NATIONWIDE FAMILY STUDIES OF CARDIOVASCULAR DISEASES - CLINICAL AND GENETIC IMPLICATIONS OF FAMILY HISTORY

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ABSTRACT

Studies of family history (FH) have long been used to estimate the heritability of cardiovascular diseases (CVDs). Genome-wide association studies (GWAS) of several CVDs, such as coronary heart disease (CHD), stroke, aortic aneurysm (AA), atrial fibrillation (AF), and venous thromboembolism (VTE), have found several novel gene loci and have revealed new biological mechanisms. However, most of the heritability for common CVDs remains to be discovered. Studies of FH will continue to be the easiest way to measure the inherited and non-genetic component of a CVD, as FH represents the sum of interactions between environmental and genetic factors. Many past FH studies of CVDs were hampered by recall and selection bias, small study sizes, retrospective case-control study designs, and a lack of follow-up data. Large nationwide register-based follow-up studies of FH have become possible in countries such as Sweden, Denmark, and Iceland. For instance, nationwide family studies of CVDs such as CHD, stroke, AA, AF, and VTE have been published. Such nationwide family studies may be very helpful for the planning of genetic studies to identify the missing heritability of CVDs. Moreover, reliable estimates of the familial risks of CVDs may be helpful for clinical risk assessment. In this article, the design, methodology, results, clinical and genetic implications, and pros and cons of nationwide FH studies are reviewed. The focus is on studies based on Swedish healthcare data. New findings from these studies will be summarised, and future opportunities will be presented.

Keywords: Cardiovascular disease, coronary heart disease, stroke, venous thromboembolism, genetics.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death and disability in the world.[1] Of the 17.3 million deaths from CVDs in 2008, coronary heart disease (CHD) was responsible for 7.3 million and stroke for 6.2 million.[1] All common CVDs are complex diseases where both environmental and genetic factors are important in the pathogenesis.[2] Genome-wide association studies (GWAS) have uncovered new genetic loci, not only for CHD, myocardial infarction (MI) and stroke, but also for other CVDs such as aortic aneurysm (AA), atrial fibrillation (AF), heart failure (HF), and venous thromboembolism (VTE).[2] VTE is the third most common CVD after CHD and stroke, and its most severe complication, pulmonary embolism (PE), is potentially lethal.[3] Though GWAS have been successful in identifying a vast number of novel genetic variants associated with CVDs, most new variants are weak and have so far not turned out to be clinically useful for risk assessment.[4] For common CVDs, only a fraction of the estimated heritability is explained by the new variants.[4] The term 'missing heritability' has therefore been introduced.[4] Several explanations for the missing heritability have been proposed, such as the presence of multiple undetected variants of smaller effect, rarer but possibly strong variants that are poorly detected by available genotyping arrays, structural variants, low power to detect gene–gene interactions, and inflated familial risks due to inadequate accounting for sharing of environments by relatives.[4]

At the moment, clinicians usually have to rely on the classic tool of family history (FH) in order to estimate whether a patient has an increased genetic risk of CVD.[5] However, many studies of FH are small case-control studies suffering from recall, selection, and ascertainment bias. There have been few prospective risk prediction studies.[5] Moreover, FH is not a binary trait.[6] The risk associated with FH is dependent on age, genetic distance to the affected relative, and number of affected relatives.[6] However, most family studies are too small to be able to give firm estimates. Nationwide family studies using official healthcare and population registers are relatively new possibilities in countries such as Sweden, Denmark, and Iceland.[7] Nationwide FH studies may not only be important for clinical risk assessment but may also be helpful for the planning of genetic studies aimed at discovering the cause(s) of missing heritability. An overview of these nationwide family studies will be presented, with a special focus on Sweden.

METHODS FOR STUDYING FAMILIAL RISKS

A central theme in genetic epidemiology is the study of diseases within families.[8] Familial aggregation of a trait is a necessary, though insufficient, condition to infer the importance of genetic susceptibility.[9] As well as genes, environmental and cultural influences may also aggregate in families, leading to familial clustering and increased familial risks.[9,10] However, without familial aggregation, which indicates a small genetic contribution to a particular disease, a further hunt for a genetic cause might not be successful.[6] If the phenotype is binary, the familial relative risk (FRR, i.e. the ratio of the risks of those with and without an FH) may be expressed as a recurrence risk ratio (λ), which is the prevalence of the disease in relatives with affected relatives divided by the prevalence in the general population.[6] Another way to express the FRR of binary phenotypes is the SIR, (standardised incidence ratio i.e. incidence rate of the disease in individuals with an FH compared with the incidence rate in those without an FH).[10] SIR is the standard method for cohort studies.[10] Other commonly used measures of the FRR are the odds ratio (OR, the ratio of the odds of disease of those with and without an FH) and hazard ratio (HR, the ratio of rates).[10] In the present review, the term FRR will be used to describe all these measures, although ORs and HRs are ratios and not relative risks.

An FRR of around two in first-degree relatives is seen in many complex diseases.[6] Although an FRR of two might appear modest, it suggests that uncovering the familial aggregation might be worthwhile.[6] However, the non-genetic contribution to familial aggregation might often be underestimated, and familial aggregation of a disease is no guarantee of success in finding causative gene variants. There are different methods for trying to disentangle genetic and environmental influences.[6,9,10] A commonly used design is the twin study. Identical twins (monozygotic) inherit identical genetic material, while dizygotic twins have the same genetic relationship as full siblings (50% shared genes) but share the same environmental factors. Another powerful method is to study risk in biological relatives of affected adoptees compared to control adoptees, because adoption creates a separation between an individual´s biological and environmental influences.[9] Studying FRRs in spouses is a way to estimate the effect of adult shared family environment (Table 1).[9-11] FRRs in spouses are low for many, but not all, complex diseases in the Swedish population. A high spousal risk suggests important familial non-genetic influences. Thus, a low spousal risk is a prerequisite for estimating biologically relevant (i.e. genetic) familial risks using nationwide registers (Table 1).[12-20] Studies of half-siblings can also help to disentangle genetic and non-genetic contributions to FH.[21] Moreover, an increased risk in second and third-degree relatives supports the interpretation that genetic factors influence familial aggregation, since individuals outside the nuclear family are less likely to have shared the same environmental exposure(s).[22] Another possibility to test for the extent of environmental sharing is to calculate FRRs according to age difference between siblings.[16] Large age differences indicate less shared environment and vice versa.

Nordic Twin and Adoption Studies

The Nordic countries have twin registers that may be used to estimate the heritability of disease.[23-26] Many important studies on CVDs have come from these registers.[27-35] While few adoption studies have been published, a recent nationwide Swedish study of 80,214 adoptees found that the familial transmission of CHD risk is related to CHD in biological parents and not in adoptive parents.[36] Though twin and adoption studies are very important for disentangling genetic and environmental influences, they are of little help for clinical risk assessment for the vast majority of patients. This report will focus on nationwide studies of the importance of family history in first, second, and third-degree relatives, which becomes possible after a nation becomes a cohort, as has happened in Sweden.[37]

Table 1. Swedish nationwide familial relative risks (FRRs) for several cardiovascular diseases (CVDs) and type 2 diabetes mellitus and Graves' disease, among spouses.

	Spouse FRR (95% CI)
CHD[12]	1.05 (1.05-1.06)
Ischaemic stroke[13]	1.06 (1.00–1.13)*
Haemorrhagic stroke[13]	0.99 (0.85–1.15)*
Subarachnoid haemorrhage[14]	1.06 (0.64–1.66)
Atrial fibrillation[15]	1.16 (1.13–1.19)
VTE[16]	1.07 (1.04–1.10)
PE[17]	1.09 (1.03–1.14)
Varicose veins[18]	1.69 (1.59–1.80)*
Type 2 diabetes mellitus[19]	1.32 (1.29–1.35)
Graves' disease[20]	2.75 (1.93–3.82)

*For wives

FRR for ischaemic stroke in husbands 1.08 (1.02–1.14)

FRR for haemorrhagic stroke in husbands 1.01 (0.86–1.17)

FRR for varicose veins in husbands 1.68 (1.58–1.79)

Nationwide Swedish Registers

Denmark,[37] Iceland,[38] and Sweden[39,40] have nationwide registries that allow individuals to be linked to their relatives. Central to performing nationwide studies in Sweden is the unique 10-digit personal identity number (PIN) assigned to each resident of Sweden for life.[41] These PINs are used to link individual data from several registers, such as the Total Population Register, the Swedish Multi-generation Register, and Swedish Inpatient Register (see below). The Multi-generation Register allows an individual to be linked to his/her relatives.[39] Statistic Sweden and the National Board of Health and Welfare maintain these registers. The most commonly used registers are listed below:

1. The Swedish Multi-generation Register contains information on the family relationships[39,40,42] of more than 9 million individuals born from 1932 onwards, with data on mothers for 97% of index persons and on fathers for 95% of index persons.

2. The Total Population Register (TPR)[42,43] contains data on place of residence, sex, age, civil status, place of birth, citizenship, immigration, and relations (married couples, offspring–parents).

3. The Swedish National Census Register[42] contains data from coordinated nationwide censuses that were completed in Sweden every fifth year between 1960 and 1990. For each individual, the register includes information on their PIN, occupation, residence, and educational level.

4. The Swedish Inpatient Register (IPR), also called the Hospital Discharge Register, contains all hospital diagnoses for all people in Sweden from 1987 onwards.[44-46] Between 1964 and 1987, the coverage was incomplete but increased steadily (1964: 6%; 1972: 36%; 1982: 71%; 1984: 86%). Every record includes the main discharge diagnosis. The validity in the IPR is generally 85-95% for the primary diagnosis.[44-46] For several CVDs, such as MI, stroke, VTE, AF, and HF the validity is around 95% for the primary diagnosis.[47-51] There is also good agreement between the Swedish National Registry for Vascular Surgery (Swedvasc) and the IPR regarding the validity for carotid, infrainguinal bypass, and abdominal AA repair (93.4%, 93.0%, and 93.1%, respectively).[52]

5. The Swedish Outpatient Care Register[46] holds information from all outpatient clinics in Sweden from 2001 onwards (not primary health care).

6. The Swedish Cause of Death Register contains data on cause and date of death from 1961 onwards and is fairly valid for a number of diagnoses.[53,54]

7. The Swedish Cancer Registry covers all diagnosed cancers since 1958.[55]

8. The Medical Birth Register holds information on practically all births in Sweden since 1973.[56]

9. The National Prescription Database contains data on drugs dispensed at pharmacies in Sweden since July 2005 (exposure data) to individuals receiving ambulatory care.[57]

10. The Swedish Conscript Register contains medical data on all Swedish conscripts born in, or since 1946, including data on height, weight, blood pressure, vision, hearing, fitness, and muscle strength, as well as psychological test results.[58]

Besides these registers there are a large number of nationwide quality registers, such as the Swedvasc,[52] the SWEDEHEART register (formerly RIKS-HIA),[59] and the Swedish stroke register (Riks-Stroke).[60]

NATIONWIDE FAMILY STUDIES

Coronary Heart Disease

GWAS have identified a large number of genetic variants with small effects on CHD.[61] However, the clinical utility of the novel GWAS findings remains uncertain.[61] A large number of family studies of CHD and MI risk in first-degree relatives have also been published (reviewed by Banerjee).[5] According to Banerjee, more long-term prospective studies are needed to determine the generalisability of FH and to quantify the risk associated with FH in asymptomatic individuals.[5] Nationwide family studies may help to fill these gaps. An example is a recent nationwide Danish study of MI in Danish citizens diagnosed in 1978-2010.[62] A high FRR (rate ratio: 4.30, 95% confidence interval, CI 3.53–5.23) was found in siblings. For offspring, the risk was dependent on the sex of the affected parent: the FRR was 2.40 (95% CI 2.20–2.60) for offspring of maternal cases and 1.98 (95% CI 1.98–2.09) for offspring of paternal cases. This supports two previous studies that found a higher parent-offspring transmission of CHD for maternal cases.[63,64] The cause of this maternal preponderance is unclear and a number of mechanisms have been suggested.[63,64] FH was also a prognostic predictor of survival in patients with MI, according to a Swedish nationwide family study by Ekberg et al.[65]

Another nationwide family study from Sweden found very high familial risks of hospitalisation and death from CHD in families with two or more affected siblings.[12] The concordant SIRs (same disease in proband and case) for hospitalised CHD patients are presented in Table 2, for individuals with one affected sibling (SIR=1.49), two affected siblings (SIR=6.92), and an affected spouse (SIR=1.05).[12] The SIR for death in individuals with two affected siblings was 7.31 (95% CI 4.76–11.19). Thus, having multiple affected siblings is a strong predictor for CHD, with relative risk that is higher than those for many established genetic and acquired risk factors.

Another possibility is to study whether different diseases share familial susceptibility.[66] Pleiotropy occurs when one gene influences multiple phenotypic traits. A mutation in a pleiotropic gene may have an effect on several traits simultaneously. It has been hypothesised that genetic variants affecting the coagulation system and the risk of VTE are also involved in the pathogenesis of CHD,[67] but previous association studies of haemostatic factors and CHD have produced varying results.[67] Zöller et al.[66] therefore determined whether CHD and VTE share familial susceptibility. However, VTE and CHD (and MI) do not aggregate in families to any great degree in Sweden (Table 2).[66] The FFR for biological relatives were similar to those for spouses. Table 2 also shows nationwide concordant (i.e same disease in proband and case) risks from a study of CHD in families with multiple affected siblings[12] and from a nationwide study of VTE.[16] The high concordant and low discordant (i.e different disease in proband and case) risks in biological relatives make it clear that CHD and VTE have completely different familial and genetic causes.[12,16,66] Thus, CHD and VTE are unlikely to share strong genetic risk factors.

Table 2. Concordant (same disease)[12,16] and discordant (different disease)[66] risks of hospitalisation for CHD and VTE among siblings and spouses.

Family history of CHD	CHD SIR (95% CI)	VTE SIR (95% CI)
One affected sibling	1.49 (1.04–2.13)	1.09 (0.75–1.59)
Two affected siblings	6.92 (4.77–10.03)	1.08 (0.72–1.62)
Affected spouse	1.05 (1.05–1.06)	1.03 (1.02–1.03)
Family history of VTE		
One affected sibling	1.18 (0.82–1.71)	2.27 (1.54–3.35)
Two affected siblings	0.70 (0.45–1.09)	51.87 (31.47–85.00)
Affected spouse	1.02 (1.01–1.03)	1.07 (1.04–1.10)

Stroke

Epidemiologic evidence supports a genetic predisposition to stroke.[68] Recent advances, primarily using the GWAS approach, are helping researchers to identify novel stroke genes.[68] However, the genetic variants identified so far are not currently useful in predicting risks for the individual patient. There is therefore, a need for large prospective nationwide family studies of stroke.[69] A Swedish nationwide study by Kasiman et al.[70] determined the FRR for ischaemic stroke in siblings. The overall familial risk of incident ischaemic stroke was significantly increased among all siblings (FRR=1.61, 95% CI 1.48–1.75). The familial risk was higher in full siblings (FRR=1.64, 95% CI 1.50–1.81) than in half-siblings (FRR=1.41, 95% CI 1.10–1.82). Familial risk of early ischaemic stroke was especially high in the siblings of individuals with stroke at a young age (FRR=1.94, 95% CI 1.41-2.67). Another nationwide family study by Sundquist et al.[13] found that ischaemic and haemorrhagic stroke do not share familial susceptibility, which suggests that familial and genetic factors for these two entities are not identical.

It has been hypothesised that genetic variants affecting the coagulation system and the risk of VTE also are involved in the pathogenesis of ischaemic stroke.[71-73] This is in analogy with the above hypothesis that thrombotic coagulation variants and CHD are associated.[67] Previous association studies of haemostatic factors and ischaemic stroke have produced varying results (just as for haemostatic variants and CHD).[67,71-73] However, a recent nationwide study found only weak familial associations between VTE and ischaemic stroke in first-degree relatives.[74] The same strengths of the associations were observed among spouses, suggesting a non-genetic contribution to the observed weak familial associations. Thus, not only CHD[66] but also ischaemic stroke is unlikely to share strong genetic risk factors with VTE.[74]

Nationwide family studies have also found an increased familial risk of subarachnoid haemorrhage in siblings and in multiplex families.[14,75]

Aortic Aneurysm

AA is a complex disease with known environmental influences, such as smoking.[76] A number of studies have shown that AA is frequently familial.[76] The pathobiology of AA is complex and largely unsolved. GWAS are now being used to elucidate the genetic basis of AA.[76] Two nationwide family studies from Sweden have been published.[77,78] The risk of AA was very high in the siblings of individuals diagnosed with AA before 50 years of age (SIR=19.69).[77] This suggests that relatives of individuals with AA should be screened for AA.[77]

Table 3. Familial relative risks (FRRs) for several CVDs (atrial fibrillation, CHD, VTE, varicose veins) and non-CVDs (type 2 diabetes mellitus, Graves' disease, and breast cancer) according to number of affected siblings.

	One affected sibling FRR (95% CI)	Two affected siblings FRR (95% CI)
CHD[12]	1.49 (1.04–2.13)	6.92 (4.77–10.03)
Atrial fibrillation[15]	2.78 (2.69–2.87)	5.72 (5.28–6.19)*
VTE[16]	2.27 (1.54–3.35)	51.87 (31.47–85.00)
PE[17]	2.49 (1.62–3.83)	114.29 (56.57–223.95)
Varicose veins[18]	2.86 (2.76–2.97)	5.88 (5.28–6.53)*
Type 2 diabetes mellitus[19]	2.77 (1.87–4.11)	36.86 (20.96–64.10)
Graves' disease[20]	5.04 (3.03–8.33)	310.34 (99.49–836.75)*

*Two or more affected siblings

Atrial Fibrillation

A large number of genetics studies of AF have been performed, and many genetic variants have been identified. However, much of the heritability of AF is still missing.[79] Arnar et al.[80] performed the first nationwide study of AF in Iceland and presented evidence of an important genetic influence on the familial risks of AF in an extended family study of first to fifth-degree relatives. High familial risks were also found in a Danish study of lone AF (LAF).[81] A Swedish nationwide family study determined the risk of AF in families with multiple affected relatives and found high familial risks in multiplex sibling families (Table 3).[15]

The relevance of family history of AF for prediction of recurrent hospitalisation for AF was previously unknown. A Swedish family study[82] determined that the familial risk of recurrent hospitalisation for LAF was 1.23 (95% CI 1.17–1.30) for individuals with affected parents, and 1.30 (95% CI 1.22–1.38) for those with affected siblings. The risk of recurrent hospitalisation for LAF in individuals with two affected parents was 1.65 (95% CI 1.44–1.90). FH was a stronger predictor for recurrent AF in younger age groups. The familial risk for recurrent hospitalisation for LAF was, however, much lower than the risk for initial LAF hospitalisation (FRR=2.08, 95% CI 2.02–2.15 for offspring and FRR=3.23, 95% CI 3.08–3.39 for siblings), suggesting that familial and possibly genetic influences are more important for initial hospitalisation for LAF than for recurrent hospitalisation for LAF.[82]

Venous Thromboembolism

Familial thrombophilia—aggregation of VTE in families—has been associated with deficiencies of antithrombin, protein C and protein S, resistance to activated protein C (APC resistance or presence of factor V Leiden=rs6025), and the prothrombin 20210G to A variant (=rs1799963).[83] However, the predictive value of FH for finding any of these defects is low.[84] The association between FH in first-degree relatives and risk of VTE has been assessed in a few case-control studies.[84-86] The FRRs in these studies of FH of VTE ranged from 2.2 to 2.7.[84-86] No family studies that used follow-up data had been published until Swedish and Danish nationwide studies assessed the familial risk in siblings, with very similar results (overall FRR=2.45 and 3.08, respectively).[16,87] The Swedish study also determined the risk of VTE when two siblings were affected and found a very high risk of VTE (FRR=51.87) (Table 2).[16] The risk among spouses was low (Table 1). Another study determined the familial risks in the offspring of affected parents (overall FRR=2.00) (Table 4).[88] When both parents were affected, the FRR was 3.97 (Table 4).[88] One Swedish study showed that VT of the legs, PE, and other types of VTE (OVTE) all share familial susceptibility.[89] Moreover, even unusual forms of VTE have increased familial risks.[90]

In another study, the familial age-specific and sex-specific risks were determined separately for VT, PE, and OVTE (Figure 1).[91] All manifestations of VTE were highly age-dependent. Family history was important for VT, PE, and OVTE at all studied ages (0-76 years), except for the first 10 years of life.[91] This is in line with the literature showing that VTE rarely occurs before 10 years of age in families with thrombophilia.[92,93] In small children, VTE is very rare and is often associated with the presence of multiple risk factors simultaneously.[94] An increased risk of fatal PE was detected in individuals with an FH of PE (FRR=1.76, 95% CI 1.38–2.21).[17] Especially high risks of PE were observed in families with multiple affected siblings (Table 3).[17] Another nationwide Swedish study by Kristinsson et al.[95] found that FH of VTE is a predictor of VTE even for patients with multiple myeloma.

Recently the familial risks of VTE in first, second, and third-degree relatives were estimated.[96] The familial OR for VTE among first-degree relatives was 2.49 in siblings (95% CI 2.40–2.58), 2.65 in offspring (95% CI 2.50–2.80), 2.09 in parents (95% CI 2.03–2.15). Among second-degree relatives, the familial OR was 2.34 in paternal half-siblings (95% CI 2.00–2.73), and 1.52 in maternal half-siblings, and 1.69 in nieces/nephews (95% CI 1.57–1.82). Among cousins (third-degree relatives), the risk was 1.47 (95% CI 1.33–1.64). Familial clustering was stronger at young ages. According to data from the national censuses, the majority of maternal half-siblings in Sweden were registered as living in the same home as each other (83%); only 3% of paternal half-siblings lived in the same home.[97] The high risk in paternal half-siblings therefore suggests a strong genetic contribution.[96] Moreover, the increased VTE risk among second and third-degree relatives indicates that the genetic component of the familial clustering of VTE is important. Familial clustering was slightly stronger for males compared with females, but was only significant for siblings and parents of probands.[96] The stronger clustering among males is in agreement with a Danish twin study,[29] but its cause is unclear.

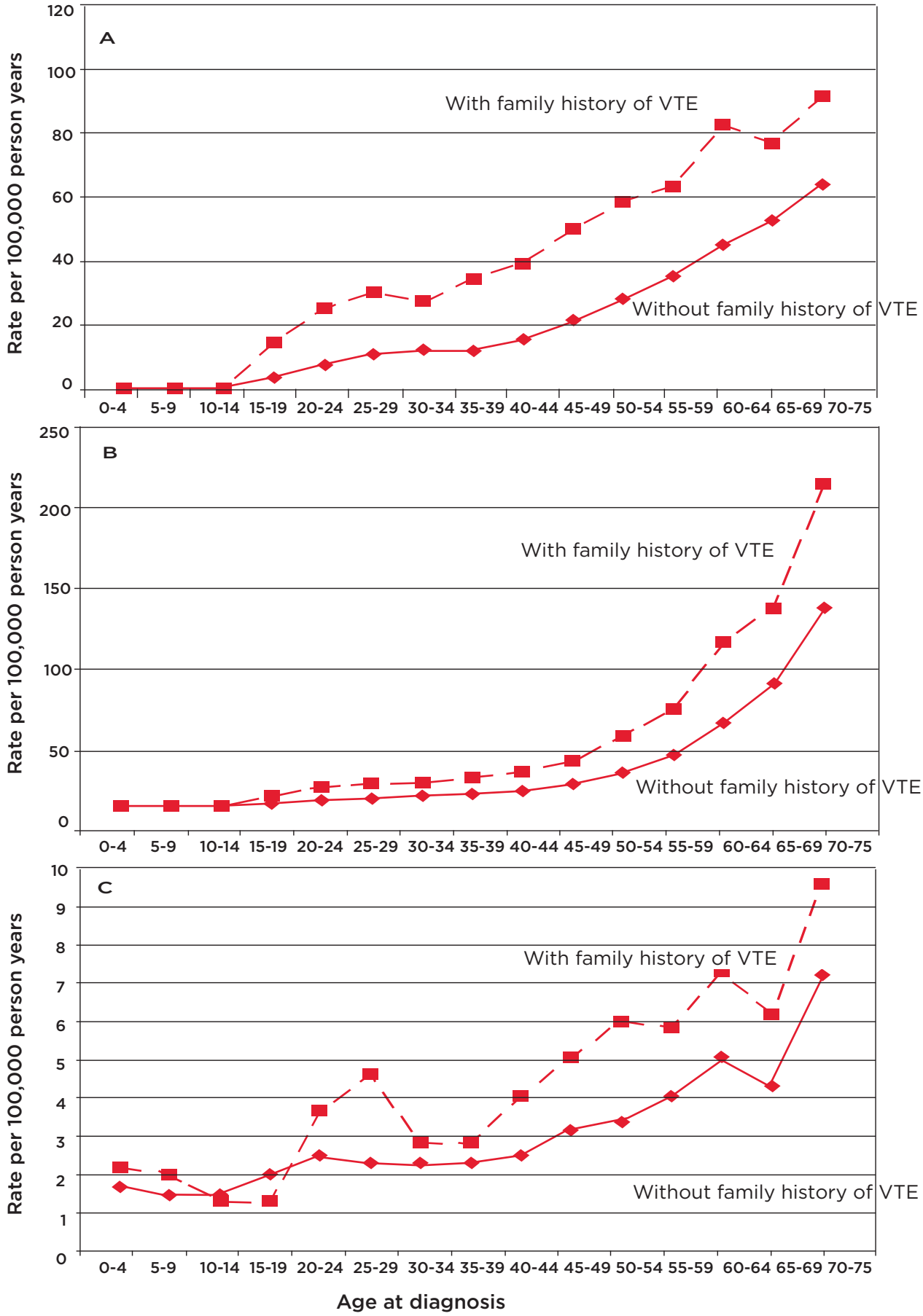

Figure 1. Age-specific incidence rates for (A) venous thrombosis of the lower extremities (VT), (B) pulmonary embolism (PE), and (C) other types of venous thromboembolism (OVTE), by family history of VTE in parents and siblings.

Reproduced from Zöller et al.[91] with permission from Thrombosis and Haemostasis (Schattauer GmbH).

Table 4. Familial relative risks (FRRs) for several CVDs (atrial fibrillation, VTE, PE, varicose veins) and non-CVDs (type 2 diabetes mellitus and Graves' disease) in offspring according to number of affected parents.

	One affected parent FRR (95% CI)	Both parents affected FRR (95% CI)
Atrial fibrillation[15]	1.95 (1.89–2.00)	3.60 (3.30–3.92)
VTE[16]	2.00 (1.94-2.05)*	3.97 (3.40–4.61)
PE[17]	1.95 (1.85–2.06)	2.74 (1.70–4.20)
Varicose veins[18]	2.39 (2.32–2.46)	5.52 (4.77–6.36)
Type 2 diabetes mellitus[19]	2.03 (1.98–2.08)	5.35 (4.56–6.24)
Graves' disease[20]	4.49 (3.82–5.24)*	4.51 (0.43–16.60)**

*One or both affected parents
**Both parents plus a sibling affected

Families with Multiple Affected Relatives (Multiplex Families)

Family history of CVD is especially important for individuals with multiple affected siblings (Table 3). Having two affected siblings was associated with high risks of AF, CHD, VTE, PE, and varicose veins (Table 3). The FRRs for VTE and PE were exceptionally high (Table 3), compared to the risks in offspring with two affected parents (Table 4). Few other nationwide studies have reported familial risks for complex diseases in families with multiple affected siblings. However, for diabetes mellitus type 2 and Graves' disease, similarly high risks in multiplex sibling families were reported (Table 3).[19,20] For AF and varicose veins, the differences between the multiplex familial risks for siblings and offspring were not so large (Tables 3 and 4). Although higher risks among multiplex families have been described for complex diseases,[6] the cause is unclear and could be different for different diseases. Among families with familial thrombophilia, interactions between rare genetic disorders, such as protein S, protein C or antithrombin deficiencies, and the more common rs6025 and rs1799963, variants have been described.[93,98-100] A 50-100 times increased risk of VTE was estimated for individuals with both protein S deficiency and the rs6025 variant.[100] Homozygosity for the rs6025 variant is also associated with a very high risk of VTE.[101] It remains to be determined whether such strong gene-gene interactions exist for other complex diseases with high multiplex sibling risks.

DISCUSSION

The nationwide family studies presented in this review serve as a good example of the possibilities that exist when a whole country becomes a cohort.[37] Nationwide health databases are invaluable for probing contradictions raised by smaller studies and for following disease progression.[102] Sweden, like Denmark, has become a dream for epidemiologists.[102] Recent nationwide family studies with long-term follow-up have shown that FH of several CVDs is a strong and clinical relevant risk factor for being affected by CVD. This sets the focus on the clinical importance of FH. It is obvious from these nationwide studies that FH of CVDs is not a binary trait; it is dependent on age, sex, number of affected relatives, and the relatedness of the affected relatives. Precise estimates of relative and absolute risks in relation to age, sex, relatedness, and number of affected relatives can be determined. Nationwide family studies may also help in the planning of genetic studies. The high risk of disease (Table 3) in multiplex sibling families suggest that selecting individuals with two or more affected siblings will increase the chance of identifying new variants considerably.

Nationwide family studies in the GWAS era

Though GWAS have been successful in identifying a large number of new genetic variants associated with CVDs, most novel variants are weak and have so far not been clinically useful for risk assessment.[4] Family history studies remain the most accessible way of measuring the hereditary component of a

disease and they represent the overall interaction between environmental, epigenetic and genetic factors.[4] It is therefore possible that even when sequencing a patient's genome may cost less than $1,000, family history will remain highly relevant for years to come.[103]

Pros and cons

The major advantage of nationwide studies is their large size. Moreover, nationwide family studies may be conducted cheaply and quickly as long-term follow-up data already exist for the entire population. Data in several Swedish registers are almost complete.[40] Thus, it is easy to test hypotheses and generate new ideas using nationwide registers, and to predict long-term follow-up risks.

There are important limitations of the Swedish databases. There is no information about individual risk factors such as smoking, weight, height, body mass index, blood pressure, and cholesterol levels. However, there is access to socioeconomic data on income, education, and occupation, which correlate with lifestyle factors.[11,42] Adjusting for socioeconomic data and comorbidities could help to diminish confounding by these factors. However, as in any observational cohort study, residual confounding remains a concern in nationwide studies.[104] Another limitation is the lack of information on the diagnostic methods used. However, many validation studies have been performed, and the validity for many CVDs is high in the Swedish Inpatient Register.[44-52]

A further limitation is that the nationwide studies are restricted to Sweden, Denmark, or Iceland and mainly reflect familial risks in the Swedish, Danish or Icelandic population, respectively. However, the Swedish population is, for instance, genetically closely related to German[105] and British[106] people and the results from Swedish nationwide family studies are likely to be valid for many individuals of Caucasian origin in Europe and the USA. However, Sweden, like many countries, has experienced dramatic demographic changes due to increasing global migration. Today, approximately 20% of all people living in Sweden are first or second-generation immigrants.[107] This large immigrant population, together with the nationwide health and sociodemographic data available, provides a unique opportunity to study the risk of many diseases among first and second-generation immigrants from multiple countries and regions around the world, and to compare the risk of different diseases in these groups with that in two corresponding generations of native-born Swedes.[108] For instance, a nationwide study of VTE risk in first and second-generation immigrants found that the country of birth affects the risk of VTE in several immigrant groups.[108]

Ethical considerations

The data in the nationwide registers mentioned here are anonymised and, as for all other research, ethics codes and laws regulate the research process.[109] Still, there is an ongoing debate about using official registers for research.[37] The majority of the Swedish population has a positive attitude towards genetic research.[110] This positive attitude is driven by altruism, and depends on the public being well informed and having trust in experts and institutions.[110]

Future opportunities

Linking nationwide quality registers[52,59,60] and data from large population-based cohort studies with the Multi-generation Register would allow incorporation of both FH and traditional risk factors in risk assessment models. Another possibility is linking nationwide registers, including the Multi-generation Register, with large biobanks. For instance, neonatal blood collected on filter paper (Guthrie cards) for screening purposes is routinely stored for decades in the Swedish National Phenylketonuria (PKU) register.[111] This could allow for nationwide genetic linkage studies with coverage of a whole country.

CONCLUSIONS

Nationwide registries are enormous and unique scientific assets and research on them will benefit society in general. Nationwide family studies have contributed much new knowledge, and may continue to be an important source of new knowledge regarding the clinical risks and genetics of CVDs.

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