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SACCULAR INTRACRANIAL ANEURYSM DISEASE AND HYPERTENSIVE DISORDERS IN EASTERN FINLAND

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Satu Kotikoski

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ABSTRACT

Saccular intracranial aneurysms (sIAs) are pouches that form on the intracranial arteries during life and usually go unnoticed. However, a rupture of the sIA wall, the most common cause of the aneurysmal subarachnoid hemorrhage (aSAH), is a severe form of stroke. Hypertension is a well-known risk factor for the sIA disease, adding the risk of aneurysm formation and rupture. Nevertheless, among sIA patients the published data on the incidence and significance of distinct forms of hypertensive disorders, such as secondary hypertension and pregnancy-induced hypertensive disorders, remains scarce.

The aim of this thesis was to deepen the understanding of the relationship between hypertensive disorders and the sIA disease. We studied the prevalence of secondary hypertension and aneurysm characteristics in the sIA patients (Study I). We also evaluated pre-eclampsia, other pregnancy-related hypertensive disorders, and gestational diabetes in the sIA patients and matched population controls (Study II). Subsequently, we examined pre-eclampsia in the sIA patients, their female relatives, and their matched population controls, as well as the familial components of pre-eclampsia and the sIA disease (Study III).

We used the Kuopio Intracranial Aneurysm Patient and Family Database that contains all cases of unruptured and ruptured sIA patients admitted to the Kuopio University Hospital (KUH) from a defined Eastern Finnish catchment population since 1980. Parents, children, siblings, nieces, and nephews of the sIA patients were identified using the Finnish personal identification codes, and random controls (3 for each sIA patient in the Kuopio Intracranial Aneurysm Patient and Family Database) were matched for age, gender, and birthplace and selected by the Digital and Population Data Services Agency. Registry data, including hospital diagnoses, prescribed medications, and causes of death, was obtained from the nationwide registries for the sIA patients, relatives, and controls.

Study I comprised a cohort of 2,704 sIA patients. We identified 2,029 (75%) sIA patients with hypertension, 208 (10%) of whom had secondary hypertension. The number of sIAs associated with secondary hypertension in a multivariate logistic regression analysis of 1,561 aSAH patients.

In study II, the frequency of pre-eclampsia was higher (13%) in the 169 sIA patients than in the 324 population controls (5%) as was the frequency of other hypertensive disorders during pregnancy (19% versus 10%), while the frequency of gestational diabetes was similar in these groups. The patients with pre-eclampsia were more likely to have irregular-shaped sIAs.

A total of 265 sIA patients, their 393 female relatives, and 546 population controls formed the basic study cohort in Study III. Pre-eclampsia was identified in 11% of the sIA patients, 9% of the daughters, 6% the of sisters, 6% of the nieces, and 6% of the matched controls. Additionally, 1,895 female sIA patients and the 12,141 female relatives were screened for pre-eclampsia diagnoses, resulting in 68 sIA patients and 375 relatives and including 32 families with familial pre-eclampsia. In seven of the 32 families, familial sIA disease and familial pre-eclampsia co-occurred.

In conclusion, the causes of secondary hypertension were identified in the sIA patients with hypertension. Secondary hypertension was associated with multiple sIAs in the aSAH patients, which may represent the effect of persistent and severe hypertension on aneurysm formation. Pre-eclampsia was significantly more frequent in the sIA patients than in their population

controls. Our results suggest that pre-eclampsia may be a novel risk factor for the sIA disease and may indicate instability in the yet unruptured sIA wall.

Keywords: saccular intracranial aneurysm, subarachnoid hemorrhage, hypertension, pre-eclampsia, familial predisposition

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TIIVISTELMÄ

Sakkulaariset intrakraniaaliset aneurysmat (sIA) ovat muutoksia, joita muodostuu aivojen pinnalla oleviin valtimoihin elämän aikana. Yleensä nämä eivät tule ilmi, mutta puhjetessaan sIA aiheuttaa aneurysmaattisen subaraknoidaalivuodon (aSAV), joka on vakava aivoverenkiertohäiriön muoto. Verenpainetauti on hyvin tunnistettu riskitekijä sIA-taudille, lisäten sekä aneurysman muodostumisen että vuodon riskiä. Kuitenkaan erilaisten verenpainetautimuotojen kuten sekundaarisen verenpainetaudin tai raskaudenaikaisten verenpainesairauksien ilmenemistä tai erityispiirteitä sIA-potilailla ei ole tutkittu.

Tämä väitöskirja koostuu kolmesta osatyöstä ja sen tavoite oli syventää ymmärrystä verenpainesairauksien ja sIA-taudin välisestä yhteydestä. Sekundaarisen verenpainetaudin yleisyyttä ja ominaisuuksia sIA-potilailla tutkittiin (Tutkimus I). Lisäksi tutkittiin pre-eklampsian, muiden raskauden aikaisten verenpainesairauksien ja raskausdiabeteksen yleisyyttä ja erityispiirteitä sIA-potilailla ja verrokeilla (Tutkimus II). Lopuksi tutkittiin pre-eklampsiaa sIA-potilailla, heidän naispuolisilla sukulaisillaan sekä verrokeillaan ja lisäksi tarkasteltiin familiaalista pre-eklampsiaa ja sIA-tautia (Tutkimus III).

Tutkimuksessa käytettiin Kuopion aneurysmatietokantaa, joka sisältää kaikki sIA- ja aSAV-potilaat, jotka ovat tulleet hoitoon Kuopion yliopistolliseen sairaalaan vuodesta 1980 lähtien. sIA-potilaiden lapset, sisarukset, vanhemmat sekä sisarusten lapset tunnistettiin käyttämällä henkilötunnuksia. Digi- ja väestötietovirasto haki jokaiselle rekisterin sIA-potilaalle yhteensä kolme sattumanvaraista verrokkihenkilöä, jotka vastaavat sIA-potilaita iältään, sukupuoleltaan ja syntymäpaikaltaan. Potilaiden, sukulaisten ja verrokkien sairaaladiagnoosit, reseptilääkkeiden ostotiedot ja kuolinsyytiedot on haettu kansallisista rekistereistä.

Tutkimus I käsitti 2704 sIA-potilaan kohortin, jossa todettiin 2029 verenpainetautia sairastavaa potilasta, joista 208 (10 %) potilaalla oli sekundaarinen verenpainetauti. Logistisessa regressioanalyysissä, joka käsitti 1561 aSAV potilasta, sekundaarinen verenpainetauti assosioitui aneurysmien lukumäärän kanssa.

Tutkimuksessa II pre-eklampsian esiintyvyys oli korkeampi (13 %) 169 sIA-potilaassa kuin 324 verrokilla (5 %) kuten myös muiden raskauden aikaisten verenpainesairauksien kohdalla (19 % vrt. 10 %), kun taas raskausdiabetes oli yhtä yleistä molemmissa ryhmissä. Pre-eklampsiapotilailla epäsäännöllisen muotoiset aneurysmat olivat yleisempiä kuin muilla sIA-potilailla.

Tutkimuksessa III 265 sIA-potilasta, heidän 393 naispuolista sukulaistaan ja 546 verrokkia muodostivat tutkimuskohortin. Pre-eklampsia havaittiin 11 %:lla sIA-naisista, 9 %:lla tyttäristä, 6 %:lla siskoista, 6 %:lla sisaruksentytöistä ja 6 %:lla verrokeista. Lisäksi 1895 naispuolista sIA-potilasta ja 12 141 naissukulaista tutkittiin pre-eklampsiadiagnoosien osalta, jolloin 68 sIA-potilasta ja 375 sukulaista tunnistettiin. Heistä löydettiin 32 perhettä, joissa esiintyi familiaalista pre-eklampsiaa, ja näistä seitsemässä perheessä familiaalinen sIA-tauti ja familiaalinen pre-eklampsia esiintyivät samanaikaisesti.

Yhteenvetona, sekundaarisen verenpainetaudin taustasyyt selvitettiin sIA-potilailla ja sen todettiin olevan yhteydessä multippeleihin aneurysmiin aSAV-potilailla, mikä voi ilmentää vakavan verenpainetaudin vaikutusta aneurysmien muodostumisessa. Pre-eklampsia oli merkittävästi yleisempi sIA-potilailla kuin heidän verrokeillaan. Tuloksemme osoittavat, että pre-

eklampsia on mahdollisesti itsenäinen riskitekijä sIA-taudille ja voi merkitä epävakautta vielä puhkeamattomassa aneurysmaseinämässä.

Avainsanat: sakkulaarinen kallonsisäinen aneurysma, subaraknoidaalivuoto, lukinkalvonalainen verenvuoto, verenpainetauti, pre-eklampsia, familiaalinen tautialtistus

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LIST OF ORIGINAL PUBLICATIONS

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CONTENTS

ABBREVIATIONS

ACoA	Anterior communicating artery
ACOG	American College of Obstetricians and Gynecologists
ADPKD	Autosomal dominant polycystic kidney disease
aSAH	Aneurysmal subarachnoid hemorrhage
ATC	Anatomic Therapeutic Chemical
BAbif	Basilar artery bifurcation
BMI	Body Mass Index
CI	Confidence Interval
COX	Cyclooxygenase
GWAS	Genome-wide association study/studies
HR	Hazard ratio
IA	Intracranial aneurysm
ICA	Internal carotid artery
ICD	International Statistical Classification of Diseases and Related Health Problems
KUH	Kuopio University Hospital
Mbif	Middle cerebral artery bifurcation
OR	Odds Ratio

PlGF	Placental growth factor
RAAS	Renin-angiotensin-aldosterone system
SAH	Subarachnoid hemorrhage
sFlt-1	Soluble fms-like tyrosine kinase 1
sIA	Saccular intracranial aneurysm
SNP	Single nucleotide polymorphism
UsIA	Unruptured saccular intracranial aneurysm
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

Saccular intracranial aneurysms (sIAs) are balloon-like pouches that form at the branching points of intracranial extracerebral arteries and affect approximately 3% of the general population.[1] Fusiform aneurysms, another subtype of intracranial aneurysms (IAs), are relatively rare, accounting for about 2% of all IAs in the Eastern Finnish population.[2] The majority of sIAs never rupture and therefore remain undetected during life. Unruptured saccular intracranial aneurysms (UsIAs) are typically incidental findings on neuroimaging for other reasons or during screening of sIA families. The sIA wall rupture is the most common cause of an aneurysmal subarachnoid hemorrhage (aSAH), the symptoms of which include sudden headache, neck stiffness, nausea, seizures, loss of consciousness, and focal neurological symptoms.[3] It is a devastating form of stroke that primarily affects the relatively young working age population and causes significant mortality and neurological morbidity.[4–8] As a complex trait, the known risk factors for the sIA disease include both acquired risk factors and genomic variants: female sex, age, smoking, hypertension, excess alcohol consumption, autosomal dominant polycystic kidney disease (ADPKD), and a family history of sIAs.[9–12] At least 10% of the sIA patients belong to sIA families.[5,13] The largest international genome-wide association study (GWAS) to date identified 17 risk loci for sIAs.[14]

Arterial hypertension is categorized as essential and secondary hypertension. Essential hypertension has no specific cause, while secondary hypertension is a form of hypertension in which an underlying cause can be identified. Secondary hypertension is characterized by resistant and severe hypertension and caused by a variety of heterogenous causes including renal and renovascular diseases, primary aldosteronism, and obstructive sleep apnea, as well as other rare causes.[15,16] Hypertension, along with smoking, is an established risk factor for aneurysm formation and rupture.[9,10] However, published data on the occurrence and significance of secondary hypertension in patients with the sIA disease remains limited. Nevertheless, more severe and treatment-

resistant hypertension is associated with an elevated risk of stroke, including aSAH.[17]

Hypertensive disorders of pregnancy including pre-eclampsia, pre-existing hypertension, and new gestational hypertension affect approximately 10% pregnancies.[18,19] Pre-eclampsia is a serious multisystem disorder characterized by hypertension and proteinuria that complicates approximately 3% to 5% of pregnancies.[20] Worldwide, pre-eclampsia is one of the leading causes of maternal mortality,[21,22] with increased long-term risk of hypertension and cardiovascular diseases.[23–25] Pre-eclampsia is an established risk factor for stroke, both during pregnancy,[26] later in life,[23,24] and in the adult offspring.[27] Nonetheless, the significance of pre-eclampsia on subsequent sIA formation or rupture has not been verified.

The pathophysiology of pre-eclampsia has not been conclusively resolved, but the current consensus holds that pre-eclampsia has a clear familial propensity as both maternal and paternal factors increase the risk,[28–30] and the familial linkage associates with more severe forms of pre-eclampsia.[29,31] Recent GWAS of pre-eclampsia have identified several genomic variants, most of which have been associated with hypertension.[32,33] Possible relation between familial sIA disease and familial pre-eclampsia has not been described in the literature.

The Kuopio Intracranial Aneurysm Patient and Family Database contains the data of all unruptured and ruptured sIAs admitted to the Kuopio University Hospital (KUH) from a defined KUH catchment area in Eastern Finland since 1980. We have studied the phenotype,[34] familial forms of the sIA disease,[13,35] outcome,[4–7,36,37] genomics of the sIA disease,[38] and various concomitant diseases, including hypertension,[10] diabetes,[39] ADPKD,[11,40] and cancer.[41]

In the present thesis, the aim was to explore the associations between the sIA disease and hypertensive disorders to deepen the understanding of the sIA disease and explore novel risk factors. This could allow a more personalized risk assessment and the development of more individualized treatment strategies for the sIA patients in the future.

2 REVIEW OF THE LITERATURE

2.1 SACCULAR INTRACRANIAL ANEURYSM DISEASE

sIAs are pouches that commonly form around the circle of Willis, at the forks of the intracranial extracerebral arteries. Some aneurysms rupture, causing aSAH, the third most frequent type of stroke.[3]

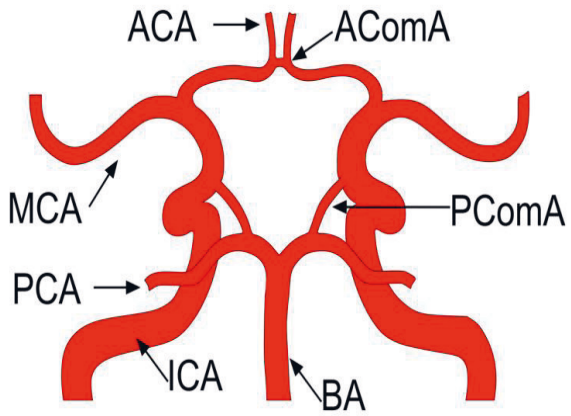

Figure 1. Illustration of the circle of Willis. Abbreviations: (ACA = anterior cerebral artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery; BA = basilar artery; AComA = anterior communicating artery; PComA = posterior communicating artery. Reprinted from Shen et al.[42] CC-BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

2.1.1 Epidemiology of saccular intracranial aneurysm disease

Globally, the overall prevalence of UsIAs is reported to be 3.2% in a population comprising 50% men and with a mean age of 50 years.[1] Of the sIA patients, 20% present with multiple sIAs.[43,44] The cumulative incidence of de novo sIAs was 0.23% per patient-year in an Eastern Finnish cohort,[45] while the estimated cumulative incidence in a meta-analysis of nearly 15,000 patients with intracranial aneurysms was 0.3% per patient-year.[46]

The overall crude incidence of aSAH is 7.9 with 95% Confidence Interval (CI) being 6.9-9.0 per 100,000 person-years globally.[47] The incidence of aSAH has previously been reported to be higher in Finland,[48,49] but the rates are decreasing, possibly due to a reduced prevalence of smoking and untreated hypertension.[50,51] An estimated incidence of aSAH in Finland is 8.9 per 100,000 person-years, which is comparable to the global rates.[50] However, there appears to be considerable regional variation in the incidence of aSAH in Finland, with a higher incidence in Eastern and Northern Finland.[52]

2.1.2 Aneurysmal subarachnoid hemorrhage

aSAH primarily affects the working age population. However, as the population ages, the average age of aSAH patients is now closer to 60 years.[50] aSAH is a notable cause of mortality and morbidity, with up to a quarter of the aSAH patients perishing in emergency rooms or before reaching the hospital.[50,53] The mortality rate of the aSAH patients reaching the hospital alive was approximately 30% at 12 months in the Finnish cohorts,[4,54] which is substantially similar to international studies.[55,56] The patients that survive the initial bleed may suffer from a rebleed or develop delayed cerebral ischemia, vasospasm, increased intracranial pressure, seizures, or hydrocephalus.[57] Among survivors, the cognitive function is impaired in approximately half of the patients in the long term.[8] aSAH patients have an increased risk of developing epilepsy along with psychiatric disorders.[7,36,58] Recently, a four-step model of progress of aSAH was proposed, in which inherited genetic factors would serve as the first one or two steps with subsequent involvement of acquired lifestyle and other clinical conditions, epigenetics, and mutations.[59]

2.1.3 Risk factors for saccular intracranial aneurysm formation

sIAs are lesions that form during life and occur rarely in adolescence.[60] Age is an acknowledged risk factor for UsIAs.[1] Other non-modifiable risk factors include female sex, family history of the sIA disease, and ADPKD.[1,11]

Smoking is the most essential behavioral risk factor for the sIA disease, as it increases the risk of aneurysm formation to at least threefold.[60] Smoking might generate an altered inflammatory response in the circulatory system and fragility of blood vessels, as nicotine, among many other harmful additives in cigarettes, has been recorded to influence endothelial and vascular smooth muscle cells and to induce extracellular matrix degradation.[61]

Hypertension is highly present among sIA patients, and it has been demonstrated to increase the risk of aneurysm formation.[10] Hypertension causes endothelial dysfunction and vascular inflammation, which might thereby predispose to sIA formation.[62,63] Along with endothelial damage, occlusion of the vasa vasorum and disturbance in the synthesis of collagen and elastin have been suggested as potential underlying mechanisms.[64] Hypertension and smoking appear to have a synergetic effect on aneurysm formation, increasing the Odds Ratio (OR) to 8.3, compared with an OR of 3.0 for current smoking alone and 2.9 for hypertension alone.[65]

Interestingly, periodontitis and gingival inflammation may induce sIA formation.[66] One of the proposed theories is transient bacteremia involved in periodontal infection, which might eventually modify the systemic inflammatory response.[67]

2.1.4 Risk factors for aneurysmal subarachnoid hemorrhage

Regardless of geographical location, the incidence of aSAH increases with age, but it is more pronounced in women over the age of 55 years.[47] Familial UsIAs are more prone to rupture compared to sporadic UsIAs.[68] aSAH occurs at a younger age and from smaller sIAs in patients with ADPKD.[11] Smoking is a substantial risk factor for aSAH and has a dose-dependent and cumulative effect on the risk of aSAH.[69] Hypertension appears to increase the risk of wall rupture by two- to threefold.[9] A recent large meta-analysis showed that the prevalence of aSAH increases linearly with elevated systolic blood pressure in the general population.[17]

Heavy alcohol use is also a risk factor for aSAH,[9] possibly due to endothelial injury, oxidative stress, and hypertension.[70] Type 2 diabetes

does not increase the risk of aSAH; instead, it has been described to have an inverse association with aSAH.[9,39] There seems to be an inverse association between the Body Mass Index (BMI) and the risk of aSAH; however, smoking and hypertension may intervene the risk.[71] Periodontitis and gingival inflammation may increase the risk of aSAH.[66]

2.1.5 Saccular intracranial aneurysms in women

Female gender is a risk factor for UsIAs, with an increasing difference in gender distribution in patients over 50 years of age.[1] A gender difference has also been described in the incidence of aSAH, as younger patients with aSAH are more often men, while after the age of 55 years the incidence shifts to be higher in women.[48] A recent meta-analysis demonstrated female-to-male adjusted hazard ratio (HR) for aneurysm rupture to be 1.39 (95% CI, 1.02-1.90) with differing patient characteristics; women are older and less often smokers, have more often internal carotid artery (ICA) as an aneurysm location, and have larger aneurysms.[72] The aggregation of sIAs within families has been shown to be slightly more pronounced for women than for men.[73] The general outcome after aSAH is primarily similar in women and men.[74]

Prevalence of anatomical configurations of the circle of Willis has been reported to differ between female and male patients.[75] These differences may influence the arterial wall shear stress and lead to more serious endothelial injury.

The prevailing theory is that hormone levels also influence the risk of sIA disease, as the risk increases after the typical age of menopause, which is characterized with decreasing estrogen levels.[74] However, the precise pathophysiology has remained unclear. The use of hormone replacement therapy appears to have a protective effect against aSAH, whereas data on the use of combined oral contraceptives, parity, and age at first menstruation is inconsistent.[9,76] Women have a greater susceptibility to the damaging effects of smoking, predisposing them to aSAH,[69] possibly due to the antiestrogenic influence of smoking in women.[77]

It seems that estrogen has several protective effects that might be involved in the process of the sIA formation, including endothelial nitric oxide synthase, presence of collagen, inflammation, and oxidative stress.[74] A recent Mendelian randomization study reported that a genetic propensity to increased serum levels of sex hormone-binding globulin with consequently decreased serum levels of bioavailable testosterone adds the risk of aSAH in women,[78] conflicting with previous studies reporting an inverse connection between sex hormone-binding globulin and vascular risk factors, including ischemic stroke.[79] This underlines the distinctive pathophysiology of aSAH compared to other forms of stroke.

The incidence of pregnancy-associated stroke has increased in Finland and globally during the last decades,[80,81] while the occurrence of pregnancy-associated SAH has not considerably changed in Finland, with an unadjusted incidence of 3.2 per 100,000 deliveries.[82] The risk of aSAH is not increased during pregnancy, labor, or puerperium,[76] but pregnancy-associated SAH is related to high mortality, up to 4.1% of all pregnancy-associated in-hospital deaths according to an American study.[83] Pregnancy-associated SAH seems to be more often non-aneurysmal of origin than SAH occurring without pregnancy.[82,83] Rupture of an aneurysm is most common in the 3rd trimester,[82] when the most notable hemodynamic changes are observed in the female cardiovascular system.[84]

2.1.6 Pathogenesis of saccular intracranial aneurysms

Brain arteries contain three layers: the innermost intima interfacing the blood flow, media, and outmost adventitia. Intima comprises a monolayer of endothelial cells and an underneath extracellular matrix, where glycoproteins, proteoglycans, and elastin are allocated. The internal elastic lamina separates the intima and media. The media is primarily formed of smooth muscle cells and extracellular matrix containing collagen. Adventitia is made up of a configuration of collagen and fibroblasts.[85] There is no external elastic lamina detaching adventitia from media, as compared with e.g. aortic arteries, which together with distinctive

distribution of elastic components might lead brain arteries to vulnerability to hemodynamic stress.

The progress of the sIA formation implicates an interaction between different cellular and molecular factors, which ultimately impairs the arterial wall. It has been described that the wall shear stress is elevated in the area where sIA is formed.[86] Endothelial dysfunction and activated proinflammatory signaling are characteristic, leading to the infiltration of inflammatory cells and loss of the normal internal elastic lamina.[87] The process induces the vascular smooth muscle cells to convert into foamy phenotypes.[88] These changes generate the reconstruction of the extracellular matrix, which is accelerated by the upregulation of proinflammatory genes, and thus, elevated levels of metalloproteinases, tumor necrosis factor alpha, monocyte chemoattractant protein 1, cyclooxygenase-2 (COX-2), and interleukins.[88] Beyond the protective effects suggested in animal studies,[89–91] the role of estrogen in the pathophysiology of the sIA disease may be complex and varied.[92]

Finally, impaired vascular smooth muscle cells go through apoptosis.[88] Both hyperplasia of myointima as a compensatory mechanism and a thin hypocellular wall have been recorded present.[93] When the altered architecture of the arterial wall can no longer endure the tension inside the saccular pouch, a rupture occurs. Thus, it is plausible that larger aneurysms have been reported rupture prone.[49] Especially irregular shaped aneurysms are associated with increased risk of rupture, independent of the sIA size, which may illustrate focal weakening of the sIA wall or thrombosis on the luminal side.[94] The tendency of the sIA to grow and rupture varies by location: sIAs in the anterior cerebral arteries, posterior communicating artery, and posterior circulation have the highest risk of aSAH, and sIAs in the ICA have the lowest risk of aSAH.[49] These differences may represent different natural history.[94–96] Additionally, anatomic configurations of the circle of Willis might contribute to the sIA formation at various locations.[75,97]

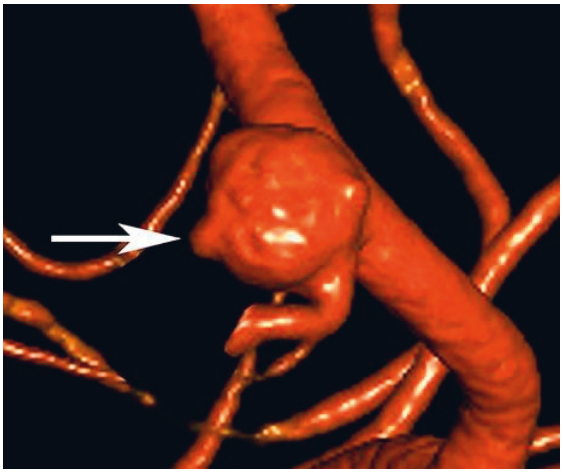

Figure 2. Saccular aneurysm with an irregular morphology. Reproduced from Samaniego et al.[98] Reprinted with permission from BMJ Publishing Group Ltd.

2.1.7 Genomics of saccular intracranial aneurysm disease

sIA disease is a complex trait, with both genomic and environmental factors modifying the risk. Some monogenic conditions have been reported to be associated with sIAs, including ADPKD, which affects 1.2% of the sIA cases.[11] Thus, the majority of the heritability is polygenic. A twin study has estimated the heritability of aSAH to be about 40%, with a relatively low concordance for both monozygotic and dizygotic twins (3.1% and 0.27%), which may represent familial aggregation of environmental risk factors.[99] sIAs are common in the offspring of couples with biparental sporadic-familial origin of the sIA disease.[35] The genetic architecture of UsIAs and ruptured sIAs appears to be remarkably similar according to studies of common variants, and these common genetic risk factors are estimated to account for more than half of the total heritability of the sIA disease.[14]

Having at least one first-degree relative with the sIA disease increases an individual's risk for UsIA by more than threefold.[1] A meta-analysis of Finnish, Dutch, and Japanese patients showed a 2.5-fold risk of aSAH in

familial UsIAs compared to sporadic UsIAs.[68] The incidence of aSAH increases with the number of relatives: if two or more first-degree relatives have had aSAH, the risk of aSAH is up to 50 times higher than without a family history.[100] Twin studies examining pairs of twins with sIAs have observed a genetic propensity for aneurysm location, as the location concordance was higher in monozygotic than dizygotic twins.[101,102] A meta-analysis of 70 Dutch, 142 Finnish, and 34 French families with familial sIA disease reported that familial aneurysms often occur and bleed in the same arterial region within families.[103] There is emerging evidence of the heritability of anatomical variations,[104] illustrating the genetic influence on vascular anatomy and aneurysm formation. Familial sIA disease associates with middle cerebral artery location, multiple aneurysms, and younger age at aSAH.[105] Hypertension and smoking are common risk factors for sIAs and often cluster in families;[106,107] still, hypertension or smoking have not been significantly associated with familial sIAs.[10,105]

Genome-wide linkage studies have described several susceptibility loci that primarily regulate the vascular endothelial function and extracellular matrix cohesion,[108] of which 19q13.3 and Xp22 have been replicated in multiple populations.[109–112] Sequencing studies among sIA families have revealed susceptibility genes, including *ADAMTS15*, *THSD1*, *ANGTL6*, *PCNT*, *ARHGEF17, RNF213*, *LOXL2*, *NFX1*, *NPNT, CBY2*, and a recent genome sequencing of three large Dutch sIA families identified six rare variants: *SYCP1*, *FMNL2*, *TBC1D2*, *ZNF782*, *CCDC180*, and *NCBP1.*[113–115] However, it has been suggested that the clinically relevant role of these rare variants may remain modest in the general sIA population,[116] a finding similar to other neurological disorders.[117,118]

Candidate gene studies have reported an association between the sIA disease and several variants, with a meta-analysis indicating significance for *COL1A2, ACE, VCAN, ENG, ELN, NOS3, IL-6,* and *HSPG2*, which are involved in the maintenance of the vascular endothelium and extracellular matrix.[108]

GWAS of sIAs have been published at an accelerating rate during the last decade.[115] The main findings from the GWAS resulting in significant loci for the sIA disease are summarized in **Table 1.** The most replicated loci include *SOX17, EDNRA,* and *CDKN2A-CDKN2B-CDKN2BAS.* The main functions of the

risk genes are involved with the regulation of the cell cycle and apoptosis, angiogenesis, blood vessel resistance, and endothelial cell function.[119–121] Several loci have common associated traits with cardiovascular disease, as well as genetic propensity for high blood pressure and smoking.[14] It has been demonstrated that the sIA-connected single nucleotide polymorphisms (SNPs) are enriched in the regulatory regions of the circle of Willis and operate on endothelial cells and fibroblasts.[122,123]

In conclusion, these findings suggest that specific genes for the complex sIA disease are unlikely to be found. Considering the genetic diversity,[124] the presence of phenocopies,[125] the interplay of genes, family, and the environment,[126–128] as well as their interferences may propose hindrance in the identification of the sIA-related genes in GWAS.

Table 1. Significant risk loci for saccular intracranial aneurysms in the genome-wide association studies.

Locus	SNP	Involved genes	References
2q23.3	rs74972714	*LYPD6*	Kurki et al. 2014 [38]
2q33.1	rs700651 rs12472355	*BOLL/PLCL1* *ANKRD44*	Bilguvar et al. 2008 [129] Kurki et al. 2014 [38]
3p14.2	rs1554600	*FHIT*	Zhou et al. 2018 [130]
4q31.22-23	rs6841581 rs6842241 rs6841581 rs58721068	*EDNRA*	Yasuno et al. 2011 [131] Low et al. 2012 [132] Bakker et al. 2020 [14] Hale et al. 2022 [133]
5q31.1	rs4705938	*SLC22A5/* *SLC22A4/P4HA2*	Bakker et al. 2020 [14]
5q31.3	rs113816216	*FSTL4*	Kurki et al. 2014 [38]
6q16.1	rs11153071	*FHL5*	Bakker et al. 2020 [14]
6q24.2	rs75018213	*EPM2A*	Kurki et al. 2014 [38]
7p21.1	rs10230207	*HDAC9*	Foroud et al. 2014 [134]

8q11.23	rs9298506 rs10958409 rs9298506 rs62516550	*SOX17*	Bilguvar et al. 2008 [129] Bilguvar et al. 2008 [129] Yasuno et al. 2010 [119] Bakker et al. 2020 [14]
9p21.3	rs1333040 rs1333040 rs6475606 rs10733376 rs1333042 rs1537373 rs4977574	*CDKN2A-CDKN2B* *CDKN2A-CDKN2B* *CDKN2B-AS1* *CDKN2B-AS1* *CDKN2B-AS1* *CDKN2B-AS1* *AL359922.1*	Bilguvar et al. 2008 [129] Yasuno et al. 2010 [119] Foroud et al. 2012 [135] Foroud et al. 2014 [134] Kurki et al. 2014 [38] Bakker et al. 2020 [14] Hale et al. 2022 [133]
10q23.33	rs11187838	*PLCE1*	Bakker et al. 2020 [14]
10q24.32	rs12413409 rs79780963	*CNNM2* *NT5C2/MARCKSL1P1*	Yasuno et al. 2010 [119] Bakker et al. 2020 [14]
11p15.5	rs2280543 rs73392700	*BET1L* *SIRT3*	Bakker et al. 2020 [14] Hale et al. 2022 [133]
12p12.2	rs11044991	*RP11-664H17.1*	Bakker et al. 2020 [14]
12q21.33	rs2681472 rs11105337	*ATP2B1*	Bakker et al. 2020 [14] Hale et al. 2022 [133]
12q22	rs7137731	*FGD6/NR2C1*	Bakker et al. 2020 [14]
13q13.1	rs9315204 rs3742321	*STARD13-KL* *STARD13*	Yasuno et al. 2010 [119] Bakker et al. 2020 [14]
15q25.1	rs8034191	*PSMA4*	Bakker et al. 2020 [14]
16q23.1	rs7184525	*BCAR1/* *RP11-252K23.2*	Bakker et al. 2020 [14]
18q11.2	rs11661542	*RBBP8*	Yasuno et al. 2010 [119] Bakker et al. 2020 [14]
20p11.23	rs4814863	*SLC24A3*	Bakker et al. 2020 [14]
22q12.1	rs39713	*MTMR3*	Bakker et al. 2020 [14]

2.1.8 Management of unruptured saccular intracranial aneurysm disease

Increasing numbers of UsIAs are discovered, especially in the aging patients, as neuroimaging has become more routinely used.[136] In particular, angiography, used in the diagnosis of both unruptured and ruptured sIAs, has become more attainable.[136] Even though the majority of sIAs will never rupture, the detection of an unruptured aneurysm often leads to worry in patients. The optimal treatment of the UsIAs is developing over time. A multidisciplinary neurovascular team is recommended to evaluate the patients' risk of rupture and risk of preventive treatment in order to avoid the devastating event of aSAH but not at the cost of losing patients' quality-adjusted life years.[137]

The PHASES score was developed based on the data of 8,382 sIA patients of six prospective cohort studies for the prediction of an aneurysm rupture risk. It comprises six key risk factors including age (70 years or older), hypertension, earlier SAH, aneurysm size, aneurysm location, and geographical area, and contingent on these factors it supplies an absolute five-year risk of rupture.[49] However, many of the acknowledged risk factors including smoking, family history of the sIA disease, and the irregular shape of the aneurysm, could not be included in the PHASES model and should be evaluated individually.[100,138,139] The most recent (2022) European Stroke Organisation Guidelines on management of UsIAs published a pooled analysis of nine prospective cohorts with an estimated one-year rupture risk of 0.81% (95% CI, 0.61-1.05).[137] The guidelines recommend preventive treatment if the evaluated five-year risk of rupture surpasses the risk of preventive treatment.[137]

There are no comprehensive recommendations on the choice of the treatment method for UsIAs, which include surgical clipping and endovascular treatment. The risk of poor outcome (modified Rankin Scale >2) at one year after the treatment varied between 3.6% and 4.2% in a randomized trial, with no significant difference between the occlusion methods.[140] According to a meta-analysis on the risk factors for treatment complications, it should be considered that female sex and wide aneurysm

neck are associated with a greater risk of complications related to endovascular treatment, whereas advanced age, anticoagulant therapy, aneurysm calcification, and posterior circulation aneurysms are associated with an elevated complication risk related to microsurgical treatment.[141] After occlusion of an unruptured aneurysm, it is advisable to perform follow-up imaging to identify potential aneurysm recurrence.[137]

With conservatively managed UsIA patients the follow-up imaging is recommended to detect aneurysm growth or change in morphology, as the absolute risk of rupture at one year after detecting aneurysm growth is estimated to be 4.3% (95% CI, 1.9-6.7).[139] Radiological follow-up with magnetic resonance angiography or computed tomography angiography is preferred, however, a definitive guidance on the imaging interval is challenging to provide, as aneurysm growth can be intermittent.[142] It has been suggested to prolong the follow-up as long as the treatment stays a possibility.[137] Treatment of hypertension with a target blood pressure level under 130/80 mmHg and smoking cessation are recommended.[137]

Radiological screening for aneurysms is recommended in individuals with at least two affected first-degree relatives.[143,144] Around 10% of the screened relatives are discovered with the sIA disease at the first screening.[145,146] However, the detection rate remains as high as 5% for every follow-up imaging, despite previous normal radiological imaging.[146] Familial screening has been reported to be cost-effective for 20 to 80 year old relatives with a screening interval of seven years.[147]

To date, no preventive drug therapy against aSAH has been recommended in the treatment guidelines.[137] However, there is emerging evidence on the role of acetylsalicylic acid and statins.[148] The indication that acetylsalicylic acid might reduce the risk of rupture, whereas COX-2 inhibitors and anti-thrombotic drugs might elevate the risk, suggests differing underlying mechanisms, other than COX-signaling or strictly anti-thrombotic effect.[148] Statins and medication for type 2 diabetes seem to have pleiotropic effects by shifting the expression of endothelial nitric oxide synthase and inhibiting inflammatory response.[149,150] Metformin has been demonstrated to regulate the phenotype switching of vascular smooth muscle cells and may therefore prevent sIA formation and

rupture.[151] Interestingly, acetylsalicylic acid and statins may have a synergetic protective influence on the sIA disease progression.[152] European Stroke Organisation Guidelines on stroke in women do not recommend initiating hormone replacement therapy in postmenopausal women in order to decrease the risk of hemorrhagic stroke.[81]

2.1.9 Management of aneurysmal subarachnoid hemorrhage

aSAH requires treatment in a neurointensive care unit by a dedicated multidisciplinary neurovascular team. The aim of the management is to prevent further damage caused by rebleeding, hydrocephalus, increased intracranial pressure, ischemic brain injury, seizures, and systemic complications.[57,143] In the event of aSAH, the contemplation on eliminating the aneurysm slightly differs from the cases with UsIAs. The most recent (2023) American Heart Association Guidelines on the management of aSAH recommend aneurysm occlusion within 24 hours of symptom onset to lower the risk of rebleeding.[57] Coiling is favored in patients with posterior circulation aSAH. However, clipping may be considered a preferred treatment method for aSAH patients under 40 years of age to achieve a more durable cure and a better outcome.[57] After occlusion of a ruptured aneurysm, it is recommended to conduct follow-up imaging to detect potential aneurysm recurrence or regrowth.[57]

2.2 SECONDARY HYPERTENSION

Arterial hypertension, defined as elevated blood pressure values, is the most prevalent chronic disease universally and is a significant risk factor for other cardiovascular diseases, stroke, chronic kidney disease, and excess morbidity and mortality.[153] The condition is often asymptomatic, therefore, identification varies globally from around 40% to 70%.[154] During the past decades, the mean blood pressure levels have decreased in Finland, including Eastern Finland.[51] After the beginning of the 21st century, the decreasing trend has abated or even stopped, and hypertension is still very frequent in Finland.[51] The FinHealth 2017 Survey found that 58% men and 48% women aged ≥30 years had hypertension, but only half of the individuals with hypertension (men 52% and 56% women) used antihypertensive medication. Among the men and women with antihypertensive medication use, 43% and 42%, had their blood pressure levels within the target levels.[155]

Arterial hypertension is classified as primary i.e., essential hypertension and secondary hypertension. Essential hypertension is multifactorial and often occurs with family history of hypertension, while secondary hypertension is defined as arterial hypertension due to an identifiable cause.[153]

2.2.1 Epidemiology and causes of secondary hypertension

Earlier, secondary hypertension has been reported to comprise about 5% to 10% of all hypertension cases.[156–159] Later, obstructive sleep apnea has been recognized as a secondary cause of hypertension.[160] Therefore, more recent estimates that have included sleep apnea as an underlying etiology and used a systematic protocol for detecting secondary hypertension have reported much higher incidence, around 40% among patients with non-treatment resistant hypertension,[161] and up to 70% among patients with resistant or severe hypertension.[161–163] Moreover, the incidence of secondary hypertension is contingent on the age distribution and the incidence of treatment-resistant or severe hypertension in the study

population.[161,164] Among all hypertensive patients, the estimated prevalence of obstructive sleep apnea is >5-15%, renal parenchymal disease 1.6-8.0%, renal artery stenosis 1-8%, primary aldosteronism 1.4-10%, thyroid disease 1-2%, Cushing's syndrome 0.5%, pheochromocytoma 0.2-0.5%, and coarctation of the aorta <1%, with higher prevalence among patients with resistant hypertension.[15] Nevertheless, secondary hypertension is an underdiagnosed condition.[163,165] The incidence of patients diagnosed with obstructive sleep apnea has increased rapidly in Finland during the last decades,[166] however, a great number of undiagnosed patients still presumably remains. Primary aldosteronism, one of the leading causes of secondary hypertension, is thus far notably underdiagnosed.[165] All possible causes of secondary hypertension were searched from the literature and are listed in the **Table 2.**[16,167–173] Systemic diseases are listed separately because, in addition to renal mechanisms,[168] they have been described to cause systemic hypertension through renovascular involvement and independent of renal function.[167,174]

Table 2. Possible causes of secondary hypertension.

Etiologies (see references [16,167–173])
Renal diseases
Polycystic kidney disease
Diabetic nephropathy
Glomerulonephritis
Tubulointerstitial nephritis
Nephritic or nephrotic syndrome
Chronic pyelonephritis
Hydronephrosis
Renal tumors
Renovascular diseases
Atherosclerosis of renal artery
Fibromuscular dysplasia
Obstructive sleep apnea
Coarctation of the aorta
Endocrine disorders
Hyperaldosteronism
Pheochromocytoma and adrenal gland tumors
Hypothyroidism
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Acromegaly
Systemic diseases
Large-vessel vasculitis
Medium-vessel vasculitis
ANCA-associated vasculitis
Immune complex and other vasculitis
Systemic lupus erythematosus
Systemic sclerosis
Sjögren’s syndrome
Amyloidosis
Carcinoid syndrome
Neurological causes
Dysautonomia
Guillain-Barre syndrome
Quadriplegia

Genetic disorders
Liddle's syndrome
Gordon syndrome
Geller syndrome
Familial hyperaldosteronism types 1-4
Autonomous aldosterone-producing adenomas
Primary aldosteronism, seizures, and neurologic abnormalities (PASNA) syndrome
11beta-hydroxylase deficiency
17alpha-hydroxylase deficiency
Apparent mineralocorticoid excess syndrome
Hypertension and brachydactyly syndrome
PPGL (TCA, HIF1/2, PI3K/AKT, RAS/MAPK)
Medications
Nonsteroidal anti-inflammatory medication
Glucocorticoids
Stimulants
Sympathomimetics
Antidepressants
Antipsychotics
Immunosuppressive agents
Inhibitors of vascular endothelial growth factor
Tyrosine kinase inhibitors
Erythropoietin
Sex hormones
Lifestyle factors
Alcohol consumption
Caffeine consumption
Licorice consumption
Salt consumption

2.2.2 Diagnosis of secondary hypertension

Hypertension definition slightly differs between different guidelines. According to the 2017 American College of Cardiology/American Heart Association clinical practice guidelines for management of high blood pressure, repeated office or out-of-office systolic blood pressure values ≥130 mmHg and/or diastolic blood pressure values ≥80 mmHg are used to diagnose hypertension.[175] Contrarily, in the newly reported 2023 European

Society of Hypertension Guidelines for the management of arterial hypertension, hypertension is defined as repeated office systolic blood pressure values ≥140 mmHg and/or diastolic blood pressure values ≥90 mmHg or repeated out-of-office systolic blood pressure values ≥135 mmHg and/or diastolic blood pressure values ≥85 mmHg.[176] To date, Finnish Current Care Guidelines are in line with these European Society of Hypertension Guidelines for diagnosing and treating hypertension.[177]

The most recent European Society of Hypertension Guidelines for the management of arterial hypertension state that it is not reasonable nor cost-effective to screen every hypertensive patient for a secondary cause. However, there are specific patient characteristics that indicate an increased probability of secondary hypertension.[15,176] These include young age, as secondary causes should be screened in patients with hypertension of any degree as a child, in patients under 30 years of age without obesity or family history of hypertension, and in patients under 40 years of age with blood pressure levels ≥160/100 mmHg. Additionally, a rapid onset of hypertension in previously normotensive patients or a sudden relapse in hypertension management among patients with once adequately controlled blood pressure is suggestive. Further, suspecting features comprise resistant hypertension, hypertensive emergency, severe blood pressure levels (≥180/110 mmHg), and hypertension-induced organ damage. In addition, secondary hypertension should be suspected if laboratory tests suggest an endocrine form of hypertension or clinical features of the patient indicate a secondary cause.[15,176] Furthermore, attention to the patient's age might be utilized to identify the most probable causes of secondary hypertension.[156,164] The diagnostic criteria for all underlying causes of secondary hypertension will not be described here due to the scope of this dissertation.

2.2.3 Pathogenesis of secondary hypertension

Pathogenesis of hypertension is based on a complicated interplay of lifestyle factors, environmental influence and genomic aspects.[153] Involvement with the renin-angiotensin-aldosterone system (RAAS) and

autonomic system are well illustrated,[178,179] as well as other vascular resistance controlling systems, such as natriuretic peptides and nitric oxide synthase.[180,181] The endothelial function has been described fundamental, including the roles of oxidative stress, inflammation, and immunology.[181,182] Eventually, these pathophysiological changes lead to arterial reconstruction, including decreased lumen diameter and vascular stiffness, as well as an alteration in the cardiac structure and function.[153]

Secondary hypertension is often characterized with severe and resistant hypertension which may augment these pathophysiological findings. Distinct secondary causes have differing pathogenesis depending on the cause. Regarding renal diseases, hypertension can both predispose to renal impairment and be a consequence of a renal disease, creating a vicious circle involving the RAAS, increased salt sensitivity, sympathetic tone, and endothelial damage.[183] In renovascular hypertension the blood flow perfusion to the kidney is decreased and alterations in the RAAS are observed.[184] Increased sympathetic activity, oxidative stress, inflammation, and endothelial dysfunction have all been linked to sleep apnea.[185,186] Endocrine causes are involved with changes in renal sodium retention, glucocorticoid metabolism, effects sympathetic activity, and systemic vascular resistance.[187–189] Vasculitis and systemic diseases might cause hypertension due to renal impair, renovascular changes, or immunological mechanisms.[16,168,190]

2.2.4 Genomics of secondary hypertension

The heritable nature of hypertension has been well recognized. In accordance with the twin studies, the estimated heritability is as high as 50% to 60%.[191] Early-onset hypertension in grandparents has been described to significantly increase the risk of hypertension in the grandchildren, independent of lifestyle factors or the presence of hypertension in parents.[106] The data of the FinnGen study described an elevated genetic risk of hypertension in women compared to men, concerning especially early-onset hypertension.[192] To date, about 30 rare

monogenic variants are reported to cause hypertension and over 1,500 SNPs are recognized to associate with hypertension.[171]

The genetic causes of secondary hypertension are listed in **Table 2**. The data on the prevalence of monogenic hypertensive disorders in the Finnish population is scarce. Furthermore, around 30% of pheochromocytomas are of genetic origin, including multiple endocrine neoplasia type 2, von Hippel-Lindau disease, neurofibromatosis type 1, and other rare genetic variants.[171,187] Additionally, patients with familial dysautonomia have baroreflex deafferentation, leading to redundant blood pressure instability, episodes of severe hypertension, and chronic renal disease.[193]

2.2.5 Secondary hypertension and cerebrovascular disease

Hypertension is a major risk factor for stroke. According to a meta-analysis of 613,815 patients, a 10 mmHg decrease in systolic blood pressure reduces the risk of stroke by 27%.[194] Similarly, the risk of aSAH increases in a linear fashion as blood pressure rises.[17] The data on the risk of stroke comparing essential and secondary hypertension as differing etiologies is scarce. There is growing evidence on the association between secondary hypertension causes and the sIA disease.

ADPKD is the most well-established risk factor for the sIA disease.[11] Of rheumatic and renal diseases, systemic lupus erythematosus presents with aSAH in around 1% patients.[195–197] Of the patients with Takayasu arteritis, 4.5% have sIAs.[198]

Insomnia along with obstructive sleep apnea are recently acknowledged risk factors for aneurysm growth and aSAH, and obstructive sleep apnea might also be a risk factor for a poor aSAH outcome.[199,200] The prevalence of obstructive sleep apnea in aSAH patients was reported five times higher compared to patients without ruptured IAs in an American study.[201] According to a recent German study, the prevalence of obstructive sleep apnea was as high as 68% in men and 34% in women among patients with UsIAs.[202] UsIA patients had more frequently hypertension with obstructive sleep apnea than without obstructive sleep apnea (70% versus 51%),[202] and a similar trend was reported in the aSAH patients (88% versus 60%).[201]

There is inconsistent evidence on the risk of sIA disease among patients with coarctation of the aorta. Earlier studies report that individuals with aortic coarctation harbor an aneurysm up to five times more often compared to the general population, while more recent studies suggest that there is no association, which might be due to the developed and timely treatment of the coarctation.[203]

Of endocrine causes of hypertension, the prevalence of hypothyroidism has been reported higher in the patients with UsIAs than in their controls (17% versus 4%) and it has been described to have a significant influence on the growth rate of large (≥7 mm) UsIAs.[204,205] A recent and larger study showed an association between UsIAs and hypothyroidism (OR 1.5, 95% CI, 1.3-1.6) with a smaller prevalence of hypothyroidism in the UsIA patients (4%) than the previous studies, whereas hyperthyroidism and thyroid hormone treatment for longer than five years were protecting factors.[206] Aforementioned studies did not report the prevalence of hypertension among UsIA patients with hypothyroidism.

Around 13% of the patients with fibromuscular dysplasia are detected with sIAs; additionally, multiple sIAs are found in up to half of these patients.[207] According to a GWAS meta-analysis, fibromuscular dysplasia appears to be genetically more similar with the sIA disease and aSAH than other stroke types; however, this is considered to at least partly originate from a genetic linkage between fibromuscular dysplasia and hypertension.[208] Among acromegalic patients, UsIAs have been described in 4-18% of the patients.[209] Familial hyperaldosteronism type 1 has been associated with the sIA disease, as 4% of the patients are affected by aSAH.[210]

2.2.6 Management of secondary hypertension

The basis of managing secondary hypertension is the recognition and treatment of the underlying etiology. Depending on the underlying cause, the preferred treatment is considered. Optimal drug therapy is essential in renal and systemic diseases and in some of the endocrine causes, such as thyroid diseases.[174,183,211] Operative treatment is considered in various

causes, including renovascular disease, obstructive uropathy, coarctation of the aorta, adrenal gland tumors, pheochromocytoma, Cushing's syndrome, hyperparathyroidism, and acromegaly.[184,187,188,212,213] Weight loss is recommended for all obese patients with obstructive sleep apnea, and continuous positive airway pressure therapy is recommended for those with moderate or severe obstructive sleep apnea.[162] In some cases, eliminating the cause, e.g. excessive licorice consumption may resolve the elevated blood pressure levels.[15]

Despite treating the underlying cause optimally, it is not uncommon that residual hypertension remains. In renal diseases, it is essential to break the vicious cycle that accelerates the progression of hypertension and renal disease.[183] The age at the treatment of the secondary cause has been demonstrated to affect the hypertension outcome,[212,214] which underlines the significance of timely treatment in order to prevent irrevocable reconstruction of the circulatory system. A patient with secondary hypertension can also have accompanying essential hypertension, however, treating the secondary hypertension cause improves blood pressure levels in these patients as well.[15]

2.3 PRE-ECLAMPSIA

The word eclampsia is originated from the Greek “eklampsis”, which means “sudden development” or “lightning”, possibly describing the sudden onset of the disease or the aura that can precede the seizure.[215] The sudden grand-mal seizures in previously healthy pregnant women were first represented by Hippocrates.[216] Pre-eclampsia has been described as “a disease of theories”, as the pathophysiology has remained incompletely understood.[217] The prevailing understanding is that several underlying causes lead to endothelial dysfunction and subsequently to pre-eclampsia.[218]

2.3.1 Epidemiology of pre-eclampsia

The global incidence of pre-eclampsia is approximately 3-5%, with regional variations.[20] Pre-eclampsia is typically a condition of primiparous women as the incidence is lower, less than 2% in multiparous women.[219] However, the risk in multiparous women is increased in those who had pre-eclampsia earlier, in one (15%) or two (32%) previous pregnancies.[219] In the Finnish studies, the prevalence of pre-eclampsia has ranged from 4.4% to 13.9%.[27,220,221] In a study that included data of the most recent pregnancy, the prevalence of pre-eclampsia was 1.6 % in women with Finnish origin.[222] In a questionnaire study investigating regional differences in pre-eclampsia, 13.9% of women in Northern Finland and 11.1% in Eastern Finland (North Karelia and Kuopio provinces) had had pre-eclampsia, more often than women in Southern Finland (7.9%), which may indicate an aggregation of shared maternal risk factors for pre-eclampsia and cardiovascular disease, as women with a history of pre-eclamptic pregnancy had an increased prevalence of metabolic syndrome. [221] In addition, strong regional genetic differences exist in the Finnish population.[223] However, there was no significant regional difference in the incidence of gestational hypertension, with a prevalence of 18.2% in Eastern Finland, possibly reflecting the different nature of pre-eclampsia.[221]

In about 15-25% women with pre-eclampsia, the condition is classified as severe.[24,224] Early-onset disease accounts for about 10-15% of the cases.[225] The incidence of eclampsia, considered the most severe subsequent form of pre-eclampsia, is rare in Finland, 1.5 per 10,000 deliveries according to the latest estimate.[226]

Several studies have shown interesting temporal trends in pre-eclampsia rates, as there has been an increase towards the 21st century and then a decrease over time.[19,227] Paradoxically, the incidence of some risk factors, e.g. obesity, diabetes, and maternal age has increased, whereas smoking, which is considered to be a protecting factor, has decreased.[19] Improved detection of pre-eclampsia, updated diagnostic criteria, preventive interventions (e.g., low-dose acetylsalicylic acid), and the development of prenatal care are likely to have influenced the observed variation in pre-eclampsia prevalence.

2.3.2 Diagnosis of pre-eclampsia

The key diagnostic criteria for pre-eclampsia have classically been new-onset proteinuria with elevated blood pressure after 20 weeks of pregnancy.[228] During the last decade, a broader definition of pre-eclampsia, in which proteinuria no longer is required, was initiated by the American College of Obstetricians and Gynecologists (ACOG) Task Force Report on Hypertension in Pregnancy in 2013 and The International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014.[229,230] The current consensus is that the diagnostic criterion is met in the absence of proteinuria, when combined with at least one other finding of maternal organ dysfunction: liver involvement, hematological complications, renal insufficiency, neurological complications, pulmonary edema, or uteroplacental dysfunction.[231,232] A broader definition has improved the identification of adverse outcomes in pregnancy.[233]

According to the most recent ACOG and ISSHP guidelines,[231,232] hypertension is diagnosed with blood pressure levels ≥140/90 mmHg on at least two readings. Proteinuria is defined as urinary excretion of ≥300 mg protein per 24-hour urine collection, protein/creatinine ratio ≥0.3, or

dipstick reading of 2+ (when other methods are unavailable). Pregnancy-related hypertension is categorized as chronic or new onset hypertension, occurring before or after 20 weeks of gestation, respectively. Superimposed pre-eclampsia is diagnosed when at least one of the preceding features of maternal organ dysfunction appears in addition to chronic hypertension. Gestational hypertension is defined as new-onset hypertension after 20 weeks of gestation without proteinuria or the preceding features of maternal organ dysfunction.

Pre-eclampsia with severe features is defined to have any of the following: blood pressure levels ≥160 mmHg systolic or ≥110 mmHg diastolic, thrombocytopenia, impaired liver function or upper quadrant or epigastric pain, renal insufficiency, pulmonary edema, or new-onset headache or visual disturbances.[231] HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) is one of the manifestations of severe pre-eclampsia. Eclampsia is characterized by new-onset seizures. Early-onset pre-eclampsia is defined as occurring before 34 weeks of gestation.[229] The Finnish Current Care Guidelines for pre-eclampsia were published in 2021 and are consistent with the abovementioned current classification of hypertensive disorders and pre-eclampsia definition.[234]

2.3.3 Risk factors for pre-eclampsia

Several diseases and clinical conditions have been identified as risk factors for pre-eclampsia and are listed in **Table 3**. It appears that early-onset and late-onset forms of pre-eclampsia differ in their risk factors; black race, chronic hypertension, SLE, antiphospholipid syndrome, congenital anomalies, prior pre-eclampsia, and binge drinking have been described more frequently in early-onset pre-eclampsia, whereas pregestational and gestational diabetes, nulliparity, young or advanced maternal age, and increased BMI have been reported more frequently in late-onset and less severe pre-eclampsia.[225,235–242] The risk of pre-eclampsia increases exponentially with the number of risk factors.[243]

Table 3. Clinical risk factors predicting pre-eclampsia.

Risk factor	Relative change in risk	References
Chronic kidney disease	1.8-10	Bartsch et al. 2016 [244] Al Khalaf et al. 2022 [245] Zhang et al. 2015 [246]
Prior pre-eclampsia	8.4	Bartsch et al. 2016 [244]
Chronic Hypertension	5.1	Bartsch et al. 2016 [244]
Low socioeconomic status	4.9	Silva et al. 2008 [247]
Pregestational diabetes	3.7	Bartsch et al. 2016 [244]
First-degree relative with pre-eclampsia	2.9	Duckitt et al. 2005 [248]
Recovered acute kidney injury	2.9	Tangren et al. 2018 [249]
Multifetal pregnancy	2.9	Bartsch et al. 2016 [244]
Antiphospholipid antibody syndrome	2.8	Bartsch et al. 2016 [244]
Prepregnancy body mass index >30	2.8	Bartsch et al. 2016 [244]
Congenital anomalies	1.5-2.6	Lisonkova et al. 2013 [225]
Systemic lupus erythematosus	2.5	Bartsch et al. 2016 [244]
Prior stillbirth	2.4	Bartsch et al. 2016 [244]
White coat hypertension	2.4	Johnson et al. 2020 [250]
Nulliparity	2.1	Bartsch et al. 2016 [244]
Migraine	2.1	Aukes et al. 2019 [251]
Prior placental abruption	2.0	Bartsch et al. 2016 [244]
Black race	2.0	Arechvo et al. 2022 [237]
Hyperthyroidism	1.8	Männistö et al. 2013 [252]
Use of assisted reproductive technology	1.8	Bartsch et al. 2016 [244]
Gestational diabetes	1.6	Ostlund et al. 2004 [253]
Subclinical hypothyroidism	1.5	Toloza et al. 2022 [254]

Maternal age >35/>40 (years)	1.2/1.5	Bartsch et al. 2016 [244]
Interpregnancy interval ≥120 months	1.3	Gebremedhin et al. 2021 [255]
Smoking	0.7	Wei et al. 2015 [256]

Chronic hypertension complicates about 0.3-1.6% of all pregnancies, with regional variations.[19] The majority of chronic hypertension in pregnancy is considered essential, while the prevalence of secondary forms of hypertension is reported to be about 10-15% in pregnant women.[173] Among pregnant women, the risk of pre-eclampsia was high in both essential hypertension (OR 10.18, 95% CI, 9.77-10.60) and secondary hypertension (OR 11.92, 95% CI, 10.98-12.95) in an American study.[173] Approximately 15-25% of pregnant women with chronic hypertension develop superimposed pre-eclampsia, with an increasing prevalence in those with hypertension for at least four years of duration.[244,257,258] Women with a genetic propensity to hypertension have an increased risk of pre-eclampsia and higher blood pressure levels during pregnancy.[259]

Globally, obesity is increasing rapidly in the general population and in women of reproductive age.[260] In Finland, the incidence of obese (BMI 30-39.9) and morbidly obese (BMI ≥40) pregnant women increased by 44% and 103% between 2004 and 2018, respectively.[261] Obesity plays a fundamental role in the majority of essential hypertension cases and is an acknowledged risk factor for pre-eclampsia with a threefold relative risk.[244,262] In addition, paternal obesity may increase the risk of pre-eclampsia.[263]

Chronic kidney disease is a significant risk factor for pre-eclampsia.[244–246] Among women with ADPKD, pre-eclampsia occurred in 8.7% compared with 2% in the control group with simple cysts in an American study.[264] It appears that concurrent hypertension considerably influences the increased risk of pre-eclampsia in the ADPKD patients.[265]

In several studies, gestational diabetes has been independently associated with pre-eclampsia,[266] increased BMI being the greatest

confounding factor.[253] The prevalence of gestational diabetes is about 14% globally,[267] and as high as 21% in Finland.[268] Gestational diabetes has been strongly associated with lifestyle factors,[269] but heterogeneity and genetic risk are increasingly recognized as well.[270]

The effect of age on pre-eclampsia follows a J-shaped curve, hence both extremes of the maternal age are at higher risk; however, women of very advanced maternal age have the highest risk of pre-eclampsia among other adverse pregnancy outcomes.[271] With younger maternal age, risk factors may be more strongly associated with socioeconomic or immunological aspects.[272] The aging process may weaken the ability to adapt to pregnancy, possibly due to age-related vascular endothelial dysfunction and defects in DNA.[273] Additionally, increasing paternal age may increase the risk of pre-eclampsia.[274] The average age of first-time fathers has increased in Finland and other Western countries.[275] Increasing paternal age may cause abnormalities in sperm chromosomes, sperm DNA damage, and epigenetic alterations.[276]

Interestingly, cigarette smoking has consistently been reported to decrease the risk of pre-eclampsia.[277–279] In Finland, the rate of smoking at the beginning of pregnancy has remained fairly stable at about 15% from 1991 to 2015, while an increase in the frequency of smoking pregnant women has been observed in Eastern Finland and in the age group of young women.[280] It has been hypothesized that nicotine inhibition of thromboxane A2 production could interpret the reduced risk of pre-eclampsia.[281] Nevertheless, smokeless tobacco has been reported to increase the risk of preterm pre-eclampsia.[282] It seems that smoking induces a pro-angiogenic setting.[278,283] The role of the heme oxygenase-1/carbon monoxide pathway has prevailed conflicting.[284]

2.3.4 Pathogenesis of pre-eclampsia

Determining the definitive pathogenesis of pre-eclampsia has proven challenging. The current consensus holds that pre-eclampsia comprises at least two subtypes with distinct pathophysiologies, early- and late-onset disease. The early-onset form is characterized by impaired placental

function, whereas late-onset disease more likely illustrates the maternal inability to adapt to the demands that a pregnancy raises, associating with an elevated burden of cardiometabolic risk factors.[285] However, the role of the placenta is essential, as only the delivery can conclusively resolve pre-eclampsia. The progress of pre-eclampsia can be divided into two phases, referred to as the Two Stage Model. First, impaired placentation, defective vascular remodelling, and oxidative stress and ischemia of the placenta occur in the first trimester. Second, the afflicted placenta induces an inordinate release of antiangiogenic factors in the second and third trimesters, finally resulting in endothelial dysfunction, vascular inflammation, and the maternal syndrome.[218] Pre-eclampsia induces extensive maternal vascular endothelial injury that might endure long after the pre-eclamptic pregnancy.[273]

In the normal process of placentation, the blastocyst adheres to the uterine wall. Subsequently, cytotrophoblasts, which are primary placental cells derived from the blastocyst, differentiate into extravillous trophoblasts at the tips of branched anchoring villi. Extravillous trophoblasts migrate away from the anchoring villi and invade the decidua, a specialized layer of the endometrium and colonize the maternal uterine spiral arteries, where they reconstruct the arterial wall into a more dilated and fibrinoid-rich form to provide a high-volume uteroplacental blood perfusion.[286,287] Several different maternal cell types in the decidua critically influence this process, including decidual macrophages, decidual dendritic cells, regulatory T cells, and uterine natural killer cells.[286,288–290] Various additional determinants of extravillous trophoblast invasion and differentiation have been described, including cytokines, chemokines, and hormones at the maternal-fetal interface.[286] Pre-eclampsia is associated with shallow trophoblast invasion and deficient reconstruction of the arterial wall, whereas in normal pregnancy the remodeling of the spiral arteries extends into the myometrium **(Figure 3).**[291] The prevalence of placental lesions indicating maternal hypoperfusion is reported to be significantly higher in early-onset pre-eclampsia than in late-onset pre-eclampsia, emphasizing the importance of placental role in the early-onset form.[292]

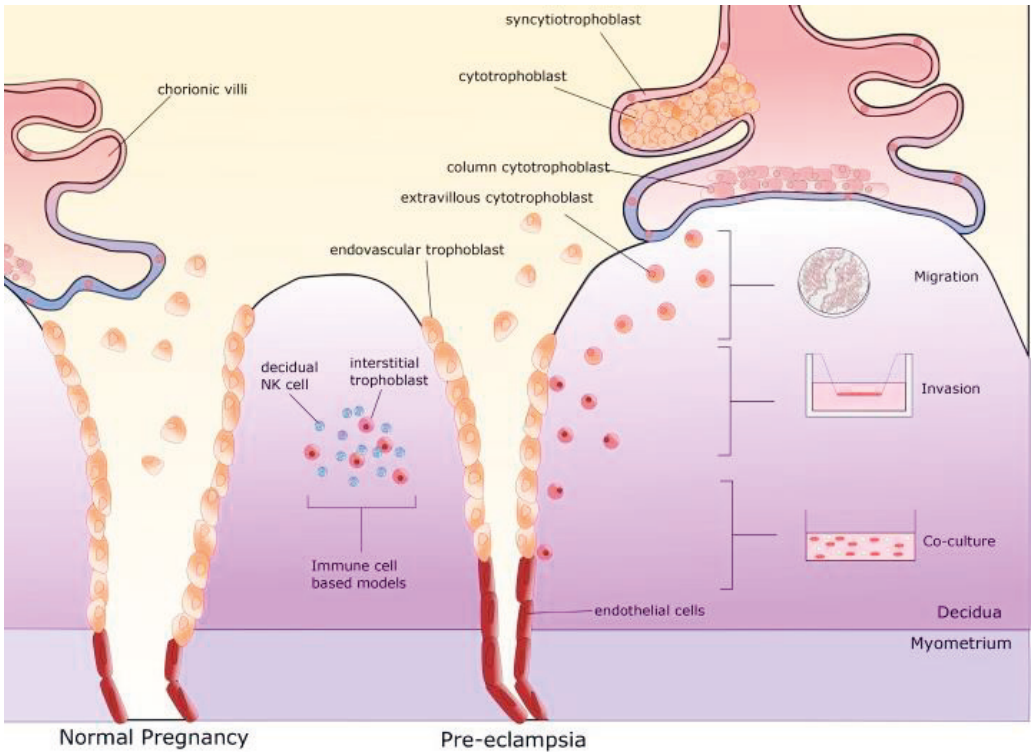

Figure 3. Remodeling of the spiral uterine arteries. Reprinted from McNally et al.[291] CC-BY 4.0 (http://creativecommons.org/licenses/by/4.0/)

Ultimately, impaired placental function results in an excess production and secretion of soluble endoglin and soluble fms-like tyrosine kinase 1 (sFlt-1).[293] sFlt-1 binds vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which are essential for the normal endothelial cell function. This inhibits the biological activity of these pro-angiogenic proteins, thus, shifting the pregnancy to a more anti-angiogenic setting.[294] Endothelial nitric oxide production is inhibited due to VEGF dysregulation and Ca^{2+} signaling.[295,296] By antagonizing VEGF receptor-regulated signaling, sFlt-1 causes endothelial cells to become abnormally sensitive to inflammatory cytokines, including tumor necrosis factor alpha and interleukin 6.[297] Pre-eclampsia has been described with enhanced complement activation.[298] The RAAS pathway has also been implicated in the pathogenesis of pre-eclampsia.[299,300]

Pre-eclampsia has also been referred to as a "metabolic syndrome of pregnancy".[301] The higher prepregnancy levels of free fatty acids, triglycerides, cholesterol, blood pressure, and even lower cardiac output have been associated with pre-eclampsia.[302–304] Insulin resistance, impaired mitochondrial function and energy metabolism, oxidative stress, and lipid dysfunction have been described as early as during the first trimester in late-onset pre-eclampsia.[305]

2.3.5 Genomics of pre-eclampsia

Pre-eclampsia has a clear familial tendency, with both maternal and paternal factors increasing the risk.[28,306–309] The familial association predicts more severe and earlier pre-eclampsia.[28,29,31] Similarly, a parental history of cardiovascular disease increases the risk of pre-eclampsia.[310]

Having at least one first-degree relative with pre-eclampsia increases an individual's risk for pre-eclampsia by approximately threefold.[248,310,311] Furthermore, approximately twofold risk of pre-eclampsia has been described in pregnancies fathered by men who were born after a pregnancy affected by pre-eclampsia[28,29] or who had fathered a pre-eclamptic pregnancy in another female.[30] Having a maternal half-sister with pre-eclampsia increases the risk of pre-eclampsia (OR 1.6, 95% CI, 0.9-2.6) as does having an affected paternal half-sister (OR 1.8, 95% CI, 1.01-2.9).[30] Interestingly, the genetic effect from fathers on the risk of pre-eclampsia does not seem to increase the fathers' risks of cardiovascular death, unlike in women with pre-eclampsia.[312]

In the majority of cases, pre-eclampsia does not follow a classical Mendelian principle,[313,314] although, monozygotic twins concordant for pre-eclampsia have been identified.[315,316] In a Swedish twin study, the estimates of heritability and nonshared environmental effect on pre-eclampsia were 0.54 (95% CI, 0-0.71) and 0.46 (95% CI, 0.29-0.67), respectively.[316] It has been estimated that regarding the genetical risk of pre-eclampsia, 35% is attributable to the mother, 20% to the fetus, 13% to the couple, <1% to the shared sibling environment, and 32% to undetermined factors. Thus, the

total maternal and paternal genetic effects were estimated as 45% and 10%, respectively.[307]

Persistent research on sequence variation has resulted in susceptibility loci in genome-wide linkage studies in Finnish,[317,318] Australian/New Zealand,[319,320] Icelandic,[321] and Dutch pre-eclampsia families.[322] Significant linkage has been found at 2p13,[321] 2p25,[317] and 9p13.[317] In several studies, the susceptibility loci have been located on chromosome 2,[317,318,320,321] but no specific locus has been replicated in different cohorts.

Additionally, several case-control candidate gene studies and subsequent meta-analyses have been conducted. The results suggest a linkage with genes related to coagulation (*F2,F5, SERPINE1*),[323,324] RAAS pathway (*ACE, AGT, AT1R*),[323,325] lipid metabolism (*LPL*),[323] and inflammation and immunology (*CTLA-4*).[323,326] *PLEKHG1*, which is associated with pre-eclampsia,[327] has also been linked to ischemic stroke.[328]

In the last decade, several GWAS on pre-eclampsia have been published. The earliest GWAS with moderate sample sizes identified several candidate SNPs, but did not reach the level of significance.[329,330] An Australian GWAS found a risk locus on 2q14, near the *INHBB* gene, but the results were not replicated in Finnish and Norwegian cohorts.[331] A GWAS of 4,380 cases of offspring born from pre-eclamptic pregnancies found a significant susceptibility locus near *FLT1*,[332] which encodes a protein whose soluble form is known to be elevated in pre-eclampsia.[294] Later, a larger GWAS including 12,150 pre-eclampsia patients and 164,098 controls with European and Central Asian origin described significant associations near the BMI and blood pressure-associated *FTO* among other blood pressure-associated genes (*ZNF831, MECOM, FGF5, SH2B3*).[32] Recently, two larger GWAS meta-analyses identified new risk loci.[33,333] It was additionally demonstrated that a polygenic risk score for hypertension is associated with pre-eclampsia.[32,259,334] The findings from the GWAS leading to significant loci for pre-eclampsia are summarized in **Table 4**.

The results indicate that the predominance of known pre-eclampsia risk loci is associated with cardiovascular traits.[32,33] Furthermore, these genetic variants have been associated with decidualization, endothelial cell function, natriuretic peptide signaling, glomerular function, and

immunology.[333,335] Additionally, there is emerging evidence on the epigenetic mechanisms on the risk of pre-eclampsia.[336]

Table 4. Significant risk loci for pre-eclampsia in the maternal genome-wide association studies.

Locus	SNP	Involved genes	References
1p36	rs149764880	*MTHFR-CLCN6*	Honigberg et al. 2023 [333]
1q42	rs708119	*WNT3A*	Honigberg et al. 2023 [333]
2q14	rs7579169 rs12711941	*INHBB*	Johnson et al. 2012 [331]
3q26	rs1918975 rs9855086 rs4245909	*MECOM*	Steinthorsdottir et al. 2020 [32] Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
4q21	rs1458038 rs16998073 rs16998073	*FGF5*	Steinthorsdottir et al. 2020 [32] Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
6p21	rs2442752 rs2596471	*MICA* *HLA/PSORS1C2*	Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
8p22	rs2653414	*FGL1*	Honigberg et al. 2023 [333]
9q22	rs5899121 rs7862828	*LINC00484* *AUH/LINC00484*	Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
11q22	rs2508372 rs3018700	*PGR* *PGR/TRPC6*	Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
12q24	rs10774624	*SH2B3* *SH2B3* *ATXN2/SH2B3*	Steinthorsdottir et al. 2020 [32] Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
13q12	rs7318880	*FLT1*	Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
16q12	rs1421085	*FTO*	Steinthorsdottir et al. 2020 [32] Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]

19p13	rs167479	*RGL3*	Honigberg et al. 2023 [333]
20q13	rs259983 rs259983 rs6026744	*ZNF831*	Steinthorsdottir et al. 2020 [32] Honigberg et al. 2023 [333] Tyrmi et al. 2023 [33]
22q11	rs17572606	*UPB1*	Honigberg et al. 2023 [333]

2.3.6 Pre-eclampsia and cerebrovascular disease

Pre-eclampsia has been linked to all forms of pregnancy-related stroke (ischemic stroke, cerebral venous thrombosis, intracerebral or subarachnoid hemorrhage) during pregnancy or puerperium.[80,337] Pre-eclampsia particularly increases the risk of pregnancy-related intracerebral hemorrhage.[80,338,339] The risk of pregnancy-related stroke in patients with pre-eclampsia is increased by chronic hypertension, more severe forms of pre-eclampsia, infections present on admission, prothrombotic states, and coagulopathies.[26] Pre-eclampsia is associated with a higher risk of pregnancy-related SAH, but in a recent Finnish study there was no independent association in the multivariate analysis, and the prevalence of pre-eclampsia in pregnancy-related SAH was similar with aneurysmal and non-aneurysmal etiologies.[82]

Accumulating evidence suggests that the effects of pre-eclampsia may induce long-term endothelial defects and epigenetic alterations that may promote the development of cerebrovascular disease.[273,340] In women with previous adverse pregnancy outcomes, stroke occurs at a younger age, especially if the pregnancy-related condition has reoccurred.[341] The long-term risk of intracerebral hemorrhage is increased along with ischemic stroke.[25,342–344] In a Finnish population cohort, the long-term overall risk of stroke was notably increased with pre-eclampsia (HR 1.40, 95% CI, 1.32-1.48).[24]

Future cardiovascular risk is higher with early-onset, severe, and recurrent pre-eclampsia.[345–347] In the long term, a history of pre-eclampsia increases the risk of chronic hypertension nearly fourfold and the risk of

type 2 diabetes more than twofold.[25,348] The risk of future kidney disease after pre-eclampsia is well established.[349,350] However, it has remained uncertain, whether the risk is related to the adverse effects on the kidney during pre-eclampsia or to the mutual risk factors.

The increased cerebrovascular and cardiovascular risk is not confined to women with a history of pre-eclampsia but is also increased in their offspring.[351] In a Finnish cohort of offspring born after pregnancies complicated by pre-eclampsia, the HR for hemorrhagic stroke was 2.0 (95% CI, 0.9-4.6) and for thrombotic stroke 1.8 (95% CI, 1.0 to 3.2).[27] A recent multinational Nordic cohort study reported an adjusted HR for hemorrhagic stroke to be 1.23 (95% CI, 1.01-1.50) in the offspring, and the risk of stroke was increased with severe pre-eclampsia.[352] In a Finnish study, as young as 8-12 years old children born after pre-eclamptic pregnancies, particularly early-onset pre-eclampsia, present with aberrant blood pressure levels and arterial stiffness.[353]

2.3.7 Management of pre-eclampsia

To date, delivery is the only cure for pre-eclampsia.[218] The use of acetylsalicylic acid (100 mg/day) is the only widely used preventive drug therapy for pre-eclampsia with an 18% risk reduction.[354] Acetylsalicylic acid use may increase PlGF levels,[355] decrease sFlt-1 concentrations,[356] enhance nitric oxide formation,[357] and beneficially shift the balance of prostacyclin and thromboxane.[358] Calcium supplementation may decrease the risk of pre-eclampsia, especially in women with low-calcium diet.[359] Magnesium sulfate is used in severe pre-eclampsia to prevent the development of eclampsia, and once eclampsia has already developed, it is effective in preventing recurrent seizures and reducing maternal mortality.[360]

A recent meta-analysis of pravastatin showed a 61% reduction in the incidence of pre-eclampsia and a 45% reduction in the incidence of preterm birth, but it appears that treatment should be started before the 30th week of pregnancy.[361] The favorable effect of statin therapy may be due to its ability to elevate the PlGF levels, thereby decreasing the sFlt-1 levels and altering the ratio of anti-angiogenic factors that induce pre-

eclampsia,[362] or by generating nitric oxide synthesis.[363] There is also increasing evidence indicating that metformin may reduce the risk of pre-eclampsia.[364]

3 AIMS OF THE STUDY

Study I

To study the prevalence of secondary hypertension in the sIA patients and its impact on the sIA disease phenotype.

Study II

To study the incidence of pre-eclampsia, other hypertensive disorders of pregnancy, and gestational diabetes in the sIA patients and their matched population controls. To evaluate the influence of pre-eclampsia on the sIA disease phenotype.

Study III

To study the familial associations of pre-eclampsia and the sIA disease by analyzing the prevalence of pre-eclampsia in the sIA patients, their female relatives, and their matched population controls, and by identifying familial sIA disease and familial pre-eclampsia in all female sIA patients and female relatives.

4 SUBJECTS AND METHODS

This thesis was conducted as a retrospective cohort study consisting of three separate studies. The data in all of these studies is based on the prospectively collected Kuopio Intracranial Aneurysm Patient and Family Database.

4.1 CATCHMENT POPULATION OF KUOPIO UNIVERSITY HOSPITAL

In Finland, there are five university hospitals that operate in their unshared catchment areas. During the study period from 1990 to 2018 Neurosurgery of the KUH NeuroCenter provided acute and elective neurosurgical services to a defined KUH catchment population in Eastern Finland, including four central hospitals. The geographical area remained the same, but the population decreased from 839,236 to 805,133.[365,366] The median age increased from 36 to 44 in men and from 39 to 48 in women, while the proportion of men remained at 49%.[365] All aSAH patients detected by computed tomography or lumbar puncture were admitted to KUH for angiography and treatment if they were not moribund or very aged. All sIA diagnoses were verified by four-vessel digital subtraction angiography, computed tomography angiography, or magnetic resonance angiography. Patients with UsIAs were referred to KUH neurosurgery for evaluation of preventive treatment.

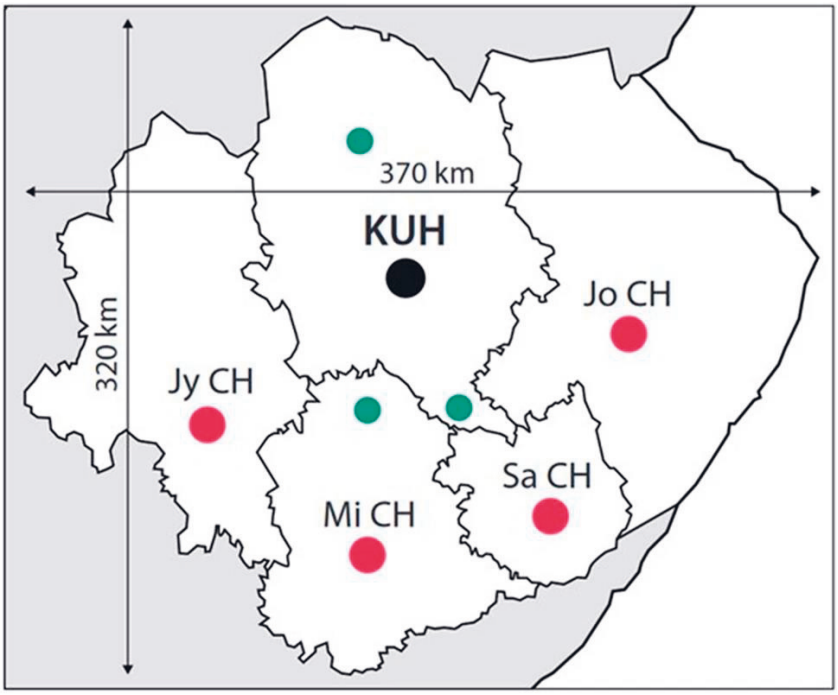

Figure 4. Catchment population of the Kuopio University Hospital (KUH). The four Central Hospitals Jyväskylä (Jy CH), Joensuu (Jo CH), Mikkeli (Mi CH), and Savonlinna (Sa CH) are marked with red circles. The three regional hospitals are shown as green circles. Reprinted from Autio et al.[366] (http://creativecommons.org/licenses/by/4.0/)

4.2 KUOPIO INTRACRANIAL ANEURYSM PATIENT AND FAMILY DATABASE

KUH Neurosurgery maintains the Kuopio Intracranial Aneurysm Patient and Family Database of all patients admitted to KUH with aSAH or UsIAs since 1980. The database has been prospective since 1990. Patients who were Finnish citizens and residents of the KUH catchment area were included. All sIAs are verified with a four-vessel angiography. The database is run by a dedicated full-time database manager, who interviews all new sIA patients, manages the informed patient consent forms, and collects comprehensive information on their neurosurgical treatment and follow-up visit. Further, the database manager codes this data into variables. This information contains data on family history of sIAs, defined as at least two

affected first-degree relatives in the family. The genealogical trees of the confirmed sIA patients were constructed using corresponding parish records dating back to the 17th century.[35] The patients were divided into two categories: patients with aSAH (at least one aSAH in history) and patients with unruptured sIA disease (no aSAH in history).

4.3 DATA FUSION FROM NATIONAL REGISTRIES

The information from the Kuopio Intracranial Aneurysm Patient and Family Database was merged with data on the prescription drug purchases, hospital diagnoses, and causes of death obtained from national registries.[7]

The Social Insurance Institution of Finland is an autonomous social security institution, supervised by the Finnish Parliament. The National Health Insurance scheme is part of the Finnish social security system, and it is administered by the Social Insurance Institution of Finland. All permanent residents of Finland are covered by the National Health Insurance scheme. The Social Insurance Institution of Finland has since 1994 maintained a prospective nationwide registry for all patients who have purchased prescribed drugs from pharmacies. Every pharmacy in Finland is included in the prospective registry. Drug purchase data, containing information from the date of first purchase with the number of purchases, has been collected using social security numbers. The drugs are classified according to World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification.

International Statistical Classification of Diseases and Related Health Problems (ICD) codes were acquired from the Care Register for Health Care (HILMO), which includes all hospital-based ICD diagnoses from secondary and tertiary referral hospitals in Finland, covering all medical specialties. Formerly this register was called the Finnish Hospital Discharge Register, and the name was changed to the Care Register in 1994. The Finnish Hospital Discharge Register has maintained nationwide data on all inpatient hospital discharges with personal identification codes since 1969. Finland used ICD-8 between 1969 and 1986, ICD-9 between 1987 and 1995, and ICD-10 since 1996. ICD-9 and ICD-10 diagnoses were obtained for the

sIA patients with the first sIA admission until December 2018. ICD-8 diagnoses were obtained for the sIA patients with the first sIA admission until the end of October 2015. Causes of death occurring between 1971 and 2018 were obtained from Statistics Finland using social security numbers and classified according to ICD codes.

For each sIA patient in the Kuopio Intracranial Aneurysm Patient and Family Database, three controls were randomly selected by the Digital and Population Data Services Agency (formerly the Finnish Population Register Centre). They were matched for age, sex, and place of residence. The first sIA admission date was the index date for matching, and at the time all controls were alive. First-degree relatives (parents, children, siblings), nieces, and nephews of the sIA patients were identified using the Finnish personal identification codes. Among the siblings, no distinction was made between full- and half-siblings. Using the Finnish personal identification codes, the data on medication purchases, hospital diagnoses, and causes of death was obtained from the national registries for the matched controls and relatives.

Table 5. Synopsis of the study design in Studies I-III.

Study	I	II	III
Design	Population-based study	Population-based case-control study	Population-based case-control study
Study period (sIA diagnosis)	1995-2014	1990-2015	1995-2018
Data	Kuopio Intracranial Aneurysm Patient and Family Database Drug purchase data, hospital diagnoses, and causes of death Medical records	Kuopio Intracranial Aneurysm Patient and Family Database Drug purchase data, hospital diagnoses, and causes of death HAIKARA Medical records	Kuopio Intracranial Aneurysm Patient and Family Database Drug purchase data, hospital diagnoses, and causes of death
Cohort	sIA patients	sIA patients and population controls	sIA patients, female relatives, and population controls
N of the study population	2704 sIA patients	169 sIA patients and 324 controls	1) 265 sIA patients, 393 female relatives, and 546 controls 2) 1895 sIA patients and 12141 female relatives
Female patients	1567 (58%)	100%	100%
Study subject	Secondary hypertension	Pre-eclampsia and hypertensive disorders of pregnancy	Pre-eclampsia

4.4 STUDY I

The aim was to study the prevalence of secondary hypertension in the sIA patients and its influence on the sIA disease phenotype.

4.4.1 Study population

The basic study population included all patients with first UsIAs or aSAH admitted to KUH from 1995 to 2014. Unruptured and aSAH patients with non-saccular aneurysm etiologies (fusiform, traumatic, mycotic) were excluded. Altogether, we included 2,704 sIA patients **(Figure 5)**. Their clinical data from the Kuopio Intracranial Aneurysm Patient and Family Database was integrated with the prescription drug purchase data, hospital diagnoses, and causes of death. The medical records of the sIA patients with suspected secondary hypertension were inspected. The prevalence of secondary hypertension and related diagnoses were analyzed. To determine clinical patient and aneurysm characteristics in the sIA patients with secondary hypertension, logistic regression was used. The sIA patients were followed until death or December 2014.

4.4.2 Variables

Diagnosis of hypertension was defined as one of the following: 1) self-proclaimed hypertension; 2) hypertension diagnosis by a physician; or 3) prescribed antihypertensive medication. Data on self-reported hypertension was obtained from the Kuopio Intracranial Aneurysm Patient and Family Database. We had data on all ICD-10 codes from 1996 to 2014, including hospital diagnoses and causes of death. Physician-diagnosed hypertension was defined as ICD-10 codes I10 or I15 in the hospital diagnoses, or as a cause of death, or a hypertension diagnosis reported by a physician in the hospital medical records. Data on prescribed antihypertensive medications was obtained from the nationwide registry with prospective data since 1994, for at least one year preceding the sIA admission. Antihypertensive medication use was defined as the purchase of antihypertensive medications with at least one of the following ATC

codes: C02 (antihypertensives), C03 (diuretics; thiazides), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system).

sIA patients were categorized as patients with secondary hypertension, essential hypertension, and no hypertension. Secondary hypertension was identified using ICD-10 code I15. Additionally, secondary hypertension was suspected in the sIA patients with hypertension and at least one concomitant morbidity that could be associated with secondary hypertension according to the literature review **(Table 2)**, but drug-induced or lifestyle induced hypertension was not included in this study. Further, the hospital medical records of the sIA patients with hypertension and at least one concomitant morbidity were inspected to confirm the diagnoses and to obtain the relevant medical history. Characteristics suggestive of secondary hypertension were recorded as described in the 2013 European Society of Hypertension Guidelines for the management of arterial hypertension.[367]. Patients with a diagnosis code I10 (essential hypertension) were not excluded from the patients that were suspected of having secondary hypertension but were individually reviewed as were the other suspected patients. After reviewing the medical records, we divided the hypertensive patients into secondary and essentially hypertensive patients. If the hypertension diagnosis was confirmed and it seemed possible that the underlying cause could have contributed to the patients' hypertension, the patient was classified with secondary hypertension. Concomitant morbidities were searched by their ICD-10 codes **(Table 6)**. The ICD code for renal failure was additionally included in the search to identify any renal parenchymal diseases.

Table 6. ICD-10 codes used to search secondary hypertension in the sIA patients.

Clinical condition	ICD-10 codes
Renal diseases	I15.1
Polycystic kidney disease	Q61.2-3
Diabetic nephropathy	E10.2, E11.2
Glomerulonephritis, nephritic and nephrotic syndrome	N00-N08
Tubulointerstitial nephritis and chronic pyelonephritis	N11-12, N14-15
Hydronephrosis	N13
Renal carcinoma	C64
Renal failure	N17-19
Renovascular diseases	I15.0
Atherosclerosis of renal artery	I70.1
Fibromuscular dysplasia	I77.3
Sleep apnea	G47.3
Coarctation of the aorta	Q25.1
Endocrine disorders	I15.2
Hyperaldosteronism	E26
Pheochromocytoma and adrenal gland tumors	D35.0, C74, E27.5
Hypothyroidism	E03
Hyperthyroidism	E05
Hyperparathyroidism	E21
Cushing's syndrome	E24, D35.2
Acromegaly	E22.0, D35.2
Systemic diseases	
Large-vessel vasculitis	M31.4-6
Medium-vessel vasculitis	M30
ANCA-associated vasculitis	M31.7, M31.3
Other vasculitis	D69.0, D89.1, M31.0-1, M05.2 M31.8-9
Systemic lupus erythematosus	M32
Systemic sclerosis	M34
Sjögren's syndrome	M35.0
Amyloidosis	E85
Carcinoid syndrome	E34.0
Neurological causes	
Dysautonomia	G90.1
Guillain-Barre syndrome	G61.0
Quadriplegia	G82.3-5

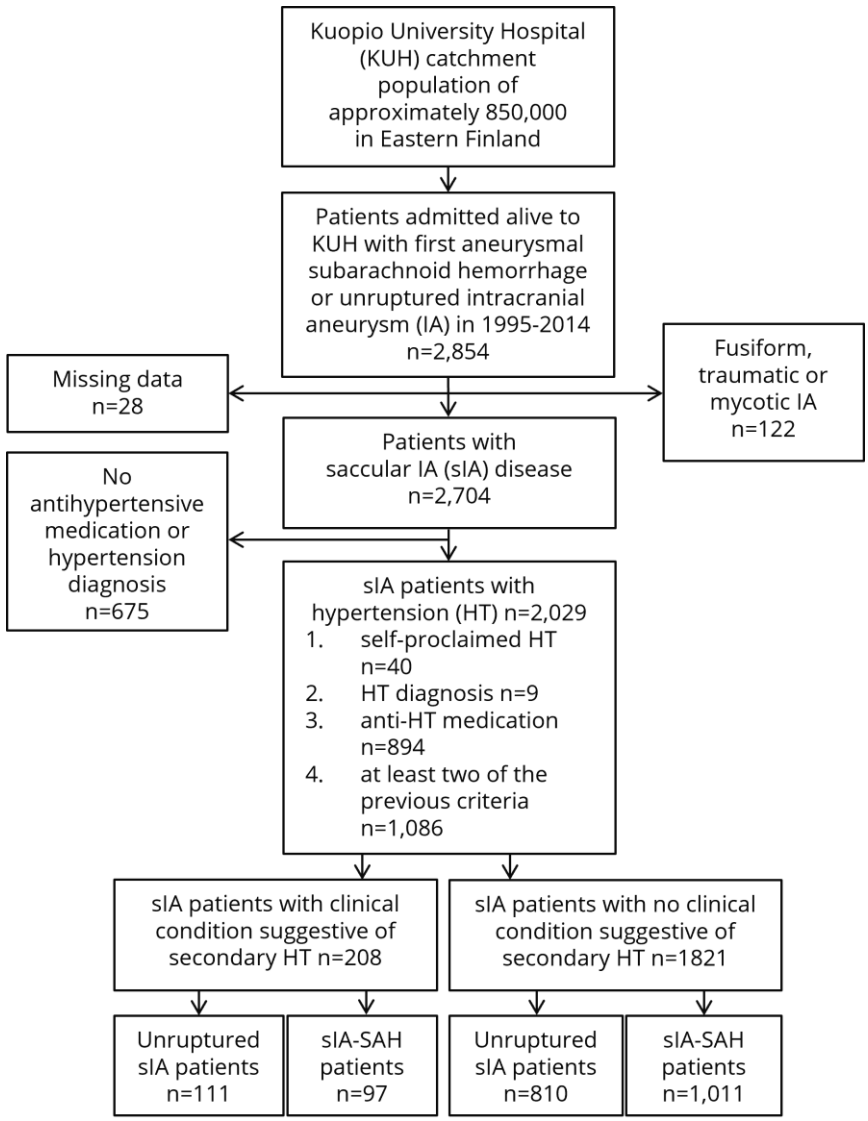

Figure 5. Flowchart of the Study I: Identification of secondary hypertension in the 2,704 sIA patients. Kotikoski et al. 2018. PLoS One / Study I, CC-BY 4.0. (https://creativecommons.org/licenses/by/4.0/)

4.5 STUDY II

The aim was to study the incidence of pre-eclampsia and other hypertensive disorders of pregnancy in the sIA patients and in their matched population controls, and to assess the impact of hypertensive disorders of pregnancy on the sIA disease phenotype.

4.5.1 Study population

The basic study population consisted of 1,915 female patients with their first diagnosis of the sIA disease between 1990 and October 2015. Unruptured and aSAH patients with non-saccular aneurysm etiologies (fusiform, traumatic, mycotic) were excluded. Their clinical data from the Kuopio Intracranial Aneurysm Patient and Family Database was fused with the prescription drug purchase data, hospital diagnoses, and causes of death. The follow-up ended at death or October 2015. One sIA female had missing birth data in 1989. We decided to include all sIA women and controls with a first birth given in 1990 or later to ensure comprehensive birth data. We identified 169 sIA patients with a first birth in 1990 or later. We searched the Kuopio Intracranial Aneurysm Patient and Family Database for matched population controls for 169 sIA patients (three controls for each sIA patient), and of those included the controls with a first birth in 1990 or later. Finally, we identified 324 controls for the 169 patients with the sIA disease **(Figure 6)**. Data on drug purchases, hospital diagnoses, and causes of death was also obtained for matched controls. We also had data on the sIA patients' first-degree relatives.

Identification of the sIA women who had given birth was based on hospital ICD diagnoses, which were confirmed to be in unison with the date of birth of their children. In the matched controls, birth data was based on hospital ICD diagnoses as we did not have data on relatives of the matched controls.

In addition to hospital ICD diagnoses, the hospital medical records of all 169 sIA women were carefully reviewed to identify all patients who met the modern diagnostic criteria for pre-eclampsia. Furthermore, we utilized the

Haikara database, developed and established in KUH in 2002, which collects all the clinical information of the pregnancy and the childbirth. Patients with gestational and chronic hypertension were identified utilizing hospital ICD diagnoses, antihypertensive medication purchases, and medical records. We did not have access to the medical records of the matched controls. In addition to hypertensive disorders, we analyzed the prevalence of gestational diabetes and type 2 diabetes using hospital ICD diagnoses and diabetes medication use.

4.5.2 Variables

Hypertensive disorders of pregnancy were classified as described in the 2013 established Report of the ACOG Task Force on hypertension in pregnancy.[229] Hypertensive disorders were divided into pre-eclampsia (including superimposed pre-eclampsia and eclampsia), chronic hypertension, and gestational hypertension. Hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg on two occasions. Proteinuria was defined as ≥300 mg per 24-h urine collection, protein/creatinine ratio ≥0.3 or a dipstick reading of 1+. Pre-eclampsia was diagnosed based on new-onset hypertension after 20 weeks of gestation and new-onset proteinuria. Proteinuria was not required if new-onset hypertension was associated with any of the following: severe organ dysfunction, including elevated liver enzymes, thrombocytopenia, elevated serum creatinine, pulmonary edema, and cerebral or visual disturbances.[229] Chronic hypertension was defined as hypertension diagnosed before pregnancy or before 20 weeks of gestation. Gestational hypertension was defined as new-onset hypertension after 20 weeks of gestation in the absence of proteinuria or maternal organ dysfunction. Superimposed pre-eclampsia occurring in a patient with preceding chronic hypertension was defined as new onset or worsening of proteinuria or significant maternal organ dysfunction. Previously, the diagnostic criterion for pre-eclampsia in Finland has been a new-onset hypertension after the 20 weeks of gestation combined with proteinuria ≥300 mg per day.

For hospital ICD diagnoses, we used revisions 9 and 10. We had data on ICD-9 diagnoses from 1987 to 1995 and ICD-10 diagnoses from 1996 to 2014. For pre-eclampsia, ICD-9 codes 6424, 6425 and 6427 and ICD-10 codes O11 and O14 were used. For eclampsia, ICD-9 codes 6426 and ICD-10 codes O15 were used. ICD-9 codes 6420, 6421 and 6422 and ICD-10 codes O10 were used for chronic hypertension during pregnancy. For gestational hypertension, ICD-9 codes 6423 and ICD-10 codes O13 were used. For chronic, not pregnancy-related hypertension, ICD-9 codes 401 and 405 and ICD-10 codes I10 and I15 were used. Gestational diabetes was identified using ICD-9 codes 6488 and ICD-10 codes O24.4. For type 2 diabetes, ICD-9 codes 250 and ICD-10 codes E11 were included.

Hypertension was defined as a physician diagnosis of hypertension or the use of prescribed antihypertensive medication with at least one of the following ATC codes: C02 (antihypertensives), C03 (diuretics; thiazides), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system). Type 2 diabetes was defined by physician diagnosis or the use of prescribed medication with at least one of the following ATC codes: A10A (insulins and analogues); A10B (blood glucose-lowering drugs); or A10X (other agents used in diabetes), and the diabetes type was confirmed from the medical records. We had data on drug prescriptions from 1994 to 2014.

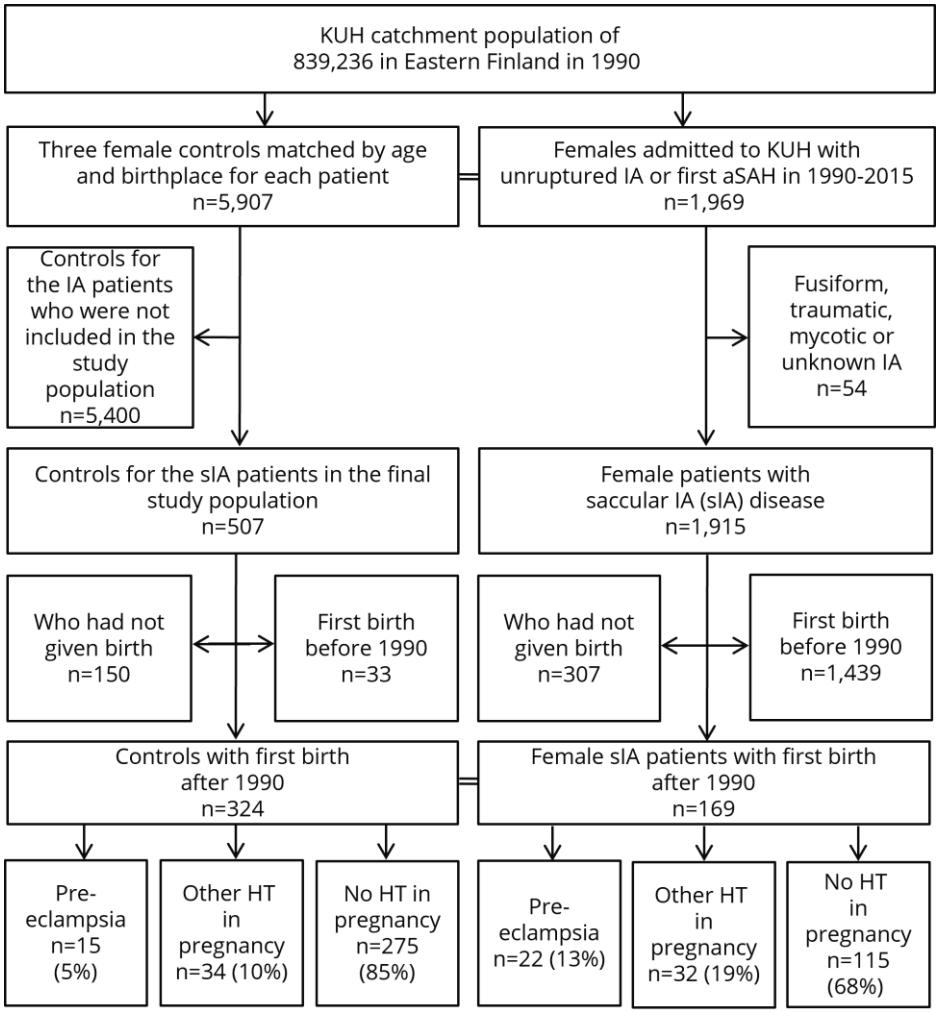

Figure 6. Flowchart of the Study II: Identification of pre-eclampsia and other pregnancy-related hypertensive (HT) disorders in the sIA patients and their matched population controls. Kotikoski et al. 2021. European Journal of Neurology / Study II. Reprinted by permission from Wiley.

4.6 STUDY III

The aim was to explore the familial associations of pre-eclampsia and the sIA disease by analyzing the prevalence of pre-eclampsia in the sIA patients, their female relatives, and their matched population controls, and by identifying familial sIA disease and familial pre-eclampsia.

4.6.1 Study population

The basic study population consisted of 1,895 female sIA patients with a first diagnosis of UsIA or aSAH between 1995 and 2018. Unruptured and aSAH patients with non-saccular aneurysm etiologies (fusiform, traumatic, mycotic) were excluded. Follow-up ended at death or December 2019. First-degree relatives (parents, children, siblings), nieces, and nephews of the sIA patients were identified along with random matched controls (3 for each sIA patient in the Kuopio Intracranial Aneurysm Patient and Family Database) **(Figure 7)**. Regarding the relatives determined for the sIA patients, there were duplicate cases in the group of relatives due to sIA families in the Kuopio Intracranial Aneurysm Patient and Family Database. These cases were handled in such a way that we ended up with a unique group of relatives. However, we decided to include the relatives who were also sIA patients in the Kuopio Intracranial Aneurysm Patient and Family Database. sIA women's clinical data from the Kuopio Intracranial Aneurysm Patient and Family Database was merged with prescription drug purchase data, hospital diagnoses, and causes of death. Data on prescription drug purchases, hospital diagnoses, and causes of death was also acquired for the relatives and matched controls of the sIA patients.

Identification of the female sIA patients who had given birth was based on hospital ICD diagnoses that were confirmed to be consistent with the date of birth of their children. The sIA patients' sisters and mothers who had given birth were identified in a similar manner to the sIA patients. Births of daughters and nieces of the sIA patients were identified using hospital ICD diagnoses. For the matched controls, birth data was based on

hospital ICD diagnoses as we did not have data on the matched controls' relatives. There was no missing birth data in 1987 or later.

First, to be able to reliably compare pre-eclampsia in the sIA women, in their female relatives, and in the matched controls, we identified all sIA women with a first birth in 1987 or later, ending up with 265 sIA patients. Then, we included their female relatives and matched controls and identified female relatives and matched controls with their first birth in 1987 or later, ending up with 394 female relatives and 546 matched controls Only one mother had a first birth in 1987 or later, therefore, mothers were excluded from the final study population, ending up with 393 female relatives **(Figure 7)**.

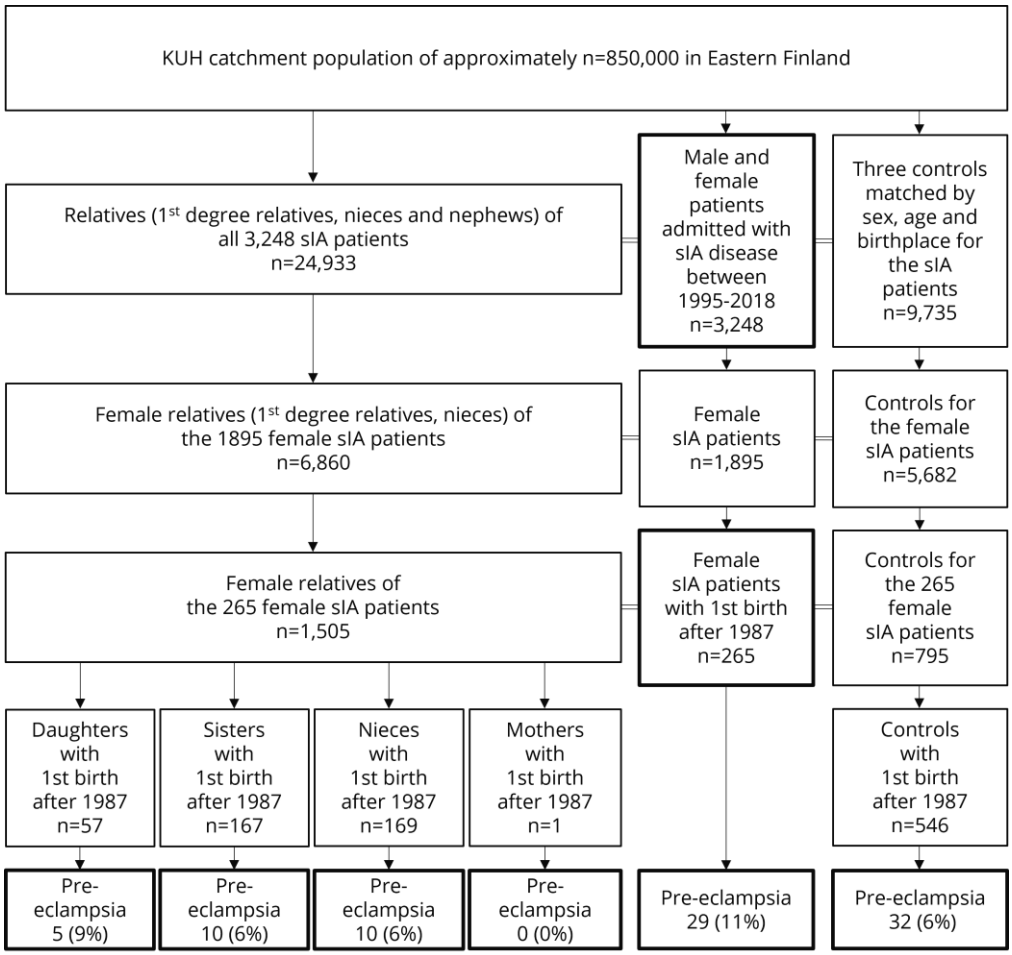

Figure 7. Identification of pre-eclampsia in a total of 265 female sIA patients, 394 female relatives, and 546 controls with their first birth in 1987 or later. Kotikoski et al. 2023. European Journal of Neurology / Study III. Reprinted by permission from Wiley.

Second, to study familial sIA disease and familial pre-eclampsia, we decided to search for all available families with these conditions by including all sIA female patients (n=1,895), and all female relatives (n=12,141) with pre-eclampsia diagnosis in any pregnancy. We identified 68 sIA patients and 375 female relatives who met the following criteria **(Figure 8)**.

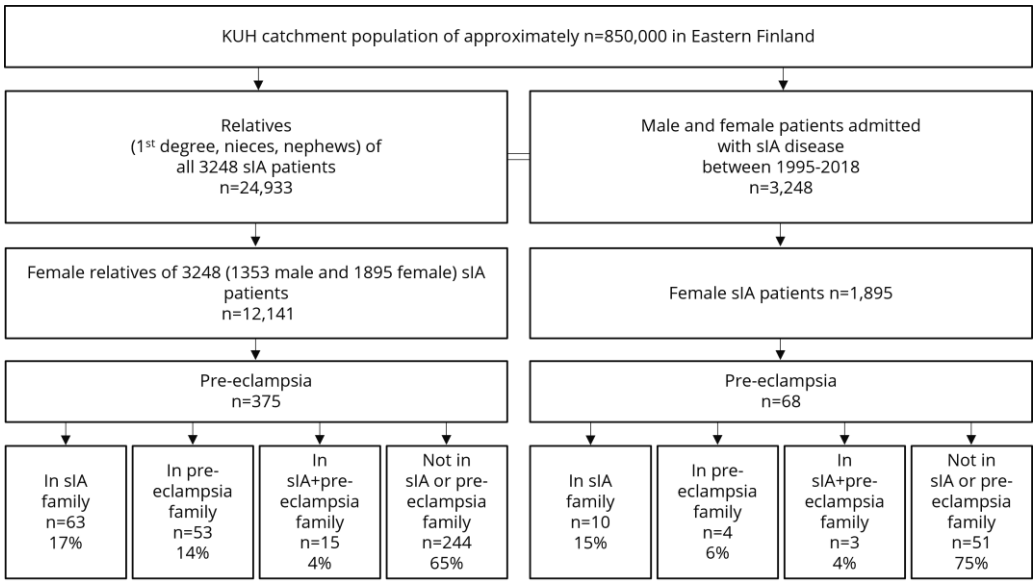

Figure 8. Identification of all female sIA patients and all female relatives with a pre-eclampsia diagnosis. Kotikoski et al. 2023. European Journal of Neurology / Study III. Reprinted by permission from Wiley.

In the present study, familial sIA disease was defined as ≥2 affected first-degree relatives in the same family, data recorded in the Kuopio Intracranial Aneurysm Patient and Family Database. Familial pre-eclampsia was defined as ≥2 affected first-degree relatives in the same family, data based on the ICD diagnoses and information on relatives of the sIA patients. The sIA+pre-eclampsia families had ≥2 first-degree relatives with sIA disease and ≥2 first-degree relatives with pre-eclampsia. Including all cases of pre-eclampsia determined earlier **(Figure 8)**, we identified all separate sIA families, pre-eclampsia families, and sIA+pre-eclampsia families **(Figure 9)**.

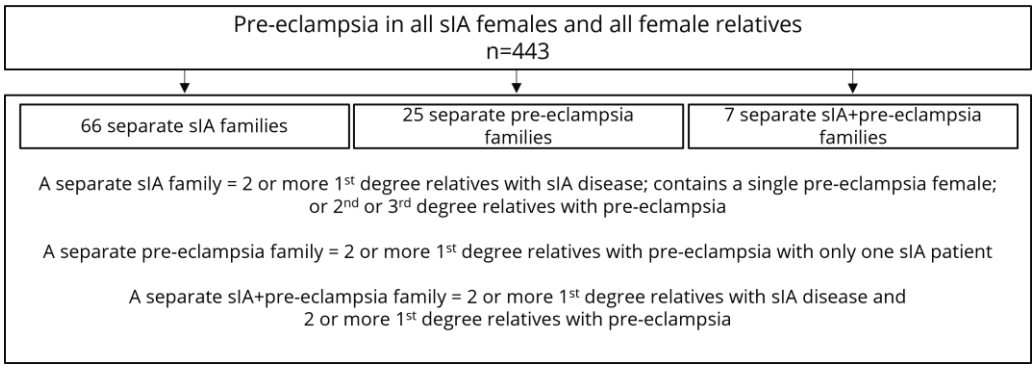

Figure 9. Identification of all separate sIA families, pre-eclampsia families, and sIA+pre-eclampsia families in the female sIA patients and all female relatives with a pre-eclampsia diagnosis. Kotikoski et al. 2023. European Journal of Neurology / Study III. Reprinted by permission from Wiley.

4.6.2 Variables

We used the data of hospital ICD codes from revisions 8, 9, and 10; ICD-8 was used between 1969 and 1986, ICD-9 was used between 1987 and 1995, and ICD-10 between 1996 and 2019 **(Table 7)**. Regarding relatives and controls, we chose to use the term IA disease instead of the sIA disease because their diagnoses were based on ICD hospital diagnoses, thus, other IA types could not be definitely excluded. However, some of the relatives were also patients in the Kuopio Intracranial Aneurysm Patient and Family Database due to familial sIA disease, and they were also included in the relatives with IA disease. For the sIA patients, the sIA diagnosis was set as described earlier, otherwise the ICD diagnoses described in **Table 7** were the same for the sIA patients, female relatives, and controls. Superimposed pre-eclampsia and eclampsia were included in pre-eclampsia. We did not review medical records to identify pre-eclampsia in this study.

Table 7. Hospital diagnoses obtained from the Finnish national registries; ICD-8, ICD-9, and ICD-10 codes for the sIA patients, their relatives, and their matched population controls.

Hospital diagnoses (1969-2019)	ICD-8 (1969-1986)	ICD-9 (1987-1995)	ICD-10 (1996-2019)
Pre-eclampsia	63703, 63704, 63709, 63799, 63710, 6612	6424, 6425, 6426, 6427	O11, O14, O15
Severe pre-eclampsia	63704, 63710, 6612	6425, 6426	O14.1, O15
Gestational diabetes	76110	6488	O24.4
ADPKD	75310	7531A	Q61.2
Intracranial aneurysm disease	43000, 43090	4300A, 4373	I60, I67.1, I69.0
Intracerebral hemorrhage	43100, 43190	431	I61, I69.1
Ischemic stroke	432-434	4330A, 4331A, 4339A, 4340A, 4341A, 4349A	I63, I69.3

Kotikoski et al. 2023. European Journal of Neurology / Study III. Reprinted by permission from Wiley.

In the sIA patients, their relatives, and their controls, the definition of hypertension and type 2 diabetes was based on medication use, for which we had data from 1994 to 2019. This allowed us to examine the use of antihypertensive medication for at least one year preceding the sIA admission and to systematically compare the use also in their relatives and their controls as we did not use other methods to identify hypertension. Medication use was determined as ≥2 purchases of prescribed medication at any time during the study period.[7] Drug-treated hypertension was

defined as the purchase of prescribed antihypertensive medication: C02 (antihypertensives), C03 (diuretics; thiazides), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system). Medically treated type 2 diabetes was defined as ≥2 purchases of prescribed A10B (blood glucose lowering drugs).

4.7 STATISTICAL METHODS

In Study I, the statistical analysis was performed with SPSS version 22.0 (IBM SPSS, Armonk, NY). Categorical variables were expressed as proportions and continuous variables as medians and interquartile ranges (25% and 75% quartiles). For categorical variables, groups were compared using the Chi-Square or Fisher's exact test, as appropriate. For all continuous variables, groups were compared using the Mann-Whitney U test. Multivariate analysis was performed using logistic regression to calculate ORs with corresponding 95% CIs for the presence of secondary hypertension with gender, age at first diagnosis, familial sIA disease, and number sIAs as variables. P values <0.05 were considered significant.

In Study II, statistical analysis was performed with SPSS version 22.0 (IBM SPSS, Armonk, NY). Categorical variables were expressed as proportions and continuous variables as medians and interquartile ranges (25% and 75% quartiles). For categorical variables, groups were compared using the Chi-Square or Fisher's exact test, as appropriate. For all continuous variables, groups were compared using the Mann-Whitney U test. P values <0.05 were considered significant. Additionally, R environment was used to calculate a figure.

In Study III, SPSS version 26.0 (IBM SPSS, Armonk, NY) was used for statistical analysis. Categorical variables were expressed as proportions and continuous variables as medians and interquartile ranges (25% and 75% quartiles). For categorical variables, groups were compared using the Chi-Square or Fisher's exact test, as appropriate. P values <0.05 were considered significant.

4.8 ETHICS APPROVAL

The study protocol was approved by the Research Ethics Committee of KUH. Data fusion from the national registries to the Kuopio Intracranial Patient and Family Database was performed with the approval of the Ministry of Social Affairs and Health of Finland. Written informed consent was obtained from all sIA patients before their data was added to the Kuopio Intracranial Patient and Family Database. In this retrospective study the requirement for consent of controls or relatives was waived as no study participants were contacted.

5 RESULTS

5.1 SECONDARY HYPERTENSION (STUDY I)

The study population included 2,704 patients with the sIA disease, of which 1,143 (42%) and 1,561 (58%) were diagnosed with unruptured sIA disease and with aSAH, respectively. Of all sIA patients, 776 died during their follow-up, resulting in a median follow-up time of 68 months.

Of all sIA patients, 2,029 (75%) had hypertension and 208 (10%) had a condition suggestive of secondary hypertension. Only 7 patients with a recorded ICD-10 code I15 were detected. Renal and renovascular diseases were the most common etiologies of secondary hypertension (N=94), followed by sleep apnea (N=57) and hypothyroidism (N=39). However, 46 (22%) had more than one condition that might be associated with secondary hypertension. Of the genetic causes, ADPKD was identified in 27 patients, representing 13% of all patients with secondary hypertension. Alternative genetic disorders were infrequent, for example, no cases of Liddle's syndrome were identified. Among the sIA patients with familial sIA disease, the frequency of hypertension (77%) and secondary hypertension (12%) did not notably differ from other sIA patients.

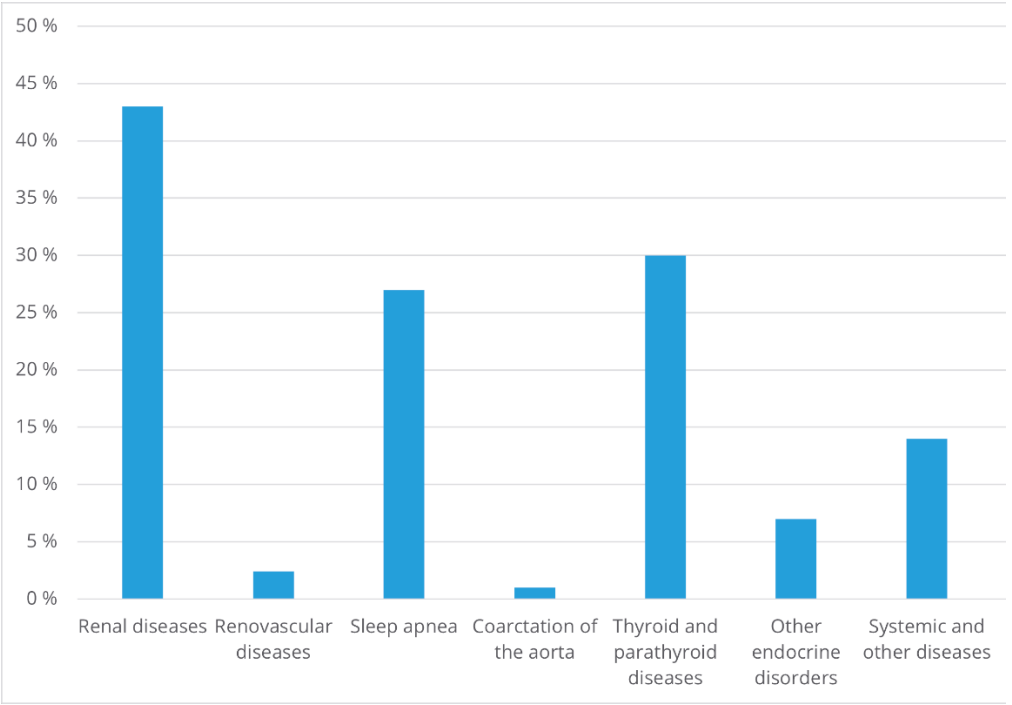

Figure 10. Frequency of underlying causes in 208 sIA patients with secondary hypertension.

When the 111 sIA patients with unruptured sIA disease and secondary hypertension were examined, the median age at first recorded diagnosis was 50 (43-58) years for hypertension, 54 (42-62) years for a condition considered as hypertension etiology, and 58 (51-65) years for unruptured sIA disease. Among the 97 aSAH patients, the median age at first recorded diagnosis was 50 (43-61) years for hypertension, 52 (40-67) years for a condition considered as hypertension etiology, and 55 (46-65) years for aSAH.

Table 8. Secondary, essential, and no detected hypertension (HT) in the 2,704 sIA patients admitted to Kuopio University Hospital from the Eastern Finnish catchment population between 1995 and 2014.

	Unruptured sIA patients n=1,143			aSAH patients n=1,561		
Variables of 2,704 sIA patients	Hypertension		No HT n=222	Hypertension		No HT n=453
	Secondary HT n=111	No secondary HT n= 810		Secondary HT n=97	No secondary HT n=1,011	
Median age at sIA diagnosis (quartiles)	58 (51-65)	59 (50-68)	50 (42-57)	55 (46-65)	55 (47-65)	50 (42-60)
Female patients	64 (58%)	475 (59%)	120 (54%)	48 (50%)	624 (62%)	236 (52%)
Familial sIA disease	18 (16%)	143 (18%)	49 (22%)	16 (16%)	105 (10%)	36 (8%)
Multiple sIAs (≥2)	32 (29%)	236 (29%)	56 (25%)	35 (36%)	310 (31%)	117 (26%)
Known positive smoking history	40 (36%)	351 (43%)	108 (49%)	48 (49%)	427 (42%)	193 (43%)

In terms of aneurysm characteristics, the aSAH patients with secondary hypertension had slightly smaller aneurysms than the sIA patients with essential hypertension or without hypertension. Irregularly shaped aneurysms were not prominent in secondary hypertension **(Table 9)**.

Table 9. Aneurysm characteristics of the 3,922 sIAs in the 2,704 sIA patients.

Variables of 3,922 sIAs	Unruptured sIA patients n=1,143			aSAH patients n=1,561		
Number of aneurysms within patient groups	Hypertension		No HT n=303	Hypertension		No HT n=639
	Secondary HT n=160	No secondary HT n=1,148		Secondary HT n=170	No secondary HT n=1,502	
Median size (mm) (quartiles)	4 (3-7)	4 (3-7)	4 (3-6)	4 (3-7)	5 (3-8)	6 (3-8)
ACoA location	25 (16%)	166 (14%)	34 (11%)	39 (23%)	376 (25%)	148 (23%)
Mbif location	55 (34%)	442 (39%)	119 (39%)	58 (34%)	433 (29%)	175 (27%)
ICA location	32 (20%)	263 (23%)	88 (29%)	38 (22%)	321 (21%)	164 (26%)
BAbif location	6 (4%)	62 (5%)	10 (3%)	8 (5%)	71 (5%)	24 (4%)
Other location	42 (26%)	215 (19%)	52 (17%)	27 (16%)	301 (20%)	128 (20%)
Irregular shape	33 (21%)	271 (24%)	83 (27%)	87 (51%)	932 (62%)	417 (65%)
Smooth shape	126 (79%)	861 (75%)	210 (69%)	80 (47%)	525 (35%)	188 (29%)
Unknown shape	1 (1%)	16 (1%)	10 (3%)	3 (2%)	45 (3%)	34 (5%)

Abbreviations: HT = hypertension; ACoA = anterior communicating artery; Mbif = middle cerebral artery bifurcation; ICA = internal carotid artery; BAbif = basilar artery bifurcation. Kotikoski et al. 2018. PLoS One / Study I, CC-BY 4.0. https://creativecommons.org/licenses/by/4.0/

Based on the multivariate logistic regression analysis of the 1,561 aSAH patients, secondary hypertension significantly associated with the quantity of sIAs (OR 1.32, 95% CI, 1.10-1.58, p=0.003) and male sex (OR 1.59, 95% CI, 1.04-2.43, p=0.034) **(Table 10)**. In contrast, none of the studied variables

were associated with secondary hypertension in the 1,143 patients with unruptured sIA disease.

Table 10. Multivariate logistic regression analysis of factors associated with secondary hypertension in the 1,561 patients with aSAH admitted to the Kuopio University Hospital from the Eastern Finnish catchment population from 1995 to 2014.

n=1,561	OR (95% CI)	p-value
Male gender	1.59 (1.04-2.43)	0.034
Age at aSAH (per year)	1.01 (0.99-1.03)	0.33
Familial sIA disease	1.74 (0.98-3.09)	0.058
Number of sIAs (per sIA)	1.32 (1.10-1.58)	0.003

5.2 HYPERTENSIVE DISORDERS OF PREGNANCY (STUDY II)

The final study population consisted of 169 female sIA patients who had their first sIA-related admission between January 1990 and October 2015, and who had their first birth in 1990 or later. For the 169 sIA patients, we identified 507 (3:1) matched controls, of whom 324 had their first birth in 1990 or later, comprising the final control group.

aSAH was detected in 57% and unruptured sIA disease in 43% of the 169 sIA women, with similar median age at sIA admission (41 years versus 40 years), respectively **(Table 11)**. Familial sIAs were detected more often with unruptured sIA disease than with aSAH (38% versus 11%), probably associated with the screening of the sIA families. The 169 sIA patients gave birth to a total of 381 children, with a median two children during the follow-up. The median age of the sIA patients at the birth of their first child was 29 years. In our study population, aSAH during pregnancy was rare, occurring in three (3%) aSAH patients. Among the 96 aSAH patients, aSAH was most frequently detected after the last birth in 74 (77%), followed by aSAH before the first pregnancy in 14 (15%) and aSAH between pregnancies in 5 (5%).

Of the 169 sIA patients, pre-eclampsia was identified in 22 (13%) during at least one of their pregnancies. Three of the sIA patients with pre-eclampsia were diagnosed based on medical record data meeting the ACOG pre-eclampsia criteria. Pre-eclampsia was more common in the patients with aSAH than in those with unruptured sIA disease (15% vs. 11%), and majority (79%) developed aSAH after pre-eclampsia.

Of the 324 controls, 15 (5%) were found to have pre-eclampsia, significantly fewer than the sIA patients (p=0.001). No cases of eclampsia were observed in either group.

We studied hypertension development before the first birth, between pregnancies, and after the last birth. Other hypertensive disorders of pregnancy **(Table 11)** comprised chronic hypertension during pregnancy and gestational hypertension. Chronic hypertension during any pregnancy was identified in 25 (15%) sIA patients. Of the sIA patients with a pregnancy-related hypertensive disorder who did not have pre-eclampsia

or chronic hypertension during any of their pregnancies, gestational hypertension was present in seven (4%). Pregnancy-related hypertensive conditions other than pre-eclampsia were more common in the sIA patients than in the control group (19% versus 10%). Of the 115 sIA patients with no pregnancy-related hypertensive disorders, 52 (45%) developed hypertension before the end of follow-up, more often than the controls with no pregnancy-related hypertensive disorders (25%).

Gestational diabetes occurred at similar rates in the female sIA patients and in their controls (13% versus 12%). In total, seven (4%) of the 169 sIA patients and 15 (5%) of the 324 controls were diagnosed with type 2 diabetes before the end of follow-up, whereas 13% of the sIA patients and 15% of the controls with gestational diabetes developed type 2 diabetes.

Table 11. Basic characteristics of the sIA patients and occurrence of pre-eclampsia and hypertensive (HT) disorders in pregnancy.

	Unruptured sIA patients n=73			aSAH patients n=96		
Variables of 169 sIA patients	Pre-eclampsia n=8	Other HT disorder in pregnancy n=11	No HT disorder in pregnancy n=54	Pre-eclampsia n=14	Other HT disorder in pregnancy n=21	No HT disorder in pregnancy n=61
Median age at sIA diagnosis (quartiles)	42 (33-49)	42 (37-47)	40 (34-45)	41 (31-45)	42 (35-47)	41 (31-46)
Familial sIA disease	2 (25%)	5 (45%)	21 (39%)	3 (21%)	4 (19%)	4 (7%)
ADPKD	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	2 (3%)
Multiple sIAs (≥2)	3 (38%)	2 (18%)	13 (24%)	2 (14%)	10 (48%)	19 (31%)
HT before any pregnancy	2 (25%)	8 (73%)	0 (0%)	0 (0%)	17 (81%)	0 (0%)
HT after pregnancy	6 (75%)	10 (91%)	24 (44%)	9 (64%)	20 (95%)	28 (46%)
Type 2 diabetes before pregnancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gestational diabetes	1 (13%)	2 (18%)	8 (15%)	2 (14%)	3 (14%)	6 (10%)
Type 2 diabetes after pregnancy	1 (13%)	1 (9%)	3 (6%)	0 (0%)	0 (0%)	2 (3%)

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Table 12 demonstrates the characteristics of 262 aneurysms among the 169 sIA women. Irregular shaped aneurysms were significantly more frequent (p=0.003) in the 22 sIA patients with pre-eclampsia (21/29=72%) than in the other sIA patients (100/233=43%).

Table 12. Aneurysm characteristics of the 262 sIAs in the 169 sIA patients.

Variables of 262 sIAs	73 Unruptured sIA patients with 107 sIAs			96 aSAH patients with 155 sIAs		
Number of aneurysms within patient groups	Pre-eclampsia n=13	Other HT in pregnancy n=18	No HT in pregnancy n=76	Pre-eclampsia n=16	Other HT in pregnancy n=36	No HT in pregnancy n=103
Median size (mm) (quartiles)	4 (3-6)	3 (3-6)	4 (2-5)	6 (5-10)	5 (4-6)	5 (3-7)
ACoA location	1 (8%)	1 (6%)	3 (4%)	6 (38%)	6 (17%)	19 (18%)
Mbif location	4 (31%)	9 (50%)	28 (37%)	4 (25%)	8 (22%)	26 (25%)
ICA location	5 (39%)	3 (17%)	24 (32%)	3 (19%)	9 (25%)	30 (29%)
BAbif location	1 (8%)	1 (6%)	2 (3%)	0 (0%)	3 (8%)	11 (11%)
Other location	2 (15%)	4 (22%)	19 (25%)	3 (19%)	10 (28%)	17 (17%)
Irregular shape	7 (54%)	4 (22%)	11 (14%)	14 (88%)	24 (67%)	61 (59%)
Smooth shape	6 (46%)	14 (78%)	65 (86%)	2 (13%)	12 (33%)	42 (41%)

Abbreviations: HT = hypertension; ACoA = anterior communicating artery; Mbif = middle cerebral artery bifurcation; ICA = internal carotid artery; BAbif = basilar artery bifurcation. Kotikoski et al. 2021. European Journal of Neurology / Study II. Reprinted by permission from Wiley.

We constructed lifelines illustrating clinical time points for the 22 sIA patients with pre-eclampsia (**Figure 11**). We included the first pre-eclampsia diagnosis in each patient. Lifelines were constructed based on the age at pre-eclampsia diagnosis (median 33 years). Pre-eclampsia was superimposed, i.e., hypertension predated pre-eclampsia in two (9%) patients. Five patients (23%) were diagnosed with the sIA disease prior to pre-eclampsia, while the majority (77%) developed the sIA disease after pre-eclampsia with a median interval of 10 years. Hypertension developed after pre-eclampsia in 13 patients with a median interval of 9 years. A total

of 68% sIA patients with pre-eclampsia were recorded with hypertension by the end of the follow-up with a median age of 41 years at the hypertension diagnosis.

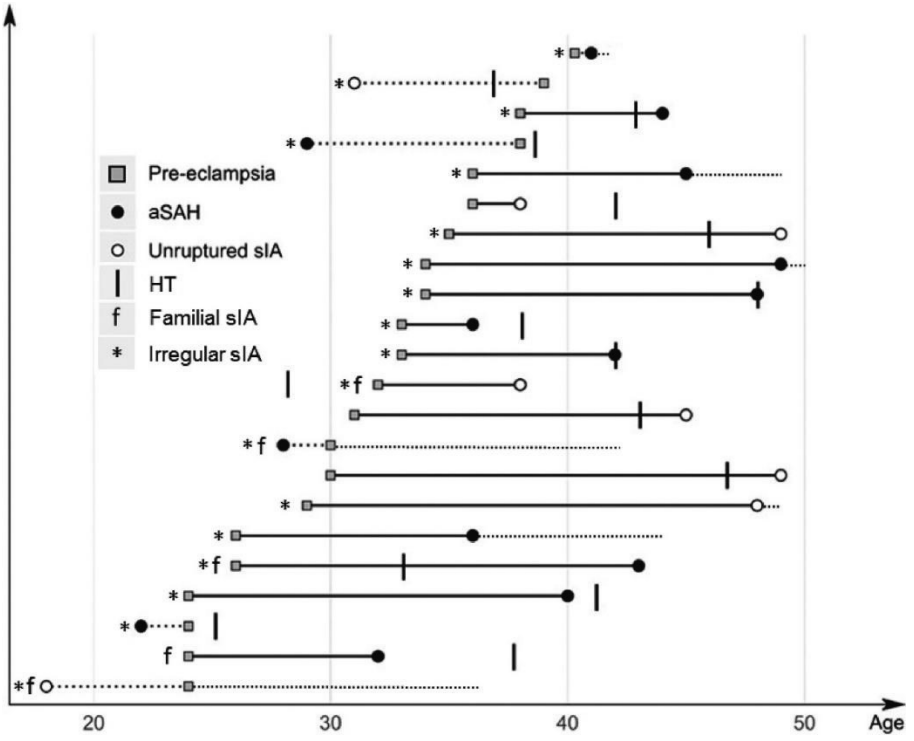

Figure 11. Clinical timelines of the 22 female sIA patients with pre-eclampsia. Ages at the diagnoses are illustrated for pre-eclampsia (grey squares), aSAH (black circles), unruptured sIA disease (white circles), hypertension (HT = Hypertension; black vertical lines), familial sIA (f) and irregular sIA (asterisks). Kotikoski et al. 2021. European Journal of Neurology / Study II. Reprinted by permission from Wiley.

5.3 FAMILIAL ASSOCIATIONS OF PRE-ECLAMPSIA AND SACCULAR INTRACRANIAL ANEURYSM DISEASE (STUDY III)

The basic study population included 265 sIA women who were first diagnosed with the sIA disease between 1995 and 2018, and who had their first birth in 1987 or later. In total, 265 sIA women gave birth to 602 (median 2) children. Familial sIA disease was detected more often in unruptured sIA disease than in aSAH (35% versus 17%), probably as a result of screening sIA families. For the 265 sIA patients, we identified 795 (3:1) matched controls, of whom 546 had their first birth in 1987 or later, forming the final control group. For the 265 sIA patients, we identified 393 female relatives who had their first birth in 1987 or later.

Pre-eclampsia occurred in 29 (11%) of the 265 sIA patients in the basic study population **(Table 13)**, and none of them had eclampsia. In 25 of them (86%) the first pre-eclamptic pregnancy predated the sIA admission, by a median of 13 years (quartiles 7-18). Pre-eclampsia occurred in two or more of the pregnancies in one of the 12 patients with unruptured sIA disease (8%) and in three of the 17 aSAH patients (18%). Severe pre-eclampsia occurred more frequently with aSAH (29%) than with unruptured sIA disease (17%). Among the 138 aSAH patients, familial sIA disease was more frequent with pre-eclampsia than without pre-eclampsia (24% versus 16%). Of the 29 sIA patients with pre-eclampsia, ADPKD was diagnosed in two patients (7%), more frequently than in the 236 sIA patients without pre-eclampsia (1%). Of the 17 aSAH patients with a diagnosis of pre-eclampsia, three women (18%) were identified to have a first-degree relative with pre-eclampsia, while none were found in the patients with unruptured sIA disease and pre-eclampsia.

The prevalence of pre-eclampsia did not differ significantly among the 393 female relatives and 546 controls, as five (9%) daughters, 10 (6%) sisters, 10 (6%) nieces, and 32 (6%) controls had pre-eclampsia. The sIA patients had a significantly higher prevalence of pre-eclampsia compared to the control group (p=0.01). Of the female relatives, one sister had eclampsia, while none of the controls had eclampsia.

The use of antihypertensive medication was analyzed in the basic study population **(Table 13)**. Of the 29 sIA patients with pre-eclampsia, 19 (66%) used antihypertensive medication, which was substantially similar to 144 of the 236 sIA patients without pre-eclampsia (61%). The sIA patients with pre-eclampsia started using antihypertensive medication at a younger age (median 38 years) compared to sIA patients without pre-eclampsia (median 42 years). In contrast, 16 out of 32 (50%) controls with pre-eclampsia used antihypertensive medication compared to 172 out of 514 (33%) controls without pre-eclampsia. Similarly, nine (36%) of the 25 female relatives with pre-eclampsia used antihypertensive medication compared to the 96 (26%) of the 368 female relatives without pre-eclampsia. The use of antihypertensive medication was generally more frequent in the sIA patients than in the controls; however, when considering the cases of severe pre-eclampsia, the use of antihypertensive medication was more frequent in the 8 out of 11 controls (73%) than in the four out of seven sIA patients (57%).

Furthermore, we studied comorbidities of all 1,505 female relatives of the 265 sIA patients to observe possible predispositions in the female relatives due to pre-eclampsia in the sIA patients **(Figure 7)**. We compared the 179 female relatives of the 29 sIA women with pre-eclampsia and the 1,326 female relatives of the 236 sIA women without pre-eclampsia. The prevalence of IA disease, intracerebral hemorrhage, ischemic stroke, ADPKD diagnosis, the use of antihypertensive or type 2 diabetes medication, or mortality did not significantly differ between these female relatives. Among all sisters, the prevalence of pre-eclampsia was higher in the 36 sisters of the 29 sIA patients with pre-eclampsia compared to the 306 sisters of the 236 sIA women without pre-eclampsia (8% versus 4%), but there were no apparent differences among daughters, mothers, or nieces.

Table 13. Basic characteristics of the sIA patients, their female relatives, and their matched population controls with the first birth in 1987 or later.

Female patients with 1st birth in 1987 or later						
Variables	Patients with unruptured sIA disease n=127	Patients with aSAH n=138	Daughters n=57	Sisters n=167	Nieces n=169	Controls n=546
Median age at sIA diagnosis (quartiles)	45 (37-50)	44 (36-49)				
Familial sIA disease	45 (35%)	23 (17%)				
Multiple sIAs	26 (20%)	38 (28%)				
ADPKD	1 (1%)	3 (2%)	0 (0%)	2 (1%)	0 (0%)	1 (0%)
Median age at the end of follow-up (quartiles)	53 (45-58)	53 (47-56)	28 (25-30)	49 (40-53)	34 (30-40)	53 (47-56)
Pre-eclampsia	12 (9%)	17 (12%)	5 (9%)	10 (6%)	10 (6%)	32 (6%)
Median age at first birth (quartiles)	28 (24-32)	27 (24-30)	24 (22-26)	27 (23-31)	25 (22-28)	28 (25-31)
Median age at first pre-eclampsia (quartiles)	32 (28-36)	33 (24-38)	25 (24-26)	30 (28-34)	21 (20-29)	30 (25-33)
Severe pre-eclampsia	2 / 12 (17%)	5 / 17 (29%)	0 / 5 (0%)	2 / 10 (20%)	2 / 10 (20%)	11 / 32 (34%)
Gestational diabetes	16 (13%)	14 (10%)	8 (14%)	20 (12%)	32 (19%)	67 (12%)
Use of anti-hypertensive drugs	74 (58%)	89 (64%)	5 (9%)	69 (41%)	31 (18%)	188 (34%)
Use of type 2 diabetes drugs	11 (9%)	6 (4%)	0 (0%)	8 (5%)	7 (4%)	37 (7%)

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In addition to the primary study population of 265 sIA patients, 393 female relatives, and 546 controls **(Figure 7)**, we screened all 1,895 female sIA patients and all 12,141 female relatives in the Kuopio Intracranial Aneurysm Patient and Family Database between 1995 and 2018 to identify all cases of pre-eclampsia **(Figure 8)**. In total, we identified 68 female sIA patients with pre-eclampsia and 375 female relatives with pre-eclampsia (111 daughters, 115 sisters, 13 mothers, 136 nieces). Of these pre-eclampsia cases, one sIA patient, one daughter, four sisters, and one niece had eclampsia. Of the 68 female sIA patients, 40 (59%) had aSAH. Among the 375 female relatives with pre-eclampsia, three (3%) of the daughters, six (5%) of the sisters, one (8%) of the mothers, and none of the nieces had an IA disease diagnosis. Of the 375 female relatives, 201 (54%) were relatives of sIA women and 174 (46%) were relatives of sIA men. Of all 443 pre-eclampsia cases, 75 (17%) had at least one first-degree relative with pre-eclampsia (familial pre-eclampsia) and 46 (10%) had at least one second-degree relative with pre-eclampsia.

In total, we discovered 32 families with familial pre-eclampsia **(Figure 9)**, 20 of which were families of female sIA patients and 12 were families of male sIA patients. Altogether, we identified seven separate sIA+pre-eclampsia families, six of which were sIA womens' families. We found no diagnoses of ADPKD in the members of these 32 pre-eclampsia families.

Among the 68 sIA patients, severe pre-eclampsia was more frequent in six of the 13 cases with familial sIA disease (46%) than in 11 of the 55 cases without familial sIA disease (20%) but did not reach statistical significance (p=0.057). Among the 68 sIA patients with pre-eclampsia, the use of antihypertensive medication did not significantly differ when comparing unruptured disease in 22 cases out of 28 (79%) to aSAH with 30 out of 40 cases (75%). In the 68 pre-eclamptic sIA patients and 375 pre-eclamptic female relatives, there was no significant difference in the use of antihypertensive medication among the different groups studied **(Figure 8)**: in sIA family (63%), in pre-eclampsia family (51%), in sIA+pre-eclampsia family (61%), and not in sIA or pre-eclampsia family (53%).

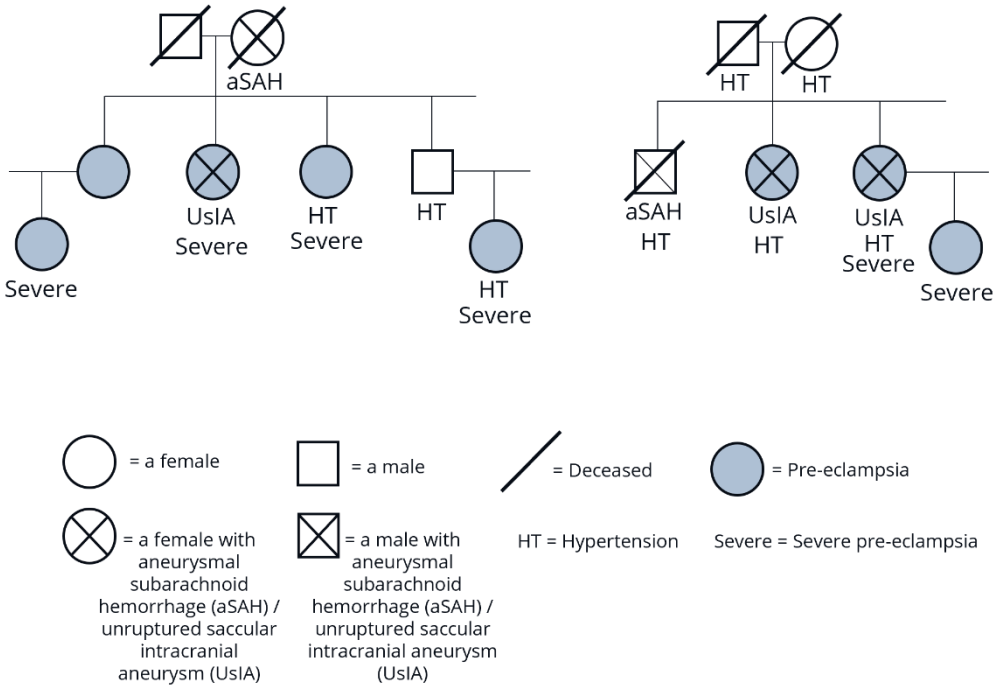

Figure 12. Illustration of two families with both familial sIA disease and familial pre-eclampsia. The family on the left side was identified from the relatives of female sIA patients, and the family on the right side was identified from the relatives of male sIA patients. Constructed pedigrees are truncated for visual clarity, focusing on the sIA disease, pre-eclampsia, and hypertension.

6 DISCUSSION

6.1 STUDY I

6.1.1 Secondary hypertension and saccular intracranial aneurysm disease

Hypertension is a major risk factor for stroke in general, as a 10 mmHg reduction in systolic blood pressure decreases the risk of stroke by 27%,[194] and a similar relationship has been described for aSAH.[17] In the recent years, there has been emerging evidence of the association between the sIA disease and some of the conditions causing secondary hypertension, including obstructive sleep apnea, hypothyroidism, and fibromuscular dysplasia.[202,204,207] However, the data on sIA disease and secondary hypertension in general is scarce.

Our retrospective population-based study demonstrated a high prevalence of hypertension in the 2,704 sIA patients, and 10% of them were suggested to have a secondary cause. Renal and renovascular diseases were the most common etiologies, followed by sleep apnea and hypothyroidism. ADPKD was a frequent genetic cause of hypertension among the sIA patients, as anticipated. In the literature, the prevalence of secondary hypertension has been traditionally described as 5-10% of hypertension,[156–159] and our results are in line with this. However, more recent estimates suggest a higher prevalence, up to 40% among the general hypertension population,[161] and up to 51-66% in resistant hypertension.[161,162]

The prevalence of renal diseases (43%), sleep apnea (27%), and hypothyroidism (19%) was high among the secondary hypertension patients. However, the prevalence in all 2,029 hypertensive sIA patients (4%, 3%, 2%, respectively) is comparable to previous estimates, whereas the prevalence of renal artery stenosis and hyperaldosteronism were lower than in the previous estimates.[15] This might be explained by methodological reasons, as renovascular disease and hyperaldosteronism

are particularly underdiagnosed.[163] In unruptured sIA patients, the overall prevalence of hypothyroidism has been reported to be higher (4-18%) than in their controls (3-4%).[204–206] Additionally, the prevalence of sleep apnea has been recorded as high as 68% in men and 34% in women in patients with unruptured sIA disease.[202] These findings could indicate that these conditions may actually be more common among sIA patients and may complicate treating hypertension in these patients.

In this study, multiple aneurysms were associated with secondary hypertension in the aSAH patients. Hypertension in general has not been associated with multiple sIAs in the Eastern Finnish population,[10] although a meta-analysis found an association.[44] Our finding may be related to characteristic features of secondary hypertension, including the hypertension severity and resistance. Fibromuscular dysplasia has been associated with multiple sIAs,[207] but it is relatively infrequent accounting for up to a few percent of identified secondary hypertension patients,[15] and was found in only one patient in our study population. ADPKD has also been associated with multiple sIAs,[11] which may have influenced our results. Aneurysm size was not considerably associated with secondary hypertension, consistent with the conception that hypertension is associated with aneurysm formation rather than with their growth.[10]

One observation that became clear already in the initial phase of this study was that the hospital-based ICD-10 codes of secondary hypertension (I15) were scarce (n=7), which would have covered only 0.3% of all sIA patients with hypertension. It seems that there is insufficient identification of secondary hypertension, or insufficient use of the appropriate ICD code, or both. Several studies have documented that secondary hypertension is an underdiagnosed condition.[163,165] Reasons for underdiagnosis may include insufficient recognition of clinical symptoms, lack of systematic protocols, laborious diagnostic process, or the long-standing consensus among physicians that secondary hypertension is rare and affects only 5-10% hypertensive patients.[163] Additionally, the most recent European Society of Hypertension Guidelines state that it is not recommended to screen all patients for secondary causes.[176] At the same time, age at treatment of the underlying cause has been shown to affect the

hypertension outcome,[212,214] highlighting the importance of timely treatment. This poses a challenge, as much depends on the clinician's consideration.

6.1.2 Strengths and limitations

To our knowledge, this is the first study in the literature to link secondary hypertension to the sIA disease. This study has several advantages arising from the Finnish health care system. The use of the KUH catchment population provides a cohort that is unselected and minimally biased. The Finnish personal identification code system allows maintaining comprehensive national registries and linking data from multiple registries. During the study period (1995-2014), the Kuopio Intracranial Aneurysm Patient and Family Database was prospectively managed in accordance with standard practice. Other subtypes of IAs were reliably excluded as all sIAs were confirmed by four-vessel angiography. We had access to medication purchases at least one year prior to sIA admission and until the end of follow-up. The medication purchase data in Finland is comprehensive due to a nationwide registry that includes all pharmacies and is maintained by The Social Insurance Institution of Finland.

Our study also has limitations. The major limitations are the features associated with a retrospective observational study. The patients were not screened for secondary hypertension at the clinical visits. We used only hospital-based diagnoses for the initial identification of secondary hypertension causes and did not include data from primary care or private health care, which might have underestimated the prevalence. The use of levothyroxine or other thyroid medications was not analyzed, which might have underestimated the prevalence of thyroid disease. The method used to identify secondary hypertension may be insensitive and represents our interpretation. Concurrently, we may have included patients in whom the comorbidity is an incidental diagnosis rather than a cause, and it is likely that we did not identify all patients with secondary hypertension. Nevertheless, defining causal relationships in secondary hypertension is challenging despite the approach used. Finally, we did not use a control

cohort because we did not have access to their medical records, thus, the analysis cannot conclude whether secondary hypertension is more common in the sIA patients than in the general population.

6.1.3 Future considerations

Hypertension is an essential modifiable factor in primary and secondary stroke prevention.[368] Post-treatment blood pressure control has been reported insufficient in patients with sIA disease and is associated with poorer long-term prognosis.[369] Effective treatment of hypertension in patients with sIA disease and in individuals with an increased risk of sIA disease is emphasized. Undiagnosed secondary hypertension is a potential cause of inadequate blood pressure control, and, thus, should not be overlooked.

Among the endocrine causes of hypertension the prevalence of hypothyroidism has been reported to be higher in patients with UsIAs than in their controls.[204,206] In our study, the number of patients with thyroid disease was also high. In the future, it would be interesting to investigate the association between thyroid diseases and the sIA disease in our sIA cohort and their controls utilizing medication purchase data. Additionally, the connection of sleep apnea and sIA disease should be further studied. As familial hyperaldosteronism type 1 has been described to be associated with aSAH (4% of the patients),[210] and activation of aldosterone receptors has been described to be involved in the pathogenesis of the sIA disease,[370] it would be interesting to study the relationship between the sIA disease and the more common but underdiagnosed primary aldosteronism.[165]

Secondary causes of hypertension should be considered in the sIA patients with hypertension, particularly in the aSAH patients with multiple sIAs. These patients should be evaluated for clinical evidence for sleep apnea, thyroid disease, or renal disease, and screening should be considered to ensure early detection of the identifiable cause of hypertension. As reaching a diagnosis of secondary hypertension may often be time-consuming and requires the input of many specialties, wider use of for example hypertension specialists and development of follow-up

protocols could be beneficial. Personalized treatment of hypertension, including selection of antihypertensive medication, could result in more optimal hypertension control in primary and secondary stroke prevention. In the future, artificial intelligence could be used to identify some of the secondary hypertension etiologies by combining data of patient biomarkers and genomics.[371] Artificial intelligence could additionally be used in the construction of clinical timelines with defined time points from the Kuopio Intracranial Aneurysm Patient and Family Database and national databases for better detection, optimal therapy, follow-up, and outcome of secondary hypertension in patients with the sIA disease.

6.2 STUDY II AND STUDY III

6.2.1 Pre-eclampsia and saccular intracranial aneurysms

Pre-eclampsia is a well-established risk factor for stroke during pregnancy and in the long term.[24] Pre-eclampsia and sIA disease have only been studied in the context of pregnancy-related aSAH.[82,372] Hypertension is a common risk factor for the development of both pre-eclampsia and sIA disease.[10,244] The significance of pre-eclampsia in the development of UsIAs or the risk of aSAH has not been confirmed.

In Study II, we found that pre-eclampsia was significantly more common in the sIA women than in the matched controls (13% versus 5%). Additionally, the prevalence of other hypertensive disorders was higher (19% versus 10%). The incidence of gestational diabetes was not notably different (13% versus 12%). Irregularly shaped aneurysms were significantly more frequent in the sIA patients with pre-eclampsia than in the other sIA patients. In Study III, we confirmed the observation that pre-eclampsia was more common in the sIA patients than in the matched controls in an extended study population. The prevalence of pre-eclampsia did not differ significantly between the relatives of the sIA patients and the matched controls. Severe pre-eclampsia and recurrent pre-eclampsia were more common with aSAH than with usIAs, but the difference was not significant. Familial pre-eclampsia and familial sIA disease were concurrent

in seven (22%) of the 32 families with familial pre-eclampsia. Severe pre-eclampsia was more commonly present with familial sIA disease than without familial sIA disease (46% versus 20%) among all sIA patients with pre-eclampsia.

In our study population, the frequency of hypertension detected by the end of the study period was high (approximately 70%), suggesting an increased cardiovascular risk burden. However, gestational diabetes, which is strongly associated with lifestyle,[269] was detected similarly in the sIA women and their controls. Superimposed pre-eclampsia was present in less than 10% of the pre-eclamptic sIA patients. Pregnant women and their blood pressure levels are carefully monitored in Finland, so underlying hypertension does not seem to contribute significantly to the process of pre-eclampsia in women with the sIA disease. However, about half of the aSAH patients with pre-eclampsia who were on antihypertensive medication started the antihypertensive medication during the study period after the aSAH diagnosis, so it is possible that there is underlying untreated hypertension that predisposes to the aneurysm rupture. On the other hand, the aSAH women in our studies were quite young (median age <45 years at aSAH diagnosis in both studies), so they may indeed have developed hypertension more frequently after aSAH because of the age distribution. In Study II, the prevalence of hypertension at the end of the follow-up was higher in the sIA patients with pre-eclampsia than in other sIA patients (68% versus 56%), whereas in Study III the difference was flattened (66% versus 61%). In Study II, the sIA female population was slightly younger than in Study III, which probably explains the difference, because when the Study III population was analyzed, the sIA patients with pre-eclampsia had their hypertension diagnosis at a younger age (median 38 years) compared to sIA women without pre-eclampsia (median 42 years).

Pre-eclampsia was more prevalent in the aSAH patients than in the unruptured patients in both Study II and Study III (15% versus 11% and 12% versus 9%, respectively). The higher overall prevalence in Study II is explained by methodological reasons, as in Study II the medical records were reviewed and only hospital diagnoses were used in Study III. It is likely

that as the different pathophysiological factors are known to be involved in the process of aneurysm formation and aneurysm rupture, and this is reflected in the prevalence of pre-eclampsia in these groups. Unfortunately, we did not have data on smoking or alcohol consumption, which are important risk factors for aSAH, and interestingly, smoking has been reported as a protecting factor for pre-eclampsia.[256] When all sIA patients with pre-eclampsia (Study III) were analyzed, there was no difference in the antihypertensive medication use between patients with unruptured and ruptured sIAs (79% versus 75%), indicating that hypertension alone does not explain the higher prevalence of pre-eclampsia in female patients with aSAH. The prevalence of gestational diabetes and the use of type 2 diabetes medication was less common in the aSAH patients with pre-eclampsia compared to unruptured sIA patients with pre-eclampsia, consistent with the previous studies suggesting that type 2 diabetes does not associate with rupture risk.[39]

Pre-eclampsia was observed to significantly associate with an irregularly shaped aneurysm wall, which is an established risk factor for aneurysm rupture.[94] During the process of aneurysm formation, endothelial dysfunction, inflammation, and oxidative stress are involved in the reconstruction of the aneurysm wall.[63] The pathogenesis of pre-eclampsia has similar vascular features, including endothelial injury, proinflammatory state, and oxidative stress,[218] and it is plausible that these mechanisms could influence aneurysm development or affect the wall structure of an already formed aneurysm. Recurrence and severity of pre-eclampsia have been associated with increased risk of cardiovascular disease,[346,347] thus, accumulating endothelial injury may explain the higher prevalence of severe form and recurrence of pre-eclampsia in the aSAH patients in our study population.

Both sIA disease and pre-eclampsia are complex traits, as an affected family member increases the risk by approximately threefold in both conditions.[1,248] In pre-eclampsia, both mother and father contribute to the familial linkages.[28,29] As GWAS have become more feasible in the recent years, more risk loci for complex traits have been identified. The results suggest that the preponderance of the identified pre-eclampsia risk loci

have associations with cardiovascular traits,[32,33] while the genetic roles of blood pressure, smoking, and endothelial cell signaling have been verified in the sIA disease. Overlap of the identified risk loci for the sIA disease and pre-eclampsia has been sparse. Of the 17 risk loci for the sIA disease in the largest GWAS to date,[14] rs2681472,[373] SLC22A4/OCTN1,[374] and SLC22A5/OCTN2[375] were also associated with pre-eclampsia. Higher ergothioneine levels were reported in pre-eclampsia, which may be due to increased SLC22A4 expression, regulated by inflammatory cytokines.[374,376] Downregulation of SLC22A5 was reported in pre-eclamptic placentas as a result of hypoxia.[375] rs2681472 has been linked to hypertension, but the association of SLC22A4 and SLC22A5 with the sIA disease remains unclear.

When we studied pre-eclampsia in the sIA patients, their relatives, and their controls, the frequency of pre-eclampsia did not differ between female relatives and matched controls, suggesting that familial aggregation of pre-eclampsia is not the cause of increased occurrence in the sIA patients. In the daughters, the incidence was slightly higher than in the controls (9% versus 6%), which could be explained by the rapidly increasing prevalence of maternal obesity reported in Finland,[261] or by new, more comprehensive guidelines for the diagnosis of pre-eclampsia published in 2013.[229]

Seven families with co-occurrence of familial sIA disease and familial pre-eclampsia were found. The frequency of severe forms of pre-eclampsia was highest in these seven families compared with other cases of pre-eclampsia, whereas the use of antihypertensive medication use did not aggregate significantly. ADPKD, a common hereditary disease, increases the risk of sIA disease and pre-eclampsia.[11,264] In our study population, ADPKD was more common with than without pre-eclampsia in the sIA patients, but not in the female relatives or controls. We found no diagnosis of ADPKD in the members of 32 pre-eclampsia families, so the co-occurrence of the sIA disease and pre-eclampsia in some of these families cannot be explained by ADPKD. It is possible that even though the co-occurrence of familial pre-eclampsia and familial sIA disease was lower than originally expected, these diseases may lead to more severe forms

when they co-occur, and there may be an undiscovered shared genetic pathway in these families.

6.2.2 Strengths and limitations

To the best of our knowledge, this is the first study in the literature that links pre-eclampsia with the sIA disease. These studies have several strengths derived from the Finnish health care system. We used an unselected KUH catchment population. The used the Finnish personal identification code system that allows us to link data from national registries. All patients with the sIA disease were confirmed by four-vessel angiography, other types of IAs excluded. During the study periods (1990-2015 and 1995-2018), the Kuopio Intracranial Aneurysm Patient and Family Database was maintained in a prospective and standardized manner. All antihypertensive and type 2 diabetes medications are sold in pharmacies by prescription in Finland, and all drug purchases were obtained from the national registry. In Finland, maternity clinics monitor pregnancies with standardized follow-up visits and check blood pressure levels and urine samples. This ensures identification of both chronic underlying hypertension and new-onset pregnancy-related hypertensive disorders. Almost all births in Finland take place in hospitals (99.4% in 2020),[377] which contributes to the availability of comprehensive national birth data during the study period, including data on pre-eclampsia. The quality of the Finnish Hospital Discharge Register improved considerably towards the 1990s, and the accuracy of the register is generally considered to be good.[378]

We also had limitations in our studies. One disadvantage is that the Kuopio Intracranial Aneurysm Patient and Family Database does not contain reliable data on the BMI or smoking habits. In Study II, there was a gap in the data on medication purchases from January 1990 to December 1993 and from January 2015 to October 2015. However, we believe this was compensated by additionally including a physician's hypertension diagnosis into the definition of hypertension. In Study III, we only used medication purchases to identify hypertension and type 2 diabetes;

however, we had access to medication purchases at least one year prior to sIA admission and one year after the end of follow-up due to the study period between 1995 and 2018 and defined medication use as at least 2 purchases to identify medication use.

As acetylsalicylic acid is used for the prevention of pre-eclampsia and for the primary and secondary prevention of cardiovascular disease, it would be important to take confounding factors into account. In Finland, acetylsalicylic acid is cheaper if it is bought without a prescription. Therefore, it is not possible to accurately identify users of acetylsalicylic acid from the prescription drug registry, and the use of acetylsalicylic acid was not studied.

In Study III, we may have missed some sIA families because we based the definition of familial sIA disease on the recorded data in the Kuopio Intracranial Aneurysm Patient and Family Database, as new diagnoses may have occurred in the relatives after the data was calculated in the database. However, we believe this method allowed a comparable analysis of the data. When we studied the familial associations of pre-eclampsia, we included all female relatives of sIA women and men in order to identify all attainable pre-eclampsia families. We did not have data on the partners of male sIA patients, which may have resulted in undetected pre-eclampsia families. We did not have ICD-8 code data for patients with the first sIA diagnosis between 2015 and 2018, including relatives and matched controls of these sIA patients, which may have led to undetected pre-eclampsia families. Regarding first-degree relatives, no distinction was made between full- and half-siblings, which may have led to an underestimation of the sibling effect. Due to the age distribution of the study population, there was limited birth data particularly for the mothers of the sIA women, as well as for daughters and nieces. We could not examine familial relationships of pre-eclampsia in the matched controls because we did not have access to the relatives of the matched controls.

6.2.3 Future considerations

Pre-eclampsia is an established risk factor for cardiovascular and cerebrovascular disease. This association may reflect the coincidence of risk factors or the causal role of pre-eclampsia, or both. However, more research is needed on screening strategies for when and how to screen the mother after a pre-eclamptic pregnancy.[379] The results of a scoping review suggest that there is a lack of education among women with a history of pregancy-related hypertensive disorder and limited knowledge among health care professionals.[380] We found a considerable time interval between pre-eclampsia and the development of hypertension (median 9 years), which should be considered in reducing the cardiovascular burden in women, including the risk of the sIA disease. Efforts to improve patient education about the long-term risk of hypertension and stroke are suggested, along with advice on smoking cessation and home blood pressure monitoring. There have been studies of polygenic risk scores that predict pre-eclampsia and subsequent cardiovascular risk,[381] as well as novel biomarkers specific for pre-eclampsia that may be used in the future.[382]

Future research on the sIA disease should continue to explore the genetic predispositions and novel risk factors. Confirmation of the association between the sIA disease and pre-eclampsia in other population-based sIA cohorts is warranted. Genetically, the Finnish population is surprisingly unlike in the West and East, which is characterized by the founder effect and genetic bottlenecks.[223] According to previous studies, Eastern and Western Finnish populations appear to differ with respect to both sIA disease and pre-eclampsia.[52,221] This study represents a defined Eastern Finnish population that may present a high-risk subpopulation for both sIA disease and pre-eclampsia. To confirm the association of these complex traits, additional research in different genetic settings is needed in the future. In addition to GWAS, investigating the role of gene-environment interactions may provide a more comprehensive understanding for both sIA disease and pre-eclampsia. Explicit

mechanisms and the full extent of the involvement of epigenetics are still areas of active investigation.[126,127,336]

In terms of clinical significance, most sIAs were discovered after the pre-eclampsia diagnosis, so a history of pre-eclampsia in particular may be a risk factor for developing sIAs later in life. Additionally, pre-eclampsia may predispose to an increased risk of instability in the yet unruptured aneurysm wall. Further research into the biomechanics of how the walls of the brain arteries are affected by pre-eclampsia is warranted and may contribute to improved prevention strategies. For both sIA disease and pre-eclampsia, research efforts should aim to establish predictive models that integrate genetic factors to allow personalized risk assessments and development of targeted therapies. Artificial intelligence could be used to construct clinical timelines with defined time points from the Kuopio Intracranial Aneurysm Patient and Family Database and national databases. This data could be used to optimize the detection, therapy, follow-up, and outcome of pre-eclampsia in patients with the sIA disease.

7 CONCLUSIONS

1. Hypertension was highly prevalent in the patients with the sIA disease. In addition to renal and renovascular causes, sleep apnea and hypothyroidism were common causes of secondary hypertension. Multiple sIAs associated with secondary hypertension in the patients with aSAH.
2. Pre-eclampsia and other hypertensive disorders of pregnancy were significantly more frequent in the patients with the sIA disease than in their population controls. Irregularly shaped aneurysms were more frequent in the sIA patients with pre-eclampsia, which may indicate an increased risk of rupture.
3. The prevalence of pre-eclampsia was not significantly different in the female relatives compared with the controls. The co-occurrence of familial sIA disease and familial pre-eclampsia was less common than initially expected. Our results indicate that sIA disease and pre-eclampsia do not significantly share risk factors, which may suggest that pre-eclampsia is a novel risk factor for the sIA disease.

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ORIGINAL PUBLICATIONS (I – III)

I

Secondary hypertension in patients with saccular intracranial aneurysm disease: A population based study

Satu Kotikoski, Jukka Huttunen, Terhi J. Huttunen, Katariina Helin, Juhana Frösen, Timo Koivisto, Mitja I. Kurki, Mikael von und zu Fraunberg, Ilkka Kunnamo, Juha E. Jääskeläinen, and Antti E. Lindgren

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RESEARCH ARTICLE

Secondary hypertension in patients with saccular intracranial aneurysm disease: A population based study

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Data Availability Statement: Major parts of our data are derived from Finnish national health registries which are regulated by the Finnish Institute of Health and Welfare. By their strict instructions we are not allowed to share our datasets openly in any form, not even anonymized, due privacy requirements of Finnish law. Interested researchers can be granted permissions to our datasets, but this requires individual evaluation of the intended use of the data. Final permission to data will be granted by Institute of Health and Welfare, after Kuopio Intracranial Aneurysm Patient

Abstract

Background

Secondary hypertension is a serious form of hypertension, involving 5% to 10% of all hypertension patients. Hypertension is a risk factor of the saccular intracranial aneurysm (sIA) disease and subarachnoid hemorrhage from ruptured sIA (aSAH), but the impact of secondary hypertension on sIA disease is poorly known. In a defined Eastern Finnish sIA population we studied the prevalence of secondary hypertension and its impact on sIA disease phenotype.

Methods

We included 2704 consecutive sIA patients first admitted to Kuopio University Hospital from 1995 to 2014. Their clinical data from Kuopio Intracranial Aneurysm patient and Family Database was fused with prescription drug usage data, hospital diagnoses and causes of death, retrieved from nationwide registries. Medical records of hypertensive sIA patients were reviewed to confirm or exclude secondary hypertension. Prevalence of secondary hypertension and associated diagnoses were calculated. Logistic regression was used to identify clinical characteristics of sIA disease that associated with secondary hypertension.

Results

We identified 2029 (75%) sIA patients with hypertension and 208 (10%) of them had secondary hypertension. Most frequent conditions associated with secondary hypertension were kidney and renovascular diseases (45%), sleep apnea (27%) and hypothyroidism (19%); 46 (22%) of the 208 patients had more than one such condition. In multivariate logistic regression analyses of 1561 aSAH patients, secondary hypertension significantly

and Family Database board has granted permission for data access. We did not have special privileges to access data from the Institute of Health and Welfare, and other qualified researchers will be able to access the data in the same manner as we did. Research coordinator of Kuopio Intracranial Aneurysm Patient and Family Database board can be contacted via web form in http://kuopioneurosurgery.fi/research-group/#dontaion_box. Authorization to access data of Institute of Health and Welfare can be applied for at https://thl.fi/en/web/thlfi-en/statistics/information-for-researchers/authorisation-application.

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associated with the number of sIAs (p = 0.003; OR 1.32; 95% CI 1.10–1.58) and male gender (p = 0.034; OR 1.59; 95% CI 1.04–2.43).

Conclusions

Secodary hypertension was relatively common (10%) among hypertensive sIA patients. Secondary causes for hypertension should be taken into account in hypertensive sIA patients, especially in aSAH patients with multiple intracranial aneurysms. Further research is indicated to evaluate the impact of secondary hypertension on the long-term rupture risk of unruptured sIA carriers and long-term outcome after aSAH.

Introduction

The prevalence of saccular intracranial aneurysm (sIA) disease in general population is around 3% [1]. Most sIAs do not cause symptoms and remain unnoticed during life [2], if not incidentally found in neuroimaging for other reasons or by screening sIA families [3]. Aneurysmal subarachnoid hemorrhage (aSAH), most often caused by rupture of sIA wall is a severe form of stroke with high mortality and neurological morbidity [4–10]. Known risk factors for sIA disease and aSAH include female gender, age, smoking, hypertension, sIA family, and autosomal polycystic kidney disease (ADPKD) [2, 9–14].

Secondary hypertension, resulting from an underlying identifiable cause, is a more serious form of hypertension, involving about 5% to 10% of all hypertension patients [15–18]. Etiologies for secondary hypertension include chronic kidney diseases [19], renovascular hypertension [20], primary aldosteronism [21], and obstructive sleep apnea [22], as well as number of rare causes [17]. Reaching the diagnosis of secondary hypertension is often challenging; indicators include young age, persistent hypertension requiring more than three types of antihypertensive medication, weakened response to previous medications, and exceptionally high blood pressure levels [23, 24]. Proper treatment of secondary hypertension may reduce the risk of serious cardiovascular complications, including heart disease, kidney failure and stroke.

Hypertension is a common risk factor of sIA disease and aSAH [2, 25], but published data on the occurrence and significance of secondary hypertension in sIA patients has remained scarce. The Kuopio Intracranial Aneurysm Patient and Family Database (www.kuopioneurosurgery.fi) contains all cases of unruptured and ruptured sIAs admitted to the Kuopio University Hospital (KUH) from a defined Eastern Finnish catchment population since 1980 [12]. The present study included 2704 sIA patients (1143 unruptured and 1561 ruptured) first admitted to KUH from 1995 to 2014. Their registry data, including the diagnoses, prescribed drugs and causes of deaths, were obtained from the nationwide registries and fused with the clinical data[2,7,8,13]. We retrospectively studied the sIA patients to define the prevalence of secondary hypertension on carriers of sIA disease and its impact on sIA disease phenotype.

Materials and methods

Study population

Kuopio Intracranial Aneurysm Patient and Family Database. During the study period from 1995 to 2014 KUH Neurosurgery exclusively provided neurosurgical services for a defined KUH catchment population in Eastern Finland. Geographical area remained the same

but population decreased from 882671 to 840587. The median age increased from 37 to 42 in males and from 40 to 45 in females, and the proportion of males remained unchanged at 49% [8, 12].

All patients with verified SAH by CT or spinal tap have been admitted to KUH for angiography and treatment if not moribund. Unruptured sIAs have been verified by four-vessel digital subtraction angiography, magnetic resonance angiography or computed tomography angiography. Patients with unruptured IAs have also had neurosurgical consultation for the treatment and follow-up. KUH Neurosurgery maintains a database of all cases ruptured and unruptured intracranial aneurysms admitted to KUH since 1980. The database has been prospective since 1990 [12]. A dedicated full-time research nurse runs the database, interviews all new cases, and collects and codes detailed information into variables, including family history, defined as at least two affected first-degree relatives [12, 26].

The basic study population included all sIA patients from 1995 to 2014 (Fig 1). The final study population consisted of unruptured and ruptured sIA patients who met the following criteria: 1) a citizen of Finland and resident of the KUH catchment area at the first diagnosis of the sIA disease from 1995 to 2014; 2) verification of the sIA disease with four-vessel angiography; 3) patients with other types of IAs (fusiform, traumatic, mycotic) excluded (Fig 1).

Antihypertensive medication

The Social Insurance Institution of Finland has since 1994 prospectively maintained a nationwide registry for all patients who have purchased prescribed drugs from the pharmacies, including all antihypertensive drugs. All pharmacies in Finland are included in the prospective registry. In Finland all antihypertensive drugs are sold in pharmacies by prescription only. The antihypertensive medication use in the study population of 2704 sIA patients (Fig 1) was analyzed between January 1, 1995, and December 31, 2014, allowing us to analyze antihypertensive medication use at least one year before the sIA diagnosis. The data contained information since the first purchase date and the number of purchases until the last date. Purchases of antihypertensive drugs with ATC codes C02 (antihypertensives), C03 (diuretics; thiazides), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the renin-angiotensin system) were included in the analysis.

Hospital diagnoses and death records

All hospital diagnoses (ICD-10), including hypertension diagnoses were obtained from the Finnish electronic hospital diagnosis registry (Care Register For Health Care HILMO, managed by the Finnish Institution for Health and Welfare) that covers all secondary and tertiary referral hospitals in Finland and encompasses all medical specialties. Death records and death diagnoses (ICD-10) were obtained from Statistics Finland. Hospital diagnoses and causes of death were then fused with the clinical data.

Diagnosis of hypertension. We defined hypertension was defined as one of the following: 1) self-proclaimed hypertension; 2) hypertension diagnosis by a physician; or 3) prescribed antihypertensive medications (Fig 1).

Diagnosis of secondary hypertension. Secondary hypertension was suspected in hypertensive sIA patients with one or more concomitant morbidities that associate with suspected secondary hypertension (Table 1), and their case reports were reviewed to confirm or exclude secondary hypertension as described in ESH/ESC (European Society of Cardiology http://www.escardio.org/Guidelines) guidelines [24].

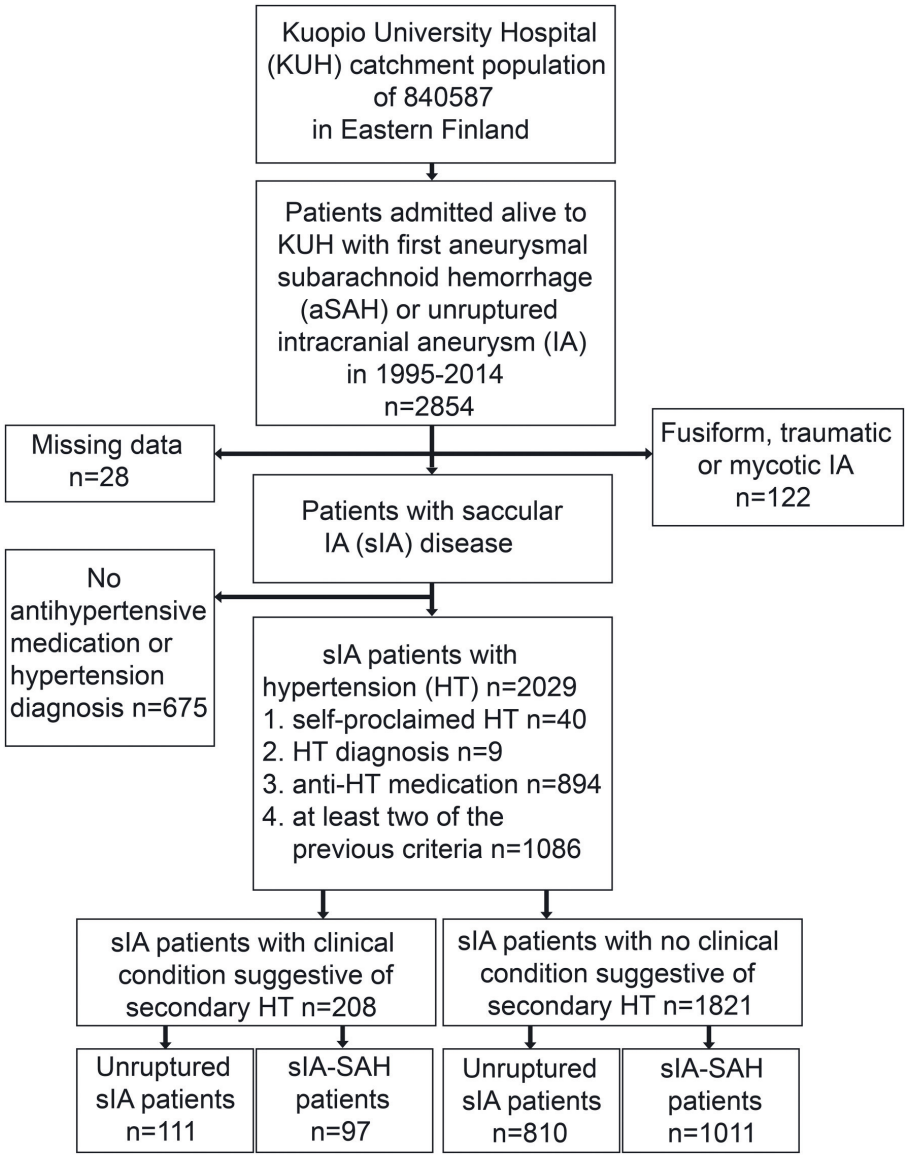

Fig 1. Flowchart of the study population: 2.704 patients with saccular intracranial aneurysm (sIA) disease admitted to the Kuopio University Hospital (KUH) with unruptured sIA disease or first subarachnoid hemorrhage (aSAH) from the Eastern Finnish catchment population from 1995 to 2014. Identification of the hypertensive sIA patients with comorbid diseases suggestive of secondary hypertension.

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Table 1. 208 sIA patients with one or more clinical conditions (n = 260) considered as etiological factors for their secondary hypertension among 2704 sIA patients admitted to Kuopio University Hospital from the Eastern Finnish catchment population in 1995–2014.

Clinical condition and ICD-10 classification	Patients n = 208
Kidney and renovascular diseases	
Polycystic kidney disease (Q61.2, Q61.3)	27 (13%)
Kidney failure (N17-19)	17 (8.2%)
Glomerulonephritis and nephrotic syndrome (N00-N08)	15 (7.2%)
Diabetic nephropathy (E10.2, E11.2)	9 (4.3%)
Hydronephrosis (N13.0, N13.1, N13.3, N13.9)	9 (4.3%)
Tubulo-interstitial nephritis and other conditions (N11-12, N14-16)	6 (2.9%)
Malignant neoplasm of kidney (C64)	6 (2.9%)
Atherosclerosis of renal artery (I15.0, I70.1)	4 (1.9%)
Fibromuscular dysplasia (I77.3)	1 (0.5%)
Coarctation of the aorta (Q25.1)	2 (1.0%)
Adrenal gland diseases	
Benign or malignant neoplasm of adrenal gland (D35.0, C74)	6 (2.9%)
Hyperaldosteronism (E26)	2 (1.0%)
Other hormonal diseases	
Hypothyroidism (E03)	39 (19%)
Hyperthyroidism (E05)	14 (6.7%)
Hyperparathyroidism (E21.0-E21.3)	10 (4.8%)
Benign neoplasm of pituitary gland (D35.2)	6 (2.9%)
Acromegaly (E22.0)	2 (1.0%)
Systemic diseases	
Sjögren's syndrome (M35.0)	5 (2.4%)
Familial dysautonomia (Riley–Day syndrome) (G90.1)	5 (2.4%)
Systemic lupus erythematosus (M32)	5 (2.4%)
Other specified or unspecified necrotizing vasculopathy (M31.8, M31.9)	3 (1.4%)
Amyloidosis (E85) with kidney failure or nephritic syndrome	2 (1.0%)
Thrombotic microangiopathy (M31.1)	2 (1.0%)
Giant cell arteritis (M31.5)	2 (1.0%)
Henoch-Schönlein purpura (D69.0)	1 (0.5%)
Rheumatoid vasculitis with rheumatoid arthritis (M05.2)	1 (0.5%)
Polyarteritis nodosa (M30.0)	1 (0.5%)
Wegener's granulomatosis (M31.3)	1 (0.5%)
Systemic sclerosis (M34)	1 (0.5%)
Sleep apnea (G47.3)	57 (27%)

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Ethical aspects

This research has been authorized by Kuopio University Hospital Reseach Ethics Committee. The patient data integration from the nationwide registries to Kuopio IA database was completed with the endorsement from National Institute of Health and Welfare. Written informed consent was obtained from all patients before their data was input to Kuopio Intracranial Patient and Family database.

Statistical analysis

Categorical variables were expressed in proportions and continuous variables in medians, quartiles, and ranges. Groups were compared using the Pearson's Chi-Square ($\chi 2$) test or the

Mann–Whitney U test. Multivariate analyses were performed using logistic regression to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for having secondary hypertension with gender, age at first diagnosis, familial sIA disease and number sIAs as variables. P values <0.05 were considered significant. SPSS 22 statistical software was used (SPSS, Inc, Chicago, IL).

Results

The study population consisted of 2704 sIA patients, 1143 (42%) with unruptured sIA disease and 1561 (58%) with aSAH, admitted to KUH between 1995 and 2014 (Fig 1). Their follow-up ended at death (n = 776) or December 2014, with total follow-up of 18751 patient-years and a median follow-up time of 68 months. Table 2 presents the characteristics of the 2704 sIA patients and their 3922 sIAs.

Of the study population, 2029 (75%) sIA patients had hypertension (Fig 1, Table 2) and 208 (10%) of them had secondary hypertension (Table 1). Of the patients with secondary hypertension, 46 (22%) had more than one condition associated with secondary hypertension. The most frequent conditions associated with secondary hypertension were kidney and renovascular diseases (45%), sleep apnea (27%) and hypothyroidism (19%) (Table 1). Of the 208 patients with secondary hypertension 88 (42%) had a positive smoking history.

Table 2. Secondary vs. essential hypertension among 2704 patients with 3922 saccular intracranial aneurysms (sIAs) admitted to Kuopio University Hospital from the Eastern Finnish catchment population in 1995–2014.

	Unruptured sIA patients n = 1143			aSAH patients n = 1561		
Variables of 2704 sIA patients	Hypertension		No hypertension n = 222	Hypertension		No hypertension n = 453
	Secondary hypertension n = 111	No secondary hypertension n = 810		Secondary hypertension n = 97	No secondary hypertension n = 1011	
Median age at sIA diagnosis (quartiles)	58 (51–65)	59 (50–68)	50 (42–57)	55 (46–65)	55 (47–65)	50 (42–60)
Females	64 (58%)	475 (59%)	120 (54%)	48 (50%)	624 (62%)	236 (52%)
Familial sIA disease	18 (16%)	143 (18%)	49 (22%)	16 (16%)	105 (10%)	36 (8%)
Multiple sIAs (≥2)	32 (29%)	236 (29%)	56 (25%)	35 (36%)	310 (31%)	117 (26%)
Known positive smoking history	40 (36%)	351 (43%)	108 (49%)	48 (49%)	427 (42%)	193 (43%)
Variables of 3922 sIAs	Hypertension		No hypertension n = 303	Hypertension		No hypertension n = 639
	Secondary hypertension n = 160	No secondary hypertension n = 1148		Secondary hypertension n = 170	No secondary hypertension n = 1502	
Median size (mm) (quartiles)	4 (3–7)	4 (3–7)	4 (3–6)	4 (3–7)	5 (3–8)	6 (3–8)
ACoA location	25 (16%)	166 (14%)	34 (11%)	39 (23%)	376 (25%)	148 (23%)
Mbif location	55 (34%)	442 (39%)	119 (39%)	58 (34%)	433 (29%)	175 (27%)
ICA location	32 (20%)	263 (23%)	88 (29%)	38 (22%)	321 (21%)	164 (26%)
BAbif location	6 (4%)	62 (5%)	10 (3%)	8 (5%)	71 (5%)	24 (4%)
Other location	42 (26%)	215 (19%)	52 (17%)	27 (16%)	301 (20%)	128 (20%)
Irregular shape	33 (21%)	271 (24%)	83 (27%)	87 (51%)	932 (62%)	417 (65%)
Smooth shape	126 (79%)	861 (75%)	210 (69%)	80 (47%)	525 (35%)	188 (29%)
Unknown shape	1 (1%)	16 (1%)	10 (3%)	3 (2%)	45 (3%)	34 (5%)

Abbreviations: sIA = saccular intracranial aneurysm; aSAH = subarachnoid hemorrhage from ruptured sIA; ACoA = anterior communicating artery; Mbif = middle cerebral artery bifurcation; ICA = internal carotid artery; BAbif = basilar artery bifurcation.

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Table 3. Multivariate logistic regression analysis of factors associated with secondary hypertension in the 1561 patients with subarachnoid hemorrhage from ruptured saccular intracranial aneurysm (aSAH) admitted to the Kuopio University Hospital from the Eastern Finnish catchment population from 1995 to 2014.

	OR (95% CI)	p-value
Male gender	1.59 (1.04–2.43)	0.034
Age at aSAH (per year)	1.01 (0.99–1.03)	0.33
Familial sIA disease	1.74 (0.98–3.09)	0.058
Number of sIAs (per sIA)	1.32 (1.10–1.58)	0.003

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In the 111 unruptured sIA patients, the median ages (25% and 75% quartiles) at diagnoses were 50 (43–58) years for hypertension, 54 (42–62) years for secondary hypertension causing condition and 58 (51–65) years for unruptured sIA disease. In the 97 aSAH patients, the median ages (25% and 75% quartiles) at diagnoses were 50 (43–61) years for hypertension, 52 (40–67) years for secondary hypertension causing condition and 55 (46–65) years for aSAH.

In total, we identified 26 (13%) carriers of autosomal dominant polycystic kidney disease (ADPKD), while other heritable traits predisposing to hypertension were rare: 5 (2.4%) patients with familial dysautonomia (Riley–Day syndrome).

Of the 367 familial sIA patients, 282 (77%) had the hypertension diagnosis and 34/282 (12%) had secondary hypertension. Of the 2337 sporadic sIA patients, 1747 (75%) had hypertension diagnosis and 174/1747 (10%) had secondary hypertension.

In multivariate logistic regression analyses of aSAH 1561 patients, secondary hypertension significantly associated with the number of sIAs (p = 0.003; OR 1.32; 95% CI 1.10–1.58) and male gender (p = 0.034; OR 1.59; 95% CI 1.04–2.43) (Table 3). For the 1143 unruptured sIA patients, no significant associations with secondary hypertension were found.

Discussion

In this population-based retrospective study of 2704 sIA patients, we showed that 75% had hypertension and 10% of them were considered to have secondary hypertension, with renovascular diseases, sleep apnea and hypothyroidism as most common associated disorders. Interestingly, secondary hypertension significantly associated with the number of sIAs in aSAH patients.

In general Finnish population, the prevalence of secondary hypertension among all hypertension patients has beeb estimated to be 5–10% in the Finnish national hypertension treatment guideline [27], in line with our results. This estimate is based on two Swedish studies [15–16]: The prevalence of secondary hypertension was 5.8% in a prospective random population sample of 7455 Swedish men [15] and 4.7% in a retrospective study of 1000 hypertension patients sent to a hypertension clinic due to treatment-resistant or newly diagnosed hypertension [16]. In a prospective Japanese study from 2003, the prevalence of secondary hypertension was 9.1% in 1020 hypertensive general outpatient clinic visitors [17]. Possible etiological conditions included aldosteronism (6%), Cushing's syndrome (1%), preclinical Cushing's syndrome (1%), pheochromocytoma (0.6%) and renovascular hypertension (0.5%). Importantly, the patients with unspecified renal failure were excluded from the study and no data on sleep apnea or hypothyroidism was given. Hypothyroidism and sleep apnea were frequent in secondary hypertension patients with IAs in our population, which is in line the prevalence estimates of 3,1% [28] for hypothyroidism in and 3,8% [29] for sleep apnea in general European population.

Our study has several strengths derived from the Finnish health care system. Firstly, Finland is divided into mutually exclusive catchment areas for the KUH and the four other

university hospitals, allowing cohorts that are unselected and minimally biased. Finnish personal identification code system allows the creation of very accurate population and clinical data registries [30] and the linking of the registry data with medical records. Secondly, during the study period (1995–2014), the Kuopio Intracranial Aneurysm and Family Database prospectively collected clinical data according to a standard protocol of all unruptured and ruptured sIA patients since their first admission from the KUH catchment population. All sIAs have been verified with four-vessel angiography, excluding the patients with other types of IAs (traumatic, fusiform and mycotic). Thirdly, in Finland, all anti-hypertensive medications are exclusively sold by the physicians' prescriptions in the pharmacies, and all prescribed drug purchases were retrieved from the national registry encompassing all pharmacies in Finland. Furthermore, the study period 1995–2014 allowed the assessment of prescription drug usage at least one year before sIA diagnosis.

Our study also has weaknesses. Firstly, our study is a retrospective registry-based study. We did not invite patients for clinical visits to be screened for secondary hypertension. The method we used to diagnose secondary hypertension may be insensitive even though it was based on thorough review medical records and combination of comprehensive nationwide registries. It is likely that we have missed patients with secondary hypertension and the actual prevalence may be even higher. Secondly, in some cases the diagnoses associated with secondary hypertension may not have been causes for hypertension, but coincidental findings. Furthermore, due to the method used, we were not able to determine the severity of hypertension. However, we feel that our large study population analyzed with a consistent method to identify patients with secondary hypertension compensates for this limitation. Moreover, identifying definite causative relations in secondary hypertension is difficult regardless of the method used.

Conclusion

In conclusion, we found that secondary hypertension is a relatively common disease in patients with sIA disease, with 10% prevalence in hypertensive sIA carriers. In clinical practice, secondary hypertension may be an overlooked risk factor in patients with subarachnoid hemorrhage. Our results indicate that secondary causes for hypertension should be taken into account in hypertensive sIA patients, especially in aSAH patients with multiple intracranial aneurysms. In these patients, screening for kidney and thyroid disorders and sleep apnea should be considered if hypertension is diagnosed. Further research is indicated to evaluate the impact of secondary hypertension on the long-term rupture risk of unruptured sIA carriers and long-term outcome after subarachnoid hemorrhage.

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II

Pre-eclampsia, gestational diabetes and hypertensive disorders in patients with intracranial aneurysms: A case-control study

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ORIGINAL ARTICLE

Pre-eclampsia, gestational diabetes and hypertensive disorders in patients with intracranial aneurysms: A case–control study

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Abstract

Background and purpose: The aim of this study was to define the prevalence of pre-eclampsia, gestational hypertension (HT), chronic HT, and gestational diabetes during pregnancy in a defined population of patients with saccular intracranial aneurysms (sIAs).

Methods: We included all patients with sIA, first admitted to the Neurosurgery Department of Kuopio University Hospital from its defined catchment population between 1990 and 2015, who had given birth for the first time in 1990 or later. The patients' medical records were reviewed, and clinical data were linked with prescription drug usage, hospital diagnoses and causes of death, obtained from nationwide registries. The prevalences of pre-eclampsia, other hypertensive disorders and gestational diabetes in patients were compared with a matched control population (n = 324). In addition, the characteristics of sIA disease in patients with pre-eclampsia were compared to those of sIA patients without pre-eclampsia.

Results: A total of 169 patients with sIA fulfilled the inclusion criteria. Of these, 22 (13%) had pre-eclampsia and 32 (19%) had other hypertensive disorders during pregnancy. In 324 matched controls who had given birth, the prevalence of pre-eclampsia was 5% (n = 15) and other hypertensive disorders were diagnosed in 10% (n = 34). There was no significant difference in prevalence of gestational diabetes (12% vs. 11%). Patients with sIA with pre-eclampsia more frequently had irregularly shaped aneurysms (p = 0·003).

Conclusions: Pre-eclampsia was significantly more frequent in patients with sIA than in their population controls. Irregularly shaped aneurysms were more frequent in sIA patients with pre-eclampsia. Further studies are required to determine whether history of pre-eclampsia may indicate an elevated risk for sIA formation or rupture.

KEYWORDS
gestational hypertension, hypertension, intracranial aneurysm, pre-eclampsia, subarachnoid hemorrhage

Statistical analysis: Antti Lindgren, MD PhD

INTRODUCTION

Intracranial aneurysms (IAs) are almost always saccular pouches (saccular intracranial aneurysms [sIAs]) on the extracerebral arteries. The prevalence of sIA disease in the general population is approximately 3% [1]. Most sIAs do not cause any symptoms and remain unnoticed during life [2] if not incidentally found in neuroimaging for other reasons or by screening sIA families [3]. However, rupture of the sIA wall causes aneurysmal subarachnoid hemorrhage (aSAH), the third most frequent form of stroke, with high mortality and neurological morbidity [4–9]. The known risk factors for sIA disease and aSAH include female sex, age, smoking, hypertension (HT), sIA family history, and autosomal polycystic kidney disease [2,10–13].

Approximately 10% of pregnancies are complicated by HT disorders, including pre-existing HT, new gestational HT, and pre-eclampsia, a serious multisystem condition [14]. Pre-eclampsia complicates approximately 3%–5% of pregnancies, but family history may elevate the risk [15]. Pre-eclampsia is commonly defined as new-onset HT and proteinuria after 20 weeks' gestation. In the absence of proteinuria, a diagnosis of pre-eclampsia is made if serious maternal organ dysfunctions are discovered, including elevated liver enzymes, thrombocytopenia, renal dysfunction, pulmonary edema, cerebral or visual disturbances [14]. Worldwide, pre-eclampsia causes extensive maternal morbidity and mortality [16] with increased risks of HT and other cardiovascular diseases [17], type 2 diabetes (T2DM) [18], end-stage renal disease [19], and premature death [20].

Pre-eclampsia is a known risk factor for stroke in general, both during pregnancy and later in life [21–23]. In addition, pre-eclampsia is also associated with increased risk of stroke in the adult offspring [24]. However, the impact of pre-eclampsia on later sIA formation or aSAH has not been defined. The Kuopio Intracranial Aneurysm Patient and Family Database (www.kuopioneurosurgery.fi) contains all cases of unruptured and ruptured sIAs admitted to the Kuopio University Hospital from a defined Eastern Finnish catchment population since 1980 [11,25,26]. In the present study we used the population-based Kuopio Intracranial Aneurysm Patient and Family Database to analyze the frequency of pre-eclampsia in female patients with sIA disease and in matched female population controls. Our hypothesis was that pre-eclampsia, a known risk factor for cardiovascular disease, is associated with sIA disease.

METHODS

Catchment population of Kuopio University Hospital

During the study period from 1990 to 2015, Kuopio University Hospital (KUH) Neurosurgery exclusively provided neurosurgical services for a defined KUH catchment population in Eastern Finland. The geographical area remained the same, but the population decreased from 839,236 to 815,021. The median age increased from 36 to 42 in males and from 39 to 45 in females, while the proportion of males remained unchanged at 49% [28].

Kuopio Intracranial Aneurysm Patient and Family Database

All patients with subarachnoid hemorrhage (SAH) verified by computed tomography or spinal tap are admitted to KUH for angiography and treatment if not moribund or very aged. Unruptured sIAs are verified by four-vessel digital subtraction angiography, magnetic resonance angiography or computed tomography angiography. Patients with unruptured IAs also receive neurosurgical consultation for treatment and follow-up. KUH Neurosurgery maintains a database of all cases of ruptured and unruptured IAs admitted to KUH since 1980 [11]. The database has been prospective since 1990 [11]. A dedicated full-time database manager runs the database, interviews all new cases, and collects and codes detailed information into variables, including family history, defined as at least two affected first-degree relatives [11]. Data on drug prescriptions (1994–2014), hospital diagnoses, and causes of death, and relatives, were obtained from national registries using Finnish personal identification codes, linked to the database and analyzed [2,8]. Data on drug prescriptions (1994–2014) and hospital diagnoses were obtained correspondingly for random controls, matched by age, sex, and birthplace, three for each patient in the Kuopio Intracranial Aneurysm Patient and Family Database, selected by the Finnish Population Register Center. The date of the first aneurysm-related admission was the index date for matching, at the time of matching all controls were alive. The matching is described in more detail in our previous reports [8].

Study population

The basic study population consisted of female patients with sIA (Figure 1) meeting the following criteria: (i) citizen of Finland and resident of the KUH catchment area at time of first diagnosis of sIA disease between 1990 and 2015; (ii) verification of sIA disease with four-vessel angiography; (iii) first birth given after 1990; and (iv) end of follow-up at death or October 2015. Patients with other types of IAs (fusiform, traumatic, mycotic, unknown) were excluded.

We searched the Kuopio database for matched population controls (age; sex; birthplace; birth of first child after 1990; alive at the index date). The index date was the calendar date of the first sIA diagnosis. We were able to identify 324 controls for the 169 patients with sIA.

Diagnostic criteria for pre-eclampsia and other HT disorders in pregnancy

We used the criteria included in the Report of the American College of Obstetricians and Gynecologists' (ACOG) Task Force on HT in Pregnancy [14]. HT disorders are divided into pre-eclampsia, superimposed pre-eclampsia, chronic HT, and gestational HT. HT is defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg on two occasions at least 4 h apart. Proteinuria

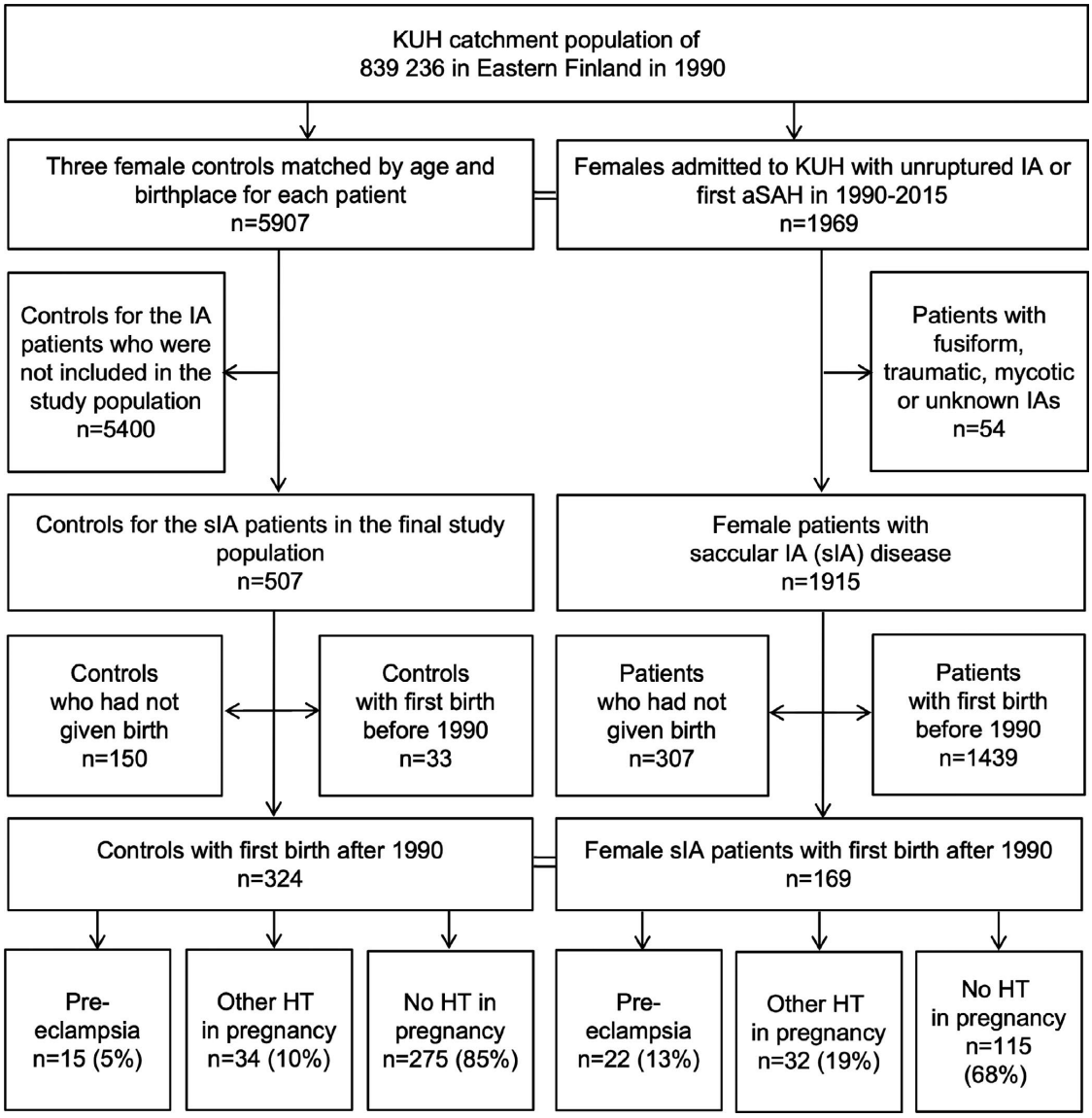

FIGURE 1 Flowchart of the study population. A total of 1915 female patients with unruptured saccular intracranial aneurysm (sIA) or first aneurysmal subarachnoid hemorrhage (aSAH) were admitted to the Kuopio University Hospital (KUH) from the Eastern Finnish catchment population between 1990 and 2015. For each patient, three random female controls, matched by age and birthplace, were obtained from the Finnish Population Registry. Clinical data for each patient and control were obtained from the Finnish national registries. A total of 169 female patients with sIA and 324 controls, who had given birth for the first time after 1990, were identified. All available clinical data on their pregnancies were reviewed to identify the cases with pre-eclampsia and other hypertensive (HT) disorders in pregnancy

is defined as ≥300 mg per 24-h urine collection, protein/creatinine ratio ≥0.3 or a dipstick reading of 1+. Diagnosis of pre-eclampsia is made based on new-onset HT after 20 weeks of gestation and new-onset proteinuria. Proteinuria is not required if new-onset HT is associated with any of the following: serious organ dysfunction, including elevated liver enzymes; thrombocytopenia; elevation of serum creatinine; pulmonary edema; and cerebral or visual disturbances [14]. Chronic HT is defined as HT detected before pregnancy or before 20 weeks' gestation. Gestational HT is defined as new-onset blood pressure elevation after 20 weeks of gestation in the absence of proteinuria or the aforementioned maternal organ dysfunction.

Hospital diagnoses of pregnancy-related disorders

We used the International Statistical Classification of Diseases and Related Health Problems, revisions 9 and 10 (ICD-9 and ICD-10) codes. In Finland, ICD-9 was used from the year 1987 and ICD-10 from 1996. The codes were obtained from the Finnish national registries. For pre-eclampsia, ICD-9 codes 6424, 6425 and 6427 and ICD-10 codes O14 were used. For chronic HT, ICD-9 codes 6420, 6421 and 6422 and ICD-10 codes O10 were used. For gestational HT, ICD-9 codes 6423 and ICD-10 codes O13 were used. For essential HT, ICD-9 codes 401 and ICD-10 codes I10 were used. In addition to HT disorders in pregnancy, gestational diabetes was identified using ICD-9 codes 6488 and ICD-10 codes O24.4. For T2DM, ICD-9 codes 250 and ICD-10 codes E11 were included.

Diagnoses of HT and T2DM

Hypertension was defined as HT diagnosis by a physician or the use of prescribed anti-HT medications (Anatomical Therapeutic Chemical [ATC] codes): C02 (anti-HTs); C03 (diuretics; thiazides); C04 (peripheral vasodilators); C07 (beta-blocking agents); C08 (calcium channel blockers); or C09 (agents acting on the renin-angiotensin system). Type 1 diabetes or T2DM was defined as a diagnosis by a physician or the use of prescribed medications (ATC codes): A10A (insulins and analogues); A10B (blood glucose-lowering drugs); or A10X (other drugs used in diabetes).

Hypertension disorders before, during and after the first pregnancy

All available clinical data on the 169 patients with sIAs and the 324 controls were carefully reviewed to confirm the presence or absence of HT disorders (Table 1, Figure 2). The diagnostic criteria for the HT disorders were the same as those used by the aforementioned ACOG Task Force. In the present study, superimposed pre-eclampsia was included in pre-eclampsia.

Ethical aspects

This research was authorized by the Ethics Committee of the KUH. Written consent was received from all patients in the Kuopio Intracranial Aneurysm Patient and Family Database.

Statistical analysis

Distribution of variables is expressed in medians and interquartile ranges for continuous variables and proportions for categorical variables. In group comparisons, the Mann–Whitney *U*-test was used for continuous variables and the chi-squared test for categorical variables. p values <0.05 were taken to indicate statistical significance. SPSS 22 statistical analysis software was used (SPSS, Inc). There was one missing value for the variable median size of sIA (1 of 262 variables [0.4%]).

RESULTS

Study cohort

In the Kuopio Intracranial Aneurysm Patient and Family Database, we identified 169 female patients with sIAs, admitted from 1990 to 2015, and who gave birth first after 1990 (Figure 1). Table 1 presents the characteristics of the 169 patients with sIAs and their total of 262 sIAs (29% had two or more sIAs). Familial sIA disease was more frequent among the patients with unruptured sIAs (38% vs. 11%), which was most likely attributable to sIA family screening with magnetic resonance angiography. Of the 169 patients with sIAs on admission, 73 (43%) had unruptured sIA (median age 40 years) and 96 (57%) had aSAH (median age 41 years). Of the 96 aSAH patients, aSAH occurred before the first pregnancy in 14 (15%), during pregnancy in three (3%), between pregnancies in five (5%), and after the last pregnancy in 74 patients (77%).

In the Kuopio Intracranial Aneurysm Patient and Family Database, there were 507 (3:1) female controls from the KUH catchment population, matched by age at sIA or aSAH diagnosis from 1990 to 2015. The final control cohort consisted of 324 females (1.9:1) who had given birth to their first child after 1990 (Figure 1).

Pre-eclampsia in the 169 patients with sIA and 324 controls

The 169 patients with sIAs gave birth to 381 (median 2) children (median age 29 years at the first birth). During any pregnancy, a total of 22 patients (13%) had pre-eclampsia (median age 33 years; Table 1, Figure 1), eight (11%) of the 74 patients with unruptured sIAs and 14 (15%) of the 96 patients with aSAH (Figure 1, Table 1, Figure 2). During any pregnancy, a total of 15 (5%) of the 324 controls had pre-eclampsia (median age 28 years), significantly fewer than in the sIA group (p=0.001; Figure 1).

Diagnoses of sIA and HT during lifelines of 22 patients with sIAs and pre-eclampsia

Figure 2 presents the clinical date point lifelines of the 22 patients with sIAs (median age 41 years at sIA diagnosis) according to age at pre-eclampsia diagnosis (median 33 years). Pre-eclampsia was preceded by sIA or aSAH in five cases and by HT in two cases. Pre-eclampsia was followed by sIA or aSAH in 17 cases, over a median period of 10 years. Pre-eclampsia was followed by HT in 13 cases, over a median period of 9 years. A total of 15 patients (68%) with

TABLE 1 Clinical characteristics of the study population of 169 female patients with saccular intracranial aneurysms (sIAs) and their 262 sIAs

	Unruptured sIA patients, *n* = 73			aSAH patients, *n* = 96		
Variables of 169 sIA patients	**Pre-eclampsia, *n* = 8**	**Other HT disorder in pregnancy, *n* = 11**	**No HT disorder in pregnancy, *n* = 54**	**Pre-eclampsia, *n* = 14**	**Other HT disorder in pregnancy, *n* = 21**	**No HT disorder in pregnancy, *n* = 61**
Median age at sIA diagnosis (quartiles), years	42 (33–49)	42 (37–47)	40 (34–45)	41 (31–45)	42 (35–47)	41 (31–46)
Familial sIA disease, *n* (%)	2 (25)	5 (45)	21 (39)	3 (21)	4 (19)	4 (7)
ADPKD, *n* (%)	0 (0%)	0 (0)	0 (0)	1 (7)	0 (0)	2 (3)
Multiple sIAs (≥2), *n* (%)	3 (38)	2 (18)	13 (24)	2 (14)	10 (48)	19 (31)
HT before pregnancy, *n* (%)	2 (25)	8 (73)	0 (0)	0 (0)	17 (81)	0 (0)
HT after pregnancy, *n* (%)	6 (75)	10 (91)	24 (44)	9 (64)	20 (95)	28 (46)
T2DM before pregnancy, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gestational diabetes, *n* (%)	1 (13)	2 (18)	8 (15)	2 (14)	3 (14)	6 (10)
T2DM after pregnancy, *n* (%)	1 (13)	1 (9)	3 (6)	0 (0)	0 (0)	2 (3)
Characteristics of262 sIAs	**Pre-eclampsia*n* = 13**	**Other HT in pregnancy *n* = 18**	**No HT in pregnancy*n* = 76**	**Pre-eclampsia*n* = 16**	**Other HT in pregnancy *n* = 36**	**No HT in pregnancy*n* = 103**
Median size (quartiles), mm	4 (3–6)	3 (3–6)	4 (2–5)	6 (5–10)	5 (4–6)	5 (3–7)
ACoA location, *n* (%)	1 (8)	1 (6)	3 (4)	6 (38)	6 (17)	19 (18)
Mbif location, *n* (%)	4 (31%)	9 (50%)	28 (37%)	4 (25%)	8 (22%)	26 (25%)
ICA location, *n* (%)	5 (39)	3 (17)	24 (32)	3 (19)	9 (25)	30 (29)
BAbif location, *n* (%)	1 (8)	1 (6)	2 (3)	0 (0)	3 (8)	11 (11)
Other location, *n* (%)	2 (15)	4 (22)	19 (25)	3 (19)	10 (28)	17 (17)
Irregular shape, *n* (%)	7 (54)	4 (22)	11 (14)	14 (88)	24 (67)	61 (59)
Smooth shape, *n* (%)	6 (46)	14 (78)	65 (86)	2 (13)	12 (33)	42 (41)

Abbreviations: ACoA, anterior communicating artery; ADPKD, autosomal dominant polycystic kidney disease; aSAH, aneurysmal subarachnoid hemorrhage; BAbif, basilar artery bifurcation; HT, hypertension; ICA, internal carotid artery; Mbif, middle cerebral artery bifurcation; sIA, saccular intracranial aneurysm; T2DM, type 2 diabetes mellitus.

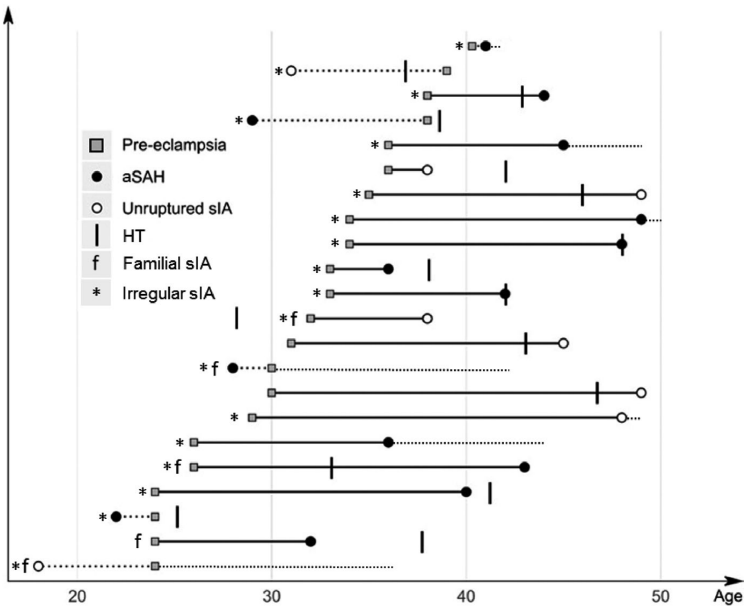

FIGURE 2 Clinical timelines of the 22 female saccular intracranial aneurysm (sIA) patients with a diagnosis of pre-eclampsia during any of their pregnancies ending up to the delivery. Timelines are arranged according to age at pre-eclampsia diagnosis. Ages at the diagnoses are denoted for pre-eclampsia (gray squares), aneurysmal subarachnoid hemorrhage (aSAH; black circles), unruptured sIA disease (white circles), hypertension (black vertical lines), familial sIA (f) and irregular sIA (asterisks)

sIAs and pre-eclampsia had an HT diagnosis (median age 41 years) before the end of follow-up.

Characteristics of 262 sIAs

The 22 patients with pre-eclampsia more often had sIAs with an irregular shape (21/29; 72% [$p = 0.003$]) than the 147 other patients with sIAs (100/233; 43% [Table 1]).

Diagnoses of sIA and HT in 115 patients with sIAs with no HT disorders during any pregnancy

Of the 115 patients with sIAs, 54 had unruptured sIA diagnosis (median age 40 years), and 24 (44%) of these patients had diagnosed HT (median age 41 years) before the end of follow-up. Of the 61 aSAH patients (median age 41 years), 28 (46%) had HT (median age 40 years).

Diagnosis of HT in 275 controls with no HT disorders during any pregnancy

Of the 275 controls, a total of 82 (25%) had diagnosed HT before the end of follow-up (median age 41 years).

Gestational diabetes

The prevalence of gestational diabetes did not differ between patients with sIA (22/169 [13%]) and matched controls (39/324 [12%]). Seven of the total 169 patients with sIA (4%) and 3/22 patients with sIA and gestational diabetes (13%) developed T2DM during the study period. Fifteen of the total 324 controls (5%) and 6/39 controls with gestational diabetes (15%) developed T2DM during the study period.

DISCUSSION

To our knowledge, this is the first study to test in humans the hypothesis that pre-eclampsia, a potentially catastrophic form of HT disorder during pregnancy, would be associated within any time period with the diagnosis of unruptured sIA or SAH from the ruptured sIA wall. In our study population of 169 patients with sIA who had given birth, 13% had pre-eclampsia compared to only 5% of matched controls. Furthermore, the occurrence of other hypertensive disorders in pregnancy was significantly higher in patients (19%) than in controls (10%). Irregularly shaped aneurysms were more frequent in patients with pre-eclampsia than in the general sIA population. Our results indicate that pre-eclampsia may be an indicator of elevated risk for IAs. Moreover, pre-eclampsia may serve as a biomarker for rupture-prone aneurysm.

There is accumulating evidence of the association of pre-eclampsia and risk of stroke, but data on pre-eclampsia and sIA disease are scarce. In a population-based case–control study of 261 young ischemic stroke patients pre-eclampsia was more frequent in patients (15%), than in 421 controls (10%), indicating an increased risk of ischemic stroke after pregnancy and the puerperium. The data in that study, however, were based on self-reported pre-eclampsia [22]. Pre-eclampsia and gestational HT have been identified as independent significant risk factors for pregnancy-related intracerebral

hemorrhage in the United States [29]. Pre-eclampsia was also associated with a long-term risk of intracerebral hemorrhage in a retrospective cohort study in Taiwan [30]. Hypertensive disorders were important independent risk factors for pregnancy-related SAH in a cohort study in the United States, however, that study included SAH etiologies other than aneurysm rupture [31]. The risk of aSAH was not increased during pregnancy, labor or the puerperium, according to a case-crossover study in Utrecht [32]. Thus, the risks for sIA disease and aSAH in patients with a history of pre-eclampsia have remained unclear.

In our study population, 68% of the patients with sIA who had pre-eclampsia had developed HT by the end of the study period, indicating an elevated risk for cardiovascular disease in general. Importantly, the median time from pre-eclampsia to HT diagnosis was 9 years, indicating that these were not cases of undiagnosed pre-existing HT found due to pregnancy-related health checkups. Furthermore, there is a sizeable time window before the development of HT after pre-eclampsia that could be used to reduce the risk of cardiovascular disease in later life. This clearly shows the need for patient education on lifelong risk of HT and stroke in patients with pre-eclampsia that should include strong recommendations for non-smoking and regular HT monitoring at home.

Pre-existing HT is a risk factor for developing pre-eclampsia [15], as well as for developing IAs [2,12]. However, the higher prevalence of pre-eclampsia in patients with sIA in the present study cannot be solely attributed to higher load of cardiovascular risk factors related to life habits, as indicated by the fact that there was no difference in frequency of gestational diabetes, which is strongly associated with lifestyle factors [33]. Only two patients with pre-eclampsia had pre-existing HT. Moreover, smoking, a strong risk factor for IAs and SAH [12,34], is in fact a protective factor for developing pre-eclampsia [35]. Furthermore, even though family history of pre-eclampsia is associated with an elevated risk of pre-eclampsia [15], familial aneurysms were not associated with pre-eclampsia in the present study population. These findings indicate that pre-eclampsia may be a novel risk factor for IA formation and rupture, not explained by previously known risk factors.

In the present study, pre-eclampsia was significantly associated with aneurysm wall irregularity, a factor associated with elevated risk of rupture [36]. Endothelial dysfunction and high oxidative stress are related to mural cell loss and degeneration of the aneurysm wall [37]. As pre-eclampsia concludes when the placenta is removed, the pathogenesis is considered essentially as a placental disorder [15] It is possible that, due to the pathophysiology of pre-eclampsia, where excessive endothelial activation and a generalized hyperinflammatory state are present due to the stimulus or too strong maternal response [15], the process might also affect aneurysm formation and wall integrity in previously developed aneurysms. In the present study population there was no significant difference when comparing the distribution of unruptured sIA and aSAH between pre-eclampsia patients and others.

The present study has several strengths which are derived from the Finnish healthcare system. Finland is divided into mutually exclusive catchment areas for the KUH and the four other university hospitals, allowing use of study cohorts that are unselected and minimally biased. The Finnish personal identification code system allows the creation of very accurate population and clinical data registries, with few lost to follow-up [38]. During the study period (1990–2015), the Kuopio Intracranial Aneurysm Patient and Family Database prospectively collected clinical data according to a standard protocol for all patients with sIA from the KUH catchment population since their first admission. The present study includes patients with sIA verified with four-vessel angiography only, excluding patients with other types of IA. In Finland, all anti-HT medications are received through physician prescription and sold exclusively in pharmacies, and all prescribed drug purchases were retrieved from the national registry for the present research. Finally, comprehensive national pregnancy and birth data available for the study period allowed the identification of all patients with sIA who had given birth.

A weakness of this study is the limited size of our cohort. We chose to include patients from the era when proteinuria was required for pre-eclampsia diagnosis [39] to reduce the risk of bias caused by changing the diagnostic criteria. Another weakness is that we did not have access to case reports on the control patients to verify the ICD code diagnoses for pre-eclampsia. All 169 patients' medical case files were screened to find the patients who fulfilled the pre-eclampsia criteria but did not have the ICD code diagnoses. Only three pre-eclampsia patients were diagnosed based on medical case files fulfilling the ACOG pre-eclampsia criteria [14] and not ICD codes. However, even if these cases were excluded, the prevalence of pre-eclampsia would still be 11%, significantly higher than in controls.

In conclusion, our results add to the accumulating evidence of the association of pre-eclampsia and intracranial vascular pathologies. In clinical practice, history of pre-eclampsia could indicate an elevated risk of sIA disease. Confirmation of this result in other population-based sIA datasets is warranted. Further studies are required to assess the significance of pre-eclampsia for development and rupture of sIAs.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Satu Kotikoski: Data curation (lead); Formal analysis (lead); Investigation (lead); Visualization (lead); Writing – original draft (lead). **Arttu Kurtelius:** Data curation (equal); Formal analysis (equal); Writing – review and editing (equal). **Heidi J Nurmonen:** Investigation (equal); Writing – review and editing (equal). **Juho Paavola:** Investigation (equal); Writing – review and editing (equal). **Virve Kärkkäinen:** Funding acquisition (equal); Project administration (equal); Writing – review and editing (equal). **Terhi J Huuskonen:** Investigation (equal); Writing – review and editing (equal). **Jukka Huttunen:** Data curation (equal); Investigation (equal); Methodology (equal); Writing – review and editing (equal). **Timo Koivisto:** Data curation (equal); Resources (equal); Supervision (equal); Writing

– review and editing (equal). **Mikael von und zu Fraunberg:** Data curation (equal); Supervision (equal); Validation (equal). **Juha Jääskeläinen:** Funding acquisition (equal); Project administration (equal); Resources (equal); Supervision (equal). **Antti Lindgren:** Conceptualization (lead); Formal analysis (equal); Project administration (lead); Resources (lead); Supervision (lead); Writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

The patient data integration from the nationwide registries was completed with the endorsement from Ministry of Social Affairs and Health of Finland. Kuopio Intracranial Aneurysm Database data that support the findings of this study are available on request from the corresponding author by request. National database data is available from their respective owners (https://www.tilastokeskus.fi/index_en.html, https://thl.fi/en/web/thlfi-en and https://www.kela.fi/web/en) by request. The data are not publicly available due to privacy or ethical restrictions.

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III

Prevalence of pre-eclampsia in 265 patients with an intracranial aneurysm, 393 female relatives versus a control cohort: A case-control study

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ORIGINAL ARTICLE

Prevalence of pre-eclampsia in 265 patients with an intracranial aneurysm, 393 female relatives versus a control cohort: A case–control study

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Abstract

Background and objectives: There is emerging evidence on the connection between pre-eclampsia and saccular intracranial aneurysms (sIAs). Our aim was to study the prevalence of pre-eclampsia in sIA patients, their female relatives, and matched controls, and to examine familial sIA disease and familial pre-eclampsia in sIA patients' families.

Methods: We included all female sIA patients in the Kuopio Intracranial Aneurysm Patient and Family Database from 1995 to 2018. First, we identified the sIA patients, their female relatives, and matched population controls with the first birth in 1987 or later and studied the prevalence of pre-eclampsia. Second, all female sIA patients and all female relatives were analyzed for familial sIA disease and familial pre-eclampsia. Using the Finnish nationwide health registries, we obtained data on drug purchases, hospital diagnoses, and causes of death.

Results: In total, 265 sIA patients, 57 daughters, 167 sisters, 169 nieces, and 546 matched controls had the first birth in 1987 or later. Among them, 29 (11%) sIA patients, 5 (9%) daughters, 10 (6%) sisters, 10 (6%) nieces, and 32 (6%) controls had pre-eclampsia. Of all the 1895 female sIA patients and 12,141 female relatives, 68 sIA patients and 375 relatives had pre-eclampsia, including 32 families with familial pre-eclampsia.

Conclusions: Pre-eclampsia was significantly more common in the sIA patients than in their matched controls. Familial sIA disease and familial pre-eclampsia co-occurred in seven families. Further studies of the mechanisms by which pre-eclampsia could affect the walls of brain arteries and increase the rupture risk in sIA disease are indicated.

KEYWORDS
hypertension, intracranial aneurysm, pre-eclampsia, stroke, subarachnoid hemorrhage

INTRODUCTION

The prevalence of saccular intracranial aneurysms (sIAs), pouches on the bifurcations of intracranial extracerebral arteries, is around 3% in the general population [1]. Most sIAs remain undiscovered during life [2] if not incidentally found in neuroimaging or by screening for familial sIAs [3]. Aneurysmal subarachnoid hemorrhage (aSAH), caused by a rupture of the sIA wall, is the third most frequent form of stroke with high morbidity and mortality [4–8]. The risk factors for sIAs and aSAH include female sex, age, smoking, hypertension, and autosomal-dominant polycystic kidney disease (ADPKD) [2, 9, 10]. sIA disease is a complex condition with at least 10% of sIA patients belonging to sIA families [11, 12].

About 4% of pregnancies in Europe are complicated by pre-eclampsia [13], a severe multisystem disorder characterized by hypertension and maternal organ dysfunction. Globally, pre-eclampsia causes substantial maternal mortality [14] and increased risks of hypertension and cardiovascular diseases [15, 16], type 2 diabetes [17], and stroke during pregnancy and later in life [16, 18]. ADPKD, a risk factor for sIA disease, is also a risk factor for pre-eclampsia [19]. Pre-eclampsia has a clear familial propensity, with both maternal and paternal factors increasing the risk [20], and familial linkage predicts more severe pre-eclampsia [21]. Of all pre-eclampsia cases, 20% are classified as severe [16, 22].

A possible connection between familial sIA disease and familial pre-eclampsia has not been reported. In our previous study, pre-eclampsia was more common in sIA patients than in their matched controls and sIA patients with pre-eclampsia had more frequently irregularly-shaped aneurysms [23]. The current study was conducted to verify the connection between pre-eclampsia and sIA disease in an extended study population. Additionally, we included female relatives to study the familial linkage of pre-eclampsia and sIAs. In the present study, we analyzed the prevalence of pre-eclampsia in 265 sIA females with the first birth since 1987, their 393 female relatives, and 546 matched population controls, using data in the Kuopio Intracranial Aneurysm (IA) Patient and Family Database and data from the Finnish nationwide health registries [24–26]. Additionally, we examined all sIA females with the first sIA disease diagnosis from 1995 to 2018 ($n = 1895$) and all female relatives ($n = 12{,}141$) for the prevalence of familial sIA disease and familial pre-eclampsia. We hypothesized about a familial aggregation of sIA disease and pre-eclampsia.

METHODS

Catchment population of Kuopio University Hospital

Kuopio University Hospital (KUH) served a defined catchment population of about 850,000 in Eastern Finland during the study period from 1995 to 2018. All patients with verified aSAH by computed tomography (CT) or spinal tap were admitted to KUH for angiography and treatment if not moribund or very aged. Unruptured sIAs were diagnosed by four-vessel digital subtraction angiography, magnetic resonance angiography, or CT angiography.

Kuopio IA Patient and Family Database

KUH Neurosurgery maintains a database of all patients with ruptured and unruptured intracranial aneurysms admitted to KUH since 1980 and has been prospective since 1990 [11]. A full-time database manager operates the database, interviews all new patients and follow-up visits, and codes this information into variables, including sIA family history defined as at least two (≥2) affected first-degree relatives [11]. Data for prescribed drug purchases, hospital diagnoses, and causes of death were obtained from national registries using Finnish personal identification codes, fused into the database, and analyzed [2, 27].

The sIA patients' first-degree relatives (parents, children, siblings), nieces, and nephews were identified using Finnish personal identification codes. Random controls (three for each sIA patient in the Kuopio IA Database) were selected by the Digital and Population Data Services Agency and matched by age, sex, and birthplace, representing the general population. The date of the first sIA-related admission was the index date for matching, at the time all controls were alive. Relatives' and controls' data for prescribed drug purchases, hospital diagnoses, and causes of death were obtained from the national registries using Finnish personal identification codes, fused into the database, and analyzed.

Definitions of familial sIA disease and familial pre-eclampsia

In the present study, familial sIA disease was defined as ≥2 affected first-degree relatives in the same family [12, 25, 28]. Familial pre-eclampsia was defined as ≥2 affected first-degree relatives in the same family. The sIA + pre-eclampsia families had ≥2 first-degree relatives with sIA disease and ≥2 first-degree relatives with pre-eclampsia.

Study population of 265 sIA patients, 393 female relatives, and 546 controls

The basic study population consisted of 1895 sIA females (Figure 1) who met the following criteria:

1. A citizen of Finland and resident of the KUH catchment area at the first diagnosis of sIA disease between January 1, 1995 and December 31, 2018.
2. Verification of sIA disease with four-vessel angiography.
3. Patients with other types of IAs (fusiform, traumatic, mycotic, unknown) excluded.
4. The end of the follow-up at death or December 31, 2019.

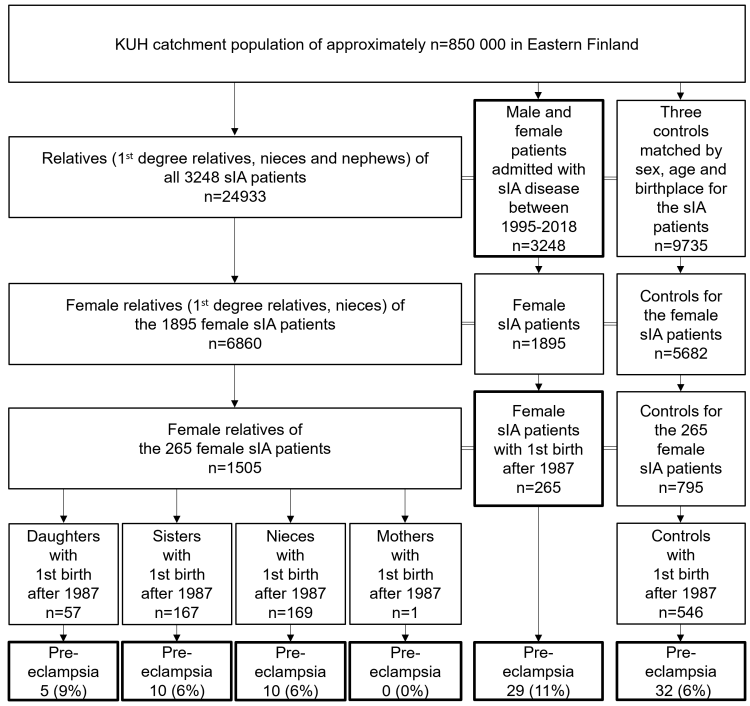

FIGURE 1 Flowchart for the 1895 female patients with the first aneurysmal subarachnoid hemorrhage (aSAH) or an unruptured saccular intracranial aneurysm (sIA) admitted to the Kuopio University Hospital (KUH) from the Eastern Finnish catchment population from 1995 to 2018. Data for the sIA patients' relatives as well as the data for population controls were obtained from the Digital and Population Data Services Agency. For each patient, three random female controls were matched by age and birthplace. Clinical data for each patient and matched control were obtained from the Finnish national registries. A total of 265 female sIA patients, 394 female relatives, and 546 controls, who had first given birth in 1987 or later, were identified, and their pre-eclampsia diagnoses searched. Mothers were excluded due to insufficient data, resulting in 393 female relatives in the final study population.

First, we searched sIA patients who, additionally, met the criterion:

5. The first birth in 1987 or later in Finland, the first year of comprehensive pregnancy and birth data for all patients, relatives, and controls available. We identified 265 sIA females who met the criterion. Of their 1505 female relatives (first-degree relatives, nieces), 394 first gave birth in 1987 or later. Only one mother first gave birth in 1987 or later; therefore, mothers were excluded, resulting in 393 female relatives in the final study population. We identified 546 matched population controls for the 265 sIA patients matched by: age, sex, birthplace, alive at the index date, and first birth in 1987 or later (Figure 1).

Study population of 1895 female sIA patients and 12,141 female relatives

Additionally, we searched the basic study population for all sIA females ($n=1895$), and all female relatives ($n=12{,}141$), who met the criterion:

6. Pre-eclampsia diagnosis in any pregnancy.

We identified 68 sIA patients and 375 female relatives who met this criterion. We included both sIA females' and sIA males' female relatives (Figure 2).

Hospital diagnoses (1969–2019) and causes of death (1971–2018)

We used the International Statistical Classification of Diseases and Related Health Problems (ICD) codes from revisions 8, 9, and 10; in Finland ICD-8 was used between 1969 and 1986, ICD-9 was used between 1987 and 1995, and ICD-10 since 1996, obtained from the Finnish national registries (Table S1). Hospital-based ICD diagnoses were acquired from the Care Register of the Finnish National Institute for Health and Welfare ("HILMO"). Causes of death were acquired from Statistics Finland. Relatives who were additionally sIA patients in the Kuopio Intracranial Aneurysm Patient and Family Database were also included in relatives with IA disease. Superimposed pre-eclampsia and eclampsia were included in pre-eclampsia. In 2013, the American College of Obstetricians published new guidelines for diagnosing pre-eclampsia, where the presence of proteinuria is no longer required if other signs of maternal organ dysfunction are present [29]. Previously, the diagnostic criteria for pre-eclampsia in Finland were a new-onset hypertension after the 20th gestational week combined with proteinuria ≥300 mg per day.

Drug purchase data (1994–2019)

The drug purchase data, obtained from the Social Insurance Institution of Finland using Finnish personal identification codes, contained information since the first purchase date and the number of purchases

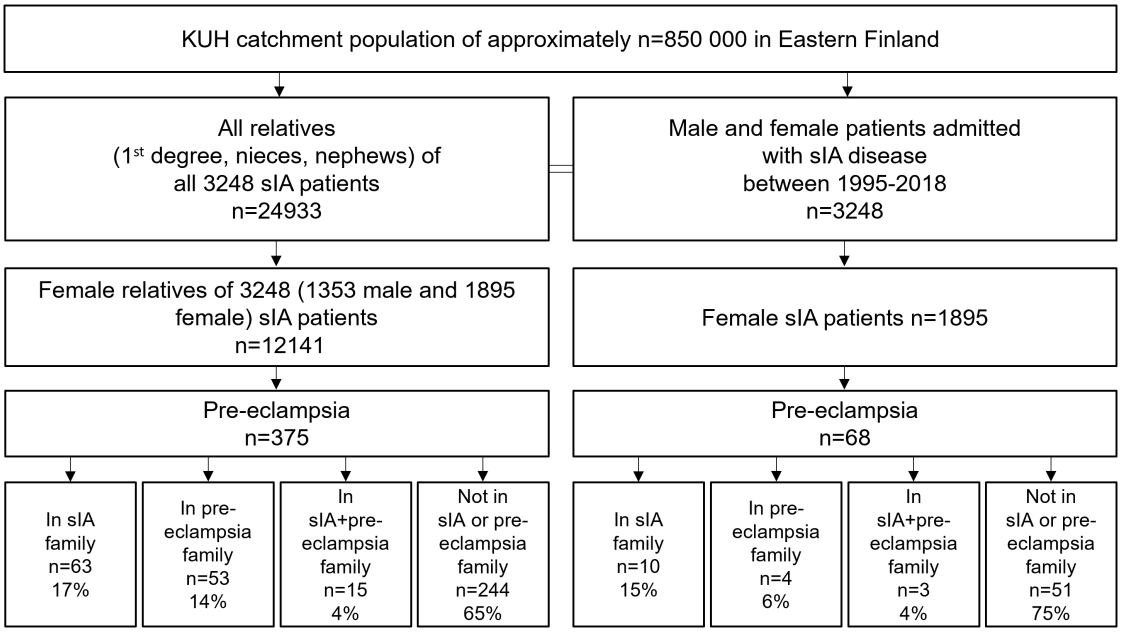

FIGURE 2 Flowchart for the search for all female saccular intracranial aneurysm (sIA) patients and all female relatives with ICD-8, ICD-9, or ICD-10 pre-eclampsia diagnosis. A total of 68 sIA females and 375 female relatives with pre-eclampsia were identified. ICD, International Statistical Classification of Diseases and Related Health Problems; KUH, Kuopio University Hospital.

until the last date. Drug use was determined as ≥2 purchases of prescribed drugs at any time during the study period [30]. Drugs were classified according to the Anatomical Therapeutic Chemical Classification maintained by the World Health Organization. Drug-treated hypertension was defined as the purchase of prescribed anti-hypertensive drugs: C02 (antihypertensives); C03 (diuretics; thiazides); C04 (peripheral vasodilators); C07 (beta-blocking agents); C08 (calcium channel blockers); C09 (agents acting on the renin–angiotensin system). Drug-treated type 2 diabetes was defined as the purchase of prescribed A10B blood glucose-lowering drugs.

Literature review

A PubMed search for articles in the English language on humans between 1990 and 2022 with the search terms (preeclampsia or pre-eclampsia) AND (stroke or "intracerebral haemorrhage" or "intracerebral hemorrhage" or "subarachnoid haemorrhage" or "subarachnoid hemorrhage" or SAH or aneurysm*) resulted in 727 hits. No relevant cohorts were identified, except for our previous study, which to our knowledge is the first study on pre-eclampsia among sIA patients [23].

Statistical analysis

Distribution of variables was expressed in medians and interquartile ranges for the continuous variables and proportions for the categorical variables. In group comparisons the chi-square or Fisher's exact test was used for the categorical variables as appropriate. *P* values <0.05 were considered significant. IBM SPSS Statistics 26.0 was used. There were no missing values.

Standard protocol approvals, registrations, and patient consents

This research was authorized by the Research Ethics Committee of the KUH. Written consent was obtained from all patients before their data were added to the Kuopio IA Database. The need for additional control or relative consent for this registry study was waived by the Ethics Committee of KUH, as no study participants were contacted. Patient data integration from the nationwide registries was completed with the endorsement of the Ministry of Social Affairs and Health of Finland.

RESULTS

Study cohort of 265 sIA patients

We identified 265 sIA females between 1995 and 2018 with the first birth since 1987 (Figure 1 and Table 1). The 265 sIA patients gave birth to 602 (median, 2) children. Familial sIA disease was more frequent with unruptured sIAs than with aSAH (35% vs. 17%), likely due to sIA family screening.

TABLE 1 Characteristics of the study population of 265 female patients with saccular intracranial aneurysm disease or first aneurysmal subarachnoid hemorrhage admitted to the Kuopio University Hospital from the Eastern Finnish catchment population from 1995 to 2018, their 393 female relatives, and 546 matched female population controls with particular reference to the occurrence of pre-eclampsia, clinical data of pregnancies, and registered drug use.

Females with first birth in 1987 or later						
Characteristic	**Females with unruptured sIA (*n* = 127)**	**Females with aSAH (*n* = 138)**	**Daughters (*n* = 57)**	**Sisters (*n* = 167)**	**Nieces (*n* = 169)**	**Controls (*n* = 546)**
Median age at sIA diagnosis (years) (quartiles)	45 (37–50)	44 (36–49)				
Familial sIA disease	45 (35%)	23 (17%)				
Multiple sIAs	26 (20%)	38 (28%)				
ADPKD	1 (1%)	3 (2%)	0 (0%)	2 (1%)	0 (0%)	1 (0%)
Median age at the end of follow-up (years) (quartiles)	53 (45–58)	53 (47–56)	28 (25–30)	49 (40–53)	34 (30–40)	53 (47–56)
Pre-eclampsia	12 (9%)	17 (12%)	5 (9%)	10 (6%)	10 (6%)	32 (6%)
Median age at first birth (years) (quartiles)	28 (24–32)	27 (24–30)	24 (22–26)	27 (23–31)	25 (22–28)	28 (25–31)
Median age at first pre-eclampsia (years) (quartiles)	32 (28–36)	33 (24–38)	25 (24–26)	30 (28–34)	21 (20–29)	30 (25–33)
Severe pre-eclampsia	2/12 (17%)	5/17 (29%)	0/5 (0%)	2/10 (20%)	2/10 (20%)	11/32 (34%)
Gestational diabetes	16 (13%)	14 (10%)	8 (14%)	20 (12%)	32 (19%)	67 (12%)
Use of antihypertensive drugs	74 (58%)	89 (64%)	5 (9%)	69 (41%)	31 (18%)	188 (34%)
Use of type 2 diabetes drugs	11 (9%)	6 (4%)	0 (0%)	8 (5%)	7 (4%)	37 (7%)

Abbreviations: ADPKD, autosomal-dominant polycystic kidney disease; aSAH, aneurysmal subarachnoid hemorrhage; sIA, saccular intracranial aneurysm.

Pre-eclampsia in 265 sIA patients

Of the 265 sIA patients, 29 (11%) had pre-eclampsia (Figure 1 and Table 1), including 17/138 (12%) aSAH patients. Among 29 pre-eclampsia patients, 25/29 had the sIA diagnosis after the first pre-eclamptic pregnancy, and the pre-eclampsia diagnosis preceded the sIA diagnosis by a median of 13 years (quartiles 7–18). Pre-eclampsia reoccurred in 1/12 (8%) of the patients with unruptured sIAs and 3/17 (18%) of the aSAH patients with pre-eclampsia. Severe pre-eclampsia was more common in patients with aSAH (5/17, 29%) than with unruptured sIAs (2/12, 17%). Familial sIA disease was more common in the aSAH patients with pre-eclampsia (4/17, 24%) than without pre-eclampsia (19/121, 16%). ADPKD was more frequent in the sIA patients with pre-eclampsia (2/29, 7%) than without pre-eclampsia (2/236, 1%). Among sIA patients with pre-eclampsia, having a first-degree relative with pre-eclampsia was more common with aSAH than with unruptured sIAs (18% vs. 0%).

Pre-eclampsia in 393 female relatives and 546 controls

The frequency of pre-eclampsia was 5/57 (9%) in daughters, 10/167 (6%) in sisters, and 10/169 (6%) in nieces. A total of 32 (6%) controls had pre-eclampsia, considerably fewer than the sIA patients ($p = 0.01$), with an increased risk of pre-eclampsia for the sIA patients compared with controls with odds ratio 1.97 (95% confidence interval, 1.17–3.34) (Table 1). When only unruptured sIA patients were compared with the controls, no statistically significant difference was reached ($p = 0.14$). There was no statistically significant difference in the frequency of pre-eclampsia in the relatives and the controls.

Use of antihypertensive drugs in 265 sIA patients, 393 female relatives, and 546 controls

Among 265 sIA females, 163 (62%) used antihypertensive drugs (Table 1). Of the 29 sIA patients with pre-eclampsia, 19 (66%) used antihypertensive drugs compared with 144/236 (61%) sIA patients without pre-eclampsia. Of the 32 matched controls with pre-eclampsia, 16 (50%) used antihypertensive drugs compared with the 172 (33%) controls without pre-eclampsia. A total of 9/25 (36%) female relatives with pre-eclampsia used antihypertensive drugs in contrast to 96/368 (26%) female relatives without pre-eclampsia. With severe pre-eclampsia, antihypertensive drug use was more common in the controls (8/11 = 73%) than in the sIA patients (4/7 = 57%).

Comparison of the 29 sIA patients with pre-eclampsia and their 179 female relatives with the 236 sIA females without pre-eclampsia and their 1326 female relatives

We analyzed comorbidities in the study population of 265 sIA patients and all their 1505 female relatives (Figure 1). There were no significant differences in the frequencies of IA disease, intracerebral hemorrhage, ischemic stroke, ADPKD diagnoses, in the use of antihypertensive or type 2 diabetes drugs, or in mortality when comparing the 179 female relatives of the 29 sIA females with pre-eclampsia and the 1326 female relatives of the 236 sIA females without pre-eclampsia. The frequency of pre-eclampsia was higher in the 36 sisters of the 29 sIA patients with pre-eclampsia compared with the 306 sisters of the 236 sIA females without pre-eclampsia (8% vs. 4%), with no noticeable prevalence difference in the other relatives.

Familial sIA disease and familial pre-eclampsia in 68 sIA patients and 375 female relatives with pre-eclampsia

In addition to the basic study population of 265 sIA patients, 393 female relatives, and 546 controls (Figure 1), we analyzed all 1895 sIA females and all 12,141 female relatives for pre-eclampsia in the Kuopio IA Database between 1995 and 2018 (Figure 2). Among 68 sIA patients with pre-eclampsia, 40 (59%) had aSAH. Of the 375 female relatives with pre-eclampsia (111 daughters, 115 sisters, 13 mothers, 136 nieces), 201 (54%) were relatives to sIA females and 174 (46%) to sIA males. Of 68 sIA patients and 375 female relatives with pre-eclampsia, 75 (17%) had first-degree relative(s) with pre-eclampsia and 46 (10%) had second-degree relative(s) with pre-eclampsia, distributed similarly in the sIA females' and sIA males' relatives.

We identified in total 32 families with familial pre-eclampsia (Figure 3); 20 were sIA females' families and 12 sIA males' families. We found seven sIA+pre-eclampsia families; 6/7 were sIA females' families. There were no ADPKD diagnoses in the 32 pre-eclampsia families.

Severe pre-eclampsia was more common with the familial sIA disease (6/13, 46%) than without the familial sIA disease (11/55, 20%) in the 68 sIA patients ($p=0.057$). Among 68 sIA patients and 375 female relatives with pre-eclampsia, the use of antihypertensive drugs did not significantly differ between the studied groups: sIA family (63%), pre-eclampsia family (51%), sIA+pre-eclampsia family (61%), and not in sIA or pre-eclampsia family (53%) (Figure 2). There was no difference in antihypertensive drug use between unruptured (22/28, 79%) and ruptured (30/40, 75%) sIA patients.

Of the 375 female relatives with pre-eclampsia, 3% (3/111) of the daughters, 5% (6/115) of the sisters, 8% (1/13) of the mothers, and none of the nieces had an IA disease diagnosis and 10% (11/115) of the sisters with pre-eclampsia had an ischemic stroke diagnosis, more often than other female relatives with pre-eclampsia.

DISCUSSION

In our study population of 265 sIA females with the first birth since 1987, 11% had pre-eclampsia compared with 6% of matched controls. Severe pre-eclampsia was more common (29% vs. 17%) and pre-eclampsia recurred more often (18% vs. 8%) with aSAH than with unruptured sIAs, respectively. We identified 32 families with familial pre-eclampsia, and familial sIA disease co-occurred in seven (22%) of the families. Severe pre-eclampsia was more common with familial sIA disease than without familial sIA disease (46% vs. 20%) among sIA patients. Collectively, our results add to the accumulating evidence of the association between pre-eclampsia and sIA disease.

Pre-eclampsia was significantly more frequent in the 265 patients with sIA than in their 546 population controls, in line with our previous study [23]. In addition, irregularly-shaped aneurysms were more frequent in the sIA patients with pre-eclampsia in our previous study, a feature associated with an elevated risk of sIA wall rupture [23, 31]. The risk for sIA disease and aSAH in patients with a history of pre-eclampsia has remained unclear, as earlier studies have primarily inspected stroke in general [16], long-term risk of intracerebral hemorrhage [32], and pregnancy-related SAH [33], as opposed to sIA disease.

The pathophysiology of pre-eclampsia is not entirely understood; the prevailing theory is that although early- and late-onset pre-eclampsia share some risk factors, they could be different entities [34]. Early-onset disease is characterized by defective placentation,

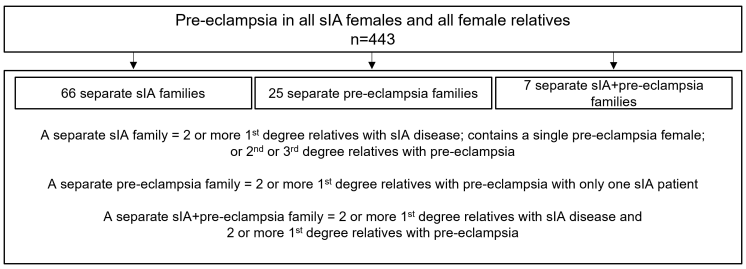

FIGURE 3 Identification of all separate saccular intracranial aneurysm (sIA) families, pre-eclampsia families, and sIA+pre-eclampsia families among 68 sIA patients with pre-eclampsia and 375 female relatives with pre-eclampsia.

whereas late-onset disease is often influenced by maternal cardiovascular and metabolic risk factors [35]. Early-onset pre-eclampsia has the strongest genetic predisposition [36] and is often severe [22]. Both maternal and paternal familial linkages have been found; for instance, higher rates of pre-eclampsia in pregnancies fathered by men who were born from pre-eclamptic pregnancies [20, 21]. Genome-wide linkage scans of pre-eclampsia have identified significant loci in 2p13 [37], 2p25 [38], and 9p13 [38]. Genome-wide association studies (GWAS) of pre-eclampsia have identified several risk loci associated with hypertension [39, 40]. Of the 17 risk loci for intracranial aneurysms in the largest international GWAS [41], rs2681472 has been associated with pre-eclampsia [42] and, additionally, with blood pressure, cardiovascular, and coronary artery disease [41]. Of the potential causative genes in the aforementioned GWAS of intracranial aneurysms, SLC22A4/OCTN1 and SLC22A5/OCTN2 have been linked to pre-eclampsia [43–45].

Pre-existing hypertension and ADPKD increase the risk of both pre-eclampsia [19, 46] and sIA disease [2, 10]. In our study, antihypertensive drug use was similar in the 265 sIA patients with and without pre-eclampsia (66% vs. 61%). When inspecting all sIA patients with pre-eclampsia ($n = 68$), there was no difference in antihypertensive drug use in patients with unruptured and ruptured sIAs (79% vs. 75%). These findings suggest that hypertension does not solely explain the increased prevalence of pre-eclampsia or rupture risk among sIA females. ADPKD was more common with than without pre-eclampsia among 265 sIA patients (7% vs. 1%), but not in the female relatives or in the controls. There were no ADPKD diagnoses in 32 pre-eclampsia families, thus ADPKD does not explain the co-occurrence of sIA disease and pre-eclampsia in these families. In our basic study population, severe pre-eclampsia was more common with aSAH (29%) than with unruptured sIA disease (17%). However, severe pre-eclampsia was also frequent (34%) in controls. Interestingly, in controls with severe pre-eclampsia, antihypertensive drug use was more frequent than in the sIA patients with severe pre-eclampsia (73% vs. 57%). This could illustrate different etiological features, although no apparent distinctions were observed in the studied variables. Nevertheless, hypertension is frequently documented after severe pre-eclampsia [47].

Both pre-eclampsia and sIA disease are complex conditions with clear familial components [12, 36]. The prevalence of pre-eclampsia in the female relatives did not differ from the controls, indicating that familial aggregation of pre-eclampsia does not explain the higher prevalence in sIA females. A slightly higher prevalence in daughters (9%) might originate from behavioral or methodological factors, as maternal obesity in Finland has increased rapidly [48], and the new guidelines for diagnosing pre-eclampsia were published in 2013 [29]. We identified seven families with both familial sIA disease and familial pre-eclampsia, fewer than initially expected. Prevalence of severe pre-eclampsia was highest in the sIA + pre-eclampsia-families, while antihypertensive drug use did not notably differ from other sIA patients and relatives with pre-eclampsia. In previous studies, hypertension has not been associated with familial sIA disease [2, 49]. It seems that familial sIA disease and familial pre-eclampsia do not significantly share risk factors. However, both diseases may result in more severe forms when they co-occur.

Our study has strengths originating from the Nordic health care system. Finland is divided into separate catchment areas for the KUH and the four other university hospitals, allowing the formation of unselected and minimally biased disease cohorts. The Finnish personal identification code system enables the congregation of accurate population and clinical data registries, with few individuals lost to follow-up. The present study included only patients with four-vessel angiography-verified sIAs, excluding other types of IAs. All antihypertensive and type 2 diabetes drugs are sold only by physicians' prescriptions in the pharmacies in Finland, and all drug purchases were traced from the national registry for this study. In Finland, maternity and child health clinics monitor pregnancies with standard follow-up visits with regular blood pressure level screenings. In Finland, nearly all births occur in hospitals (99.4% in 2020) [50] ensuring comprehensive national pregnancy and birth data available for the study period, and therefore our pre-eclampsia data are minimally biased.

This study also has limitations. Our study was retrospective while the database was prospective during the study period. One weakness is the limited size of our cohort. We chose to use the ICD-8, ICD-9, and ICD-10-codes to categorize sIA patients, relatives, and controls into individuals with and without pre-eclampsia. We did not have access to the ICD-8 codes for patients with the first sIA diagnosis between 2015 and 2018, including those patients' relatives and controls, which might have led to undiscovered pre-eclampsia cases. There were no data available for the relatives of the controls. Because of the age distribution of our study population, there are insufficient pregnancy data for the sIA patients' mothers, daughters, and nieces. Unfortunately, the sIA registry does not maintain reliable data on body mass index or smoking.

Among the first-degree relatives, no distinction was made between full or half-siblings, which might have led to underestimated sibling influence. In studying the familial aggregation of pre-eclampsia we chose to include all sIA females' and sIA males' female relatives, considering maternal and paternal linkages in pre-eclampsia [21]. We did not have data for the sIA males' partners, which apparently resulted in undiscovered pre-eclampsia families.

Considering clinical practice, the history of pre-eclampsia indicates an elevated risk of sIA disease and may associate with an elevated risk for instability in the yet unruptured sIA walls. Confirmation of this result in other population-based datasets is warranted. Further studies of the mechanisms by which pre-eclampsia could affect the walls of brain arteries and increase the risk of aneurysm rupture are indicated.

AUTHOR CONTRIBUTIONS

Satu Kotikoski: Investigation; writing – original draft; visualization; formal analysis; data curation; funding acquisition. **Juho Paavola:** Data curation; writing – review and editing; investigation. **Heidi J. Nurmonen:** Writing – review and editing; investigation; data

curation. **Virve Kärkkäinen:** Funding acquisition; writing – review and editing; project administration. **Jukka Huttunen:** Writing – review and editing; methodology; investigation; data curation. **Timo Koivisto:** Writing – review and editing; resources; data curation. **Mikael von und zu Fraunberg:** Supervision; writing – review and editing; data curation; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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SATU KOTIKOSKI

Saccular intracranial aneurysms (sIAs) are pouches that form on the intracranial arteries during life. Rupture of the sIA wall causes aneurysmal subarachnoid hemorrhage, a devastating form of stroke. Hypertension is an important risk factor for the sIA disease. In this thesis, secondary hypertension and pre-eclampsia were studied in an Eastern Finnish sIA cohort to deepen the understanding of the relationship between sIAs and hypertensive disorders as well as their familial associations.

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