperlipidemia (ICD-8: code 279; ICD-9: code 272; ICD-10: code E78); and hospitalization for diabetes mellitus (ICD-8 and ICD-9: code 250; ICD-10: code E10-E14).

Statistical Analysis

Person years were calculated for adoptees from the start of the follow-up on January 1, 1973, until the first hospital admission for CHD, death, emigration, or the end of the study on December 31, 2008. Age-specific incidence rates (defined as first hospitalization rates during the study period) were calculated for the entire follow-up period. The results are shown as standardized incidence ratios (SIRs) with 95% confidence intervals (CI) assuming a Poisson distribution [29]. The European standard population is a notional population that is commonly used to standardize rates and this standard population was used in the calculations (http://www.wmpho.org.uk/localprofiles/metadata.aspx?id=META_EUROSTD, accessed Feb 26, 2011). SIRs were calculated for sex, age group, income, time period, region and hospitalization for hypertension, hyperlipidemia, and diabetes. Familial risks were calculated for adoptees with at least one biological or adoptive parent affected by CHD, compared with adoptees whose biological or adoptive parents were not affected by CHD.

The SIRs for were calculated as the ratio of the observed to the expected number of cases using the indirect standardization method, as specified:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

Where $O = \sum o_j$ denotes the total observed number of cases in the study group; E^* is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group to the stratum-specific person-year (n_j) experience of the study group. o_j represents the observed cases that the cohort subjects contribute to the jth stratum and J represents the strata defined by the cross-classification of various adjustment variables.

For comparison, we also calculated Cox regression models; results were almost identical.

Ethics

The study was approved by the Ethics committee at the Karolinska Institute, Stockholm, Sweden.

Sources of funding

Funding was provided by the Swedish Research Council (VR), and the Swedish Council for Working Life and Social Research (FAS). The funding was independent of the design and conduct of the study. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Of the 80,214 adoptees, there were 3,410 who had a first hospitalization for CHD during the study period (1973 through 2008) (Table 1a). The age-adjusted CHD rates were higher among both men and women with at least one biological parent with CHD. Overall, the CHD rates were 242.5 among adoptees with at least one biological parent with CHD compared with 165.2 per 100,000 person years among adoptees without a biological parent with CHD. Table 1b shows the distribution of the entire population of adoptees by sex and income and stratified by CHD in biological and adoptive parents (yes/no).

The SIRs for CHD in adopted men and women with at least one biological parent with CHD compared with adopted men or women without a biological parent with CHD are shown in Table 2. The overall SIR for men and women with at least one biological parent with CHD were 1.58 (95% CI 1.45-1.72) and 1.39 (95% CI 1.21-1.60), respectively, after adjustment for age at first hospitalization for CHD, income, study time period, geographic region of residence and hospitalization for hypertension, hyperlipidemia, and diabetes. When both the biological father and the biological mother had CHD, the overall SIR among adopted men and women was 2.93 (95% CI 2.20-3.82, cases = 54), (data not shown in tables). The magnitude of the SIRs tended to be stronger in the younger age groups and decline with age.

The SIRs for CHD in adopted men and women with at least one adoptive parent with CHD compared with adopted men or women without an adoptive parent with CHD are shown in Table 3. In contrast to the increased SIRs among adoptees with at least one biological parent with CHD, the overall SIRs for adoptees with at least one adoptive parent with CHD were very close to the reference (1.00), after adjustment for age at first hospitalization for CHD, income, study time period, geographic region of residence and hospitalization for hypertension, hyperlipidemia, and diabetes. When both the adoptive father

and the adoptive mother had CHD the overall SIR among adopted men and women was not significant (SIR = 1.14, 95% CI 0.90-1.43, cases = 76), (data not shown in tables).

Results from additional analyses (data not shown in tables)

For comparison, we also performed an analysis that excluded adoptees and was restricted to the rest of the Swedish population born in or after 1932, i.e. offspring that had grown up with their biological parents. The men and women with at least one biological parent with CHD had an overall SIR of 1.45 (95% CI = 1.43-1.46).

We performed an additional analyses of the association between premature parental CHD (<55 years in father or <65 years in mother) and CHD in the adoptee. The association between premature parental CHD in the biological parent and CHD in the adoptee was stronger (overall SIR = 2.23, 95% CI = 1.90-2.59) than the association between non-premature CHD in the biological parent and CHD in the adoptee (overall SIR = 1.40, 95% CI = 1.29-1.52). No association was found between premature parental CHD in the adoptive parent and CHD in the adoptee.

We also performed an additional analysis including fatal CHD only as the outcome variable and the results were almost identical.

Discussion

This follow-up study of 80,214 Swedish adoptees linked to both their biological and adoptive parents shows that men and women with at least one biological parent with CHD were 1.4 to 1.6 times more likely to have CHD than adoptees without a biological parent with CHD. In contrast, men and women with at least one adoptive parent with CHD were not at increased risk of the disease. This was the case even among those adoptees where both the adoptive mother and the adoptive father had been diagnosed with CHD.

Although it is well established that genetic factors contribute to the risk of CHD, our findings that genetic factors seem to be more strongly related to the familiar transmission of CHD than family environmental factors represent a new contribution. The novelty lies in the potential to disentangle the contributions of genetic versus family environmental factors in the familiar transmission of CHD because adoptees do not share the same family environment as their biological parents. While our findings are new, they are partly in agreement with a 1988 study of premature death in adult adoptees [30] but partly contradict previous related research that has shown an association between social networks and obesity, a well-established risk factor for CHD [19] .

The importance of family history on the development of CHD has been shown in previous studies that have been conducted with biological parents and offspring [1-10]. For example, data from the Framingham Study showed that a family history of parental death from CHD was associated with a 29% increased risk for CHD [5]. The Physicians' Health Study and the Women's Health Study showed that a parental history of myocardial infarction was associated with increased relative risks of cardiovascular disease. Relative risks varied between 1.15 and 2.05 and was higher if both parents were affected [6]. Another study from the U.S. that included only men found that paternal history of myocardial infarction was related

to an increased risk of coronary artery surgery [8]. In contrast, a cohort study from Glasgow found no differential effects between mothers and fathers on the intergenerational transmission of CHD [9].

In addition to genetic factors, there are other potential mechanisms that could explain the biological transmission of CHD to offspring. For example, maternal transmission of CHD could partly be mediated through the intrauterine environment. The Barker Fetal Origin Hypothesis suggests that low birth weight resulting from fetal malnutrition is associated with CHD [31,32]. Maternal factors, which determine the mother's own risk for CHD, are also factors that are related to an adverse intrauterine environment [33]. Previous research has shown that maternal transmission of CHD is stronger than paternal transmission [10]

Strengths and limitations

One important strength of the present study is the use of validated hospital admission data. The validity of the hospital diagnoses for CHD was considered to be high in an evaluation performed by the National Board of Health and Welfare [34]. Another advantage is that the use of hospital diagnoses allows for the elimination of any recall bias of parent's CHD. Individual recall and self-report bias is otherwise a common problem in many case-control studies and other studies on familiar transmission of CHD that rely on self-report [1-4,6,8,9]. Self-report bias is likely to be especially problematic in adoptee studies because many adoptees have no knowledge of the health status of their biological parents. The unique Swedish Population Registers are highly complete with very few missing data. For example, data on individual income were 98.8% complete. Finally, the use of a personal identification number made it possible to track each individual in the different data registers, which implied that there were no losses to follow-up.

A potential limitation of this study is the lack of comprehensive information on individual risk factors for CHD, although we did include hospitalization for hypertension, hyperlipidemia and diabetes as covariates in the analysis. Previous studies have firmly established associations between CHD and the following risk factors: hypertension, diabetes, elevated blood cholesterol, obesity, physical inactivity, tobacco use, and a poor diet [24,35-37]. However, as the partial lack of information on individual risk factors most likely affected the biological and adoptive parents and the different subcategories of adoptees (adoptees with biological or adoptive parents with CHD and adoptees without biological or adoptive parents with CHD) to an equal extent, it is likely that the nature of this potential bias is non-differential. In addition, some previous studies have been able to adjust for several CHD risk factors and have demonstrated that parental CHD is an independent risk factor for CHD in offspring [6,7]. The results were also adjusted for income as the indicator of socioeconomic status, which in turn is strongly associated with the primary risk factors for CHD. The lack of out-patient data was partly compensated by the long study period of 36 years, which increased the probability of detecting CHD cases in the population in the hospital records. Non-paternity is a potential bias in studies of familiar transmission. Adoptee studies include non-paternity as well as non-maternity that may result from hidden adoptions: that is, when a child is never told he or she was adopted. Our study, however, had a minimum of this potential bias because all adoptions in Sweden are registered in a nationwide database. Children might also have been adopted by their biological relatives. This scenario would, however, imply a problem only if we would have found a transmission of CHD from adoptive parents to their offspring, which was not the case. Another limitation is that we had no information about what age the adoption took place although it is likely that most adoptions occurred in infancy or early childhood. Finally, adoptive parents were older than biological parents; this difference was significant for both mothers and fathers. However, this would most likely bias

the results toward the null hypothesis as adoptive parents had a longer time on average to develop CHD than biological parents, in which case the reported SIRs in this analysis would have underestimated the true effect sizes.

Conclusions

The findings of the present study of the entire Swedish population of adoptees (born in or after 1932) show that genetic/biological factors are strongly related to CHD whereas family environmental factors do not appear to play an important role in the familiar transmission of CHD. These findings represent new knowledge that is applicable for the entire population, i.e. not only the population of adoptees. A stronger emphasis on familial history may be needed in order to apply appropriate preventive measures of CHD among individuals with a positive familial history because environmental factors can be modified in contrast to genetic factors. These findings also demonstrate the importance of continuing the search for specific genes and possible interactions between genes-genes and genes-environment that are related to the development of CHD.

Conflicts of Interest and Financial Disclosures

There are no conflicts of interest among the authors.

Specific author contributions

The first author of the manuscript had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

KS: conception and design, acquisition of data, and interpretation of data; and drafting the article and revising it critically for important intellectual content.

MW: conception and design, interpretation of data, and revising the article critically for important intellectual content.

XL: analysis and interpretation of data, and revising the article critically for important intellectual content.

JJ: analysis and interpretation of data, and revising the article critically for important intellectual content.

KH: conception and design, interpretation of data, and revising the article critically for important intellectual content.

JS: conception and design, acquisition of data, and interpretation of data; and revising the article critically for important intellectual content.

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Table 1a. Population size, number of cases and age-adjusted hospitalization rates (per 100,000 person years) of coronary heart disease (CHD) in adoptees born in or after 1932. Sweden, follow-up between January 1, 1973, and December 31, 2008.

	Men		Women		Total	
	No.	Rate	No.	Rate	No.	Rate
Population, all adoptees	39,933		40,281		80,214	
Cases of CHD among adoptees	2,408	265.3	1,002	99.9	3,410	175.2
CHD in biological parents						
Yes	548	309.2	201	180.0	749	242.5
No	1,860	254.5	801	91.9	2,661	165.2
CHD in adoptive parents						
Yes	735	263.7	274	82.2	1,009	162.8
No	1,673	266.3	728	106.8	2,401	179.7

Table 1b: Distribution by sex and income of the entire population of adoptees (n = 80,214 individuals), stratified by CHD in biological and adoptive parents (yes/no).

	CHD in biological parents		CHD in adoptive parents	
	Yes	No	Yes	No
Sex				
Men	7280	32653	11121	28812
Women	7382	32899	10855	29426
Income				
Low	3316	17526	4757	16085
Medium	7825	31816	11766	27875
High	3521	16210	5453	14278

Table 2. SIRs in adoptees with at least one biological parent with coronary heart disease (CHD) compared with adoptees without a biological parent with CHD. Sweden, follow-up between January 1, 1973, and December 31, 2008.

Adoptee's age at	Men				Women				Total			
first hospitalization	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
<50	196	**1.54**	**1.33**	**1.77**	55	1.30	0.98	1.70	251	**1.48**	**1.30**	**1.67**
50-59	246	**1.44**	**1.27**	**1.64**	89	1.15	0.93	1.42	335	**1.35**	**1.21**	**1.51**
≥ 60	106	1.14	0.94	1.38	57	1.22	0.92	1.58	163	**1.17**	**1.00**	**1.36**
All	548	**1.40**	**1.29**	**1.53**	201	**1.21**	**1.05**	**1.39**	749	**1.35**	**1.25**	**1.45**

SIR, standardized incidence ratio. CI, confidence interval.

Bold type indicates statistical significance as the 95% CI does not include 1.00.

Table 3. SIRs in adoptees with at least one adoptive parent with coronary heart disease (CHD) compared with adoptees without an adoptive parent with CHD. Sweden, follow-up between January 1, 1973, and December 31, 2008.

Adoptee's age at	Men				Women				Total			
first hospitalization	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
<50	213	0.97	0.84	1.11	65	0.84	0.65	1.07	278	0.94	0.83	1.05
50-59	317	0.91	0.81	1.02	122	0.95	0.79	1.14	439	0.92	0.84	1.01
≥ 60	205	0.95	0.83	1.09	87	**0.73**	**0.59**	**0.91**	292	**0.88**	**0.78**	**0.98**
All	735	0.94	0.87	1.01	274	**0.84**	**0.75**	**0.95**	1009	**0.91**	**0.86**	**0.97**

SIR, standardized incidence ratio. CI, confidence interval.

Bold type indicates statistical significance as the 95% CI does not include 1.00.