Type 2 Diabetes and Risk of Rupture of Saccular Intracranial Aneurysm in Eastern Finland

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OBJECTIVE—Type 2 diabetes is a risk factor for other forms of stroke, but its association with subarachnoid hemorrhage (SAH) from ruptured saccular intracranial aneurysm (sIA) has remained unclear.

RESEARCH DESIGN AND METHODS—Kuopio Intracranial Aneurysm Database (www.uef.fi/ns) includes all ruptured and unruptured sIA cases from a defined catchment population in eastern Finland since 1980. We compared the age-adjusted incidences of type 2 diabetes in 1,058 ruptured and 484 unruptured sIA patients during 1994–2008, using the national registry of prescribed medicine purchases.

RESULTS—Of the 1,058 ruptured sIA patients, 43% were males and 57% females, with a median age at rupture of 51 and 56 years, respectively. From 1994 to 2008 or until death, 9% had been prescribed antidiabetes medication (ADM) with a median starting age of 58 years for males and 66 years for females. Of the 484 unruptured sIA patients, 44% were males and 56% females, with a median age at the diagnosis of 53 and 55 years, respectively, and 9% had used ADM, with a median starting age of 61 years for males and 66 years for females. The incidence of type 2 diabetes was highest in the age-group 60–70 years, with no significant differences between the ruptured and unruptured sIA patients.

CONCLUSIONS—Our study suggests that type 2 diabetes does not increase the risk of rupture of sIA, which is by far the most frequent cause of nontraumatic SAH.

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Aneurysmal subarachnoid hemorrhage (SAH) is a devastating form of stroke that affects primarily the working-age population (1). In ~95% of cases, SAH is caused by the rupture of a saccular intracranial aneurysm (sIA) at the fork of intracranial extracerebral arteries in contrast to their infrequent fusiform, mycotic, and traumatic aneurysms. Some 2% of the general population develops sIAs (2–3) during life, but most do not rupture, as the general annual incidence of SAH is 4–7 per 100,000 (4–5). The sIA disease is a complex trait, affected by genomic (6–8) and acquired risk factors (3), the mechanisms of which in the formation, progress, and rupture of sIA pouches are poorly understood. Risk factors include age, female sex, smoking, hypertension, and excess drinking (3), and at least 10% of ruptured sIA patients have a family history (9–12). In a genome-wide association study, susceptibility loci at 2q33.1, 8q11.23, and 9p21.3 have been identified in Finnish subjects (7).

Type 2 diabetes is a complex trait affecting the arterial wall through several different mechanisms (13–16). Type 2 diabetes is a well-established risk factor for brain infarction and may predispose to intracerebral hemorrhage (17–19). Instead, the association between type 2 diabetes and sIA disease has remained unclear. Three recent studies (20–22) and our present review of the literature suggest that diabetes is a protecting factor for rupture of sIA (Table 1; Fig. 1*A*) (23–29). Both type 2 diabetes and sIA disease are associated with the 9p21.3 locus (6–8,30,31), although not with the same LD block, but they do not seem to share other loci in genome-wide association studies.

Kuopio Intracranial Aneurysm Database (www.uef.fi/ns) contains all cases of unruptured and ruptured sIAs admitted to the Kuopio University Hospital (KUH) from a defined eastern Finnish catchment population since 1980 (11,12). We have studied the phenotype (11), familial form (2,9), risk factors (32), outcome (12,33), concomitant diseases (12), and genomics of sporadic and familial sIA disease (6–8,34). Here, we investigated retrospectively whether type 2 diabetes predisposes to sIA rupture by comparing 1,058 ruptured sIA patients with 484 unruptured sIA patients with first diagnosis between 1995 and 2007. In this study, we tested the hypothesis that arterial long-term effects of type 2 diabetes predispose to the rupture of the sIA wall rather than the formation of the sIA pouch. We also performed a review of the literature of the published cohorts to summarize the previous data on the association of type 2 diabetes and sIA disease.

RESEARCH DESIGN AND METHODS

Catchment population of KUH

During the study period from 1995 to 2007, Neurosurgery of KUH had solely provided full-time acute and elective neurosurgical services for the KUH catchment population in eastern Finland. The KUH area contains four central hospitals with neurologic units of their own. From 1995 to 2007, the geographic area remained the same but the population

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Table 1—*Previous studies on the association of diabetes and intracranial aneurysm disease* since 2001*

Reference Year	Country	Type of study	Cases and controls	Mean age ± SD (years)	DM cases (%)	Association of DM and IA disease	Criteria of DM
Shiue et al. 2012	Australia	Case-control Multicenter	432 aSAH 473 controls	56.5 ± 16.8	20 (5) 37 (8)	n.s. multivariate	Medical records
Cui et al. 2011	Japan	Prospective Multicenter Follow-up 12 years	111 aSAH		3 (3)	n.s. multivariate	See the reference
Inagawa 2010	Japan	Case-control Single center	798 aSAH 798 controls 266 unruptured sIAs 798 controls	64 ± 12 66 ± 11 	37 (5) 72 (9) 37 (14) 72 (9)	OR 0.41; 0.26–0.64; $P < 0.001$ n.s. for unruptured sIAs 	Medical records
Koshy et al. 2010	India	Case-control Multicenter	163 aSAH 150 controls	52 ± 11	5.5 14.7	Univariate OR 0.34; 0.15–0.76; $P = 0.009$	Interview
Ruiz-Sandoval et al. 2009	Mexico	Retrospective Multicenter	231 aSAH 231 controls	52	16 (7) 35 (15)	OR 0.34; 0.17–0.68; $P = 0.05$	Medical records
Okamoto et al. 2005	Japan	Case-control Single center	201 aSAH 402 controls	59.1	15 (7.5) 12 (3)	n.s. multivariate	Structured questionnaire
Ohkuma et al. 2003	Japan	Case-control Multicenter	390 aSAH 390 controls	58 ± 13	23 (6) 31 (8)	n.s. univariate	Structured questionnaire
Kissela et al. 2002	U.S.	Case-control Multicenter	107 aSAH 197 controls		5.6 9.1	n.s. univariate	Interview and medical records
Qureshi et al. 2001	U.S.	Case-control Single center	323 aSAH 969 controls	52.7 ± 14	25 (8) 101 (10)	n.s. multivariate	Structured questionnaire and examination
Kubota et al. 2001	Japan	Case-control Multicenter	127 aSAH 127 controls	52 ± 10	2 (2) 4 (3)	n.s. univariate	Structured questionnaire

aSAH, aneurysmal subarachnoid hemorrhage; IA, intracranial aneurysm; DM, diabetes mellitus; n.s., not significant; OR, odds ratio in multivariate analysis. *The type of intracranial aneurysm, whether saccular vs. fusiform, mycotic, and traumatic, was not always available in the referred cohorts.

decreased from 880,914 to 851,066. The median age increased from 38 to 42 years in males and from 41 to 45 years in females, and the proportion of males remained unchanged at 49% (11).

Kuopio Intracranial Aneurysm Database

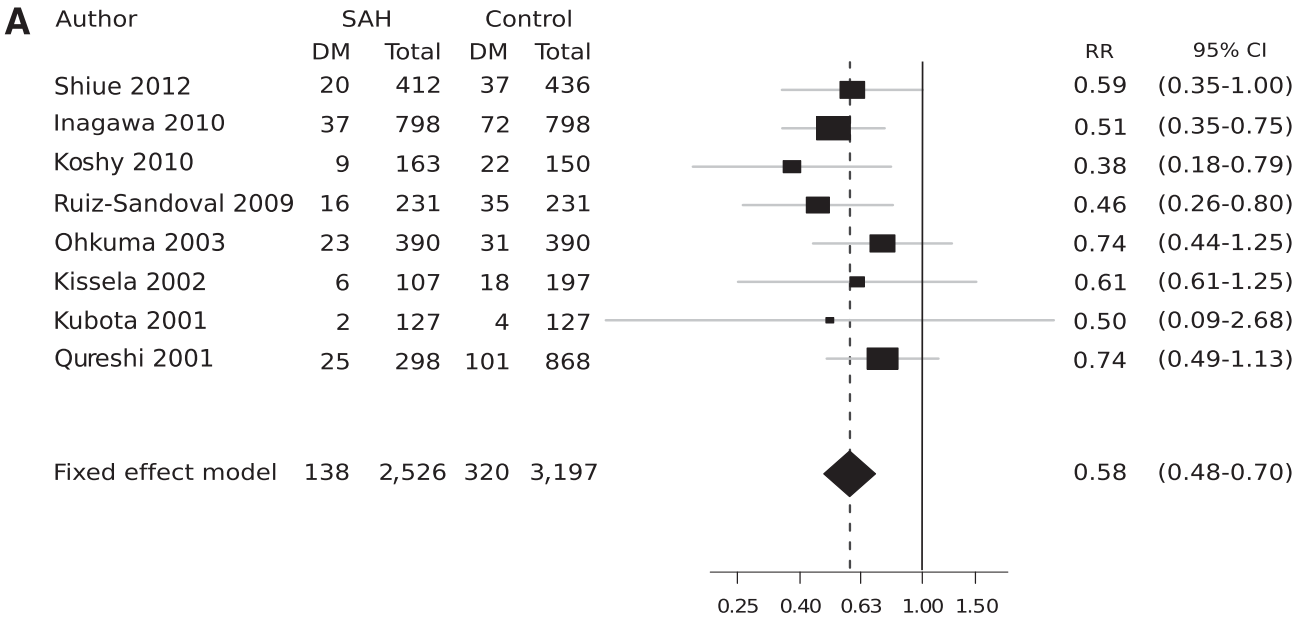
All cases of SAH diagnosed by spinal tap or computed tomography in the KUH catchment area have been acutely admitted to KUH for angiography and treatment if not moribund or very aged. Cases with unruptured intracranial aneurysm(s) but no SAH have also had neurosurgical consultation for elective occlusion. They were detected mostly as incidental findings in neuroimaging for other causes, less often as symptomatic, or by screening sIA family members. The findings were confirmed by four-vessel catheter angiography, magnetic resonance angiography (MRA), or computed tomography angiography (CTA). The exact numbers of rejected cases are not available. KUH Neurosurgery maintains a database on all cases of unruptured and ruptured intracranial aneurysms admitted to the KUH since 1980. The database has been prospective since 1990, and earlier cases have been entered from hospital records. The database is run by a dedicated full-time nurse, who interviews all new case subjects, and collects and codes variables with detailed information, including the family history. The criterion for an sIA family is at least two affected first-degree relatives (11). Clinical data from the hospital periods and follow-up visits are entered. The use of prescribed medications (1995–2008) before and after the sIA diagnosis, occurrence of cancer and other diagnosed diseases, and causes of death have been entered from national registries. The phenotype, genomics, and outcome of eastern Finnish sIA disease have been analyzed in several studies (2,6–9,11,12,33,34).

Study population

The inclusion criteria were citizenship of Finland and residence in the KUH catchment area at first diagnosis of sIA disease between 1 January 1995 and 31 December 2007; admission alive to KUH, and verification of sIA(s) by angiography or at autopsy. The exclusion criteria were rupture of an intracranial aneurysm other than a saccular one (e.g., fusiform, traumatic, mycotic) or any other vascular malformation.

Antidiabetes or antihypertension medication

The diagnosis for type 2 diabetes was made based on the database of purchased antidiabetes drugs. The Social Insurance Institution of Finland maintains a nationwide registry of all prescribed drugs purchased from the pharmacies since 1994. Information on purchases of all prescribed drugs by the 1,542 sIA patients between 1 January 1994 and 31 December 2008 was obtained from the Social Insurance institute of Finland and linked to Kuopio Intracranial Aneurysm Database. The recruitment period, from 1 January 1995 to 31 December 2007, allows data on purchased drugs for at least 1 year before and 1 year after the diagnosis of sIA. Antidiabetes (ADM) and



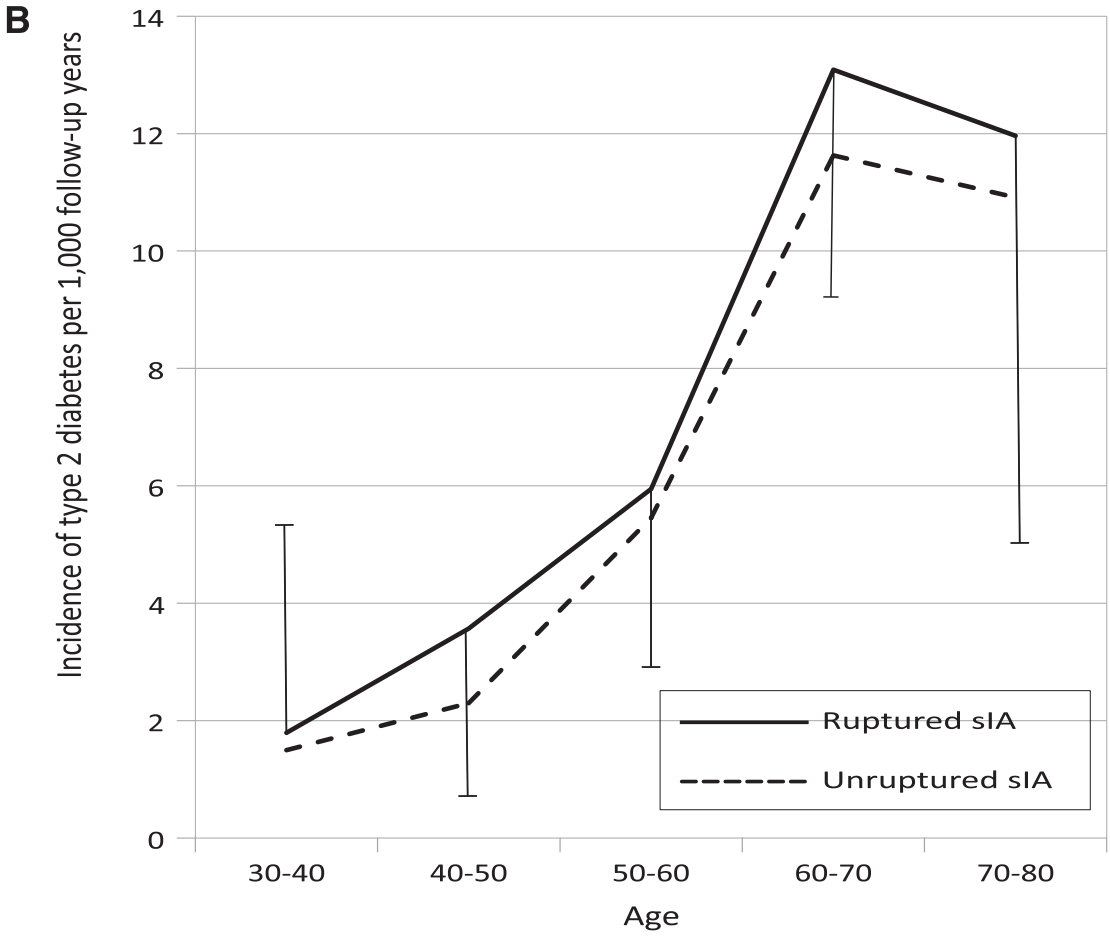


Figure 1—A: *Review of the literature of the association of diabetes and SAH in case-control studies published 2001–2012. The horizontal lines represent the 95% CIs of the OR or risk ratios (RRs). The size of the black box indicates the relative effect on the final fixed-effect estimate. The* x*-axis is logarithmic.* B: *Incidence of type 2 diabetes in 1,058 ruptured (aneurysmal SAH) and 484 unruptured sIA patients by age-group and 95% CIs.*

Table 2—*Clinical characteristics and ADM of 1,542 sIA patients admitted to KUH 1995–2007*

	Unruptured sIA disease n = 484			Ruptured sIA disease n = 1,058		
	No ADM	ADM	Univariate P	No ADM	ADM	Univariate P
sIA patients	441 (91)	43 (9)		968 (91)	90 (9)	
Females	252 (57)	21 (49)	n.s.	557 (58)	51 (55)	n.s.
ADM	441 (91)	43 (9)		968 (91)	90 (9)	
Median starting age (quartiles)		64 (57–70)			62 (53–68)	n.s.
Before sIA diagnosis		14/43 (33)			30/90 (33)	n.s.
After sIA diagnosis		29/43 (67)			60/90 (67)	
Antihypertensive medication	327 (74)	40 (93)	0.006	596 (62)	80 (89)	<0.000
Median starting age (quartiles)	53 (47–64)	59 (49–63)	n.s.	54 (46–65)	59 (51–66)	0.007
Before sIA diagnosis	206/327 (63)	32/40 (80)	0.001	307/596 (52)	43/80 (54)	0.002
After sIA diagnosis	121/327 (37)	8/40 (20)		289/596 (48)	37/80 (46)	
Antihypercholesterolemic medication	194 (44)	28 (65)	0.008	245 (25)	58 (64)	<0.000
Median starting age (quartiles)	58 (51–66)	66 (56–68)	0.015	58 (53–67)	62 (56–68)	0.05
Before sIA diagnosis	80/194 (41)	15/28 (54)	n.s.	88/245 (36)	14/58 (25)	n.s.
After sIA diagnosis	114/194 (59)	13/28 (46)	n.s.	157/245 (64)	44/58 (75)	n.s.
sIA disease diagnosis						
Median age (quartiles)	54 (46–64)	63 (55–69)	0.001	53 (45–64)	61 (51–69)	<0.000
Familial sIA disease	117 (27)	6 (14)	n.s.	133 (14)	12 (13)	n.s.
Multiple sIAs	121 (27)	6 (14)	n.s.	272 (28)	26 (28)	n.s.
Age at sIA diagnosis (years)						
≤44	87 (20)	1 (2)		242 (25)	13 (14)	
45–54	146 (33)	9 (21)		279 (28)	17 (19)	
55–64	100 (23)	14 (33)		225 (23)	26 (29)	
≥65	108 (25)	19 (44)		222 (23)	34 (38)	
Location of sIAs	Unruptured sIAs			Ruptured sIAs		
ICA	147 (24)	11 (20)	n.s.	208 (21)	22 (24)	n.s.
ACoA	68 (11)	5 (9)	n.s.	283 (29)	29 (32)	n.s.
A2–5	22 (4)	4 (7)	n.s.	52 (5)	4 (4)	n.s.
Mbif	253 (41)	20 (36)	n.s.	279 (29)	21 (23)	n.s.
VA	11 (2)	3 (5)	n.s.	32 (3)	6 (7)	n.s.
BAbif	31 (5)	5 (9)	n.s.	50 (5)	2 (2)	n.s.
Others	80 (13)	8 (14)	n.s.	64 (7)	8 (9)	n.s.
Median size (mm)				8.4 (n = 968)	7.9 (n = 92)	n.s.

Data are n (%) unless otherwise indicated. Site distribution by all unruptured sIAs—not by sIA patients. A2–5, distal segments of anterior cerebral artery; ACoA, anterior communicating artery; BAbif, basilar artery bifurcation; ICA, internal carotid artery; Mbif, middle cerebral artery bifurcation; n.s., not significant; VA, vertebral artery.

antihypertension medications were classified according to the anatomic therapeutic chemical (ATC) classification system. The patients with type 1 diabetes, first identified according to their insulin use and by their special reimbursement code and finally verified from the case reports, were excluded from the analysis.

Variables

The variables used in the analyses were as follows for all sIA patients: *1*) sIA disease carrier (sex, age at first sIA diagnosis or at rupture of sIA, sporadic vs. familial sIA patient, use and starting age of antihypertensive medication, and use and starting age of ADMs) and 2) sIA disease (location and diameter of the primary sIA and one versus two or more sIAs.

Statistical analysis

Univariate analyses were performed using the Mann-Whitney U test. Multivariate analyses were performed using the binomial logistic regression model. To account for difference of age at the diagnosis of sIA disease between the unruptured and ruptured groups, we standardized the age to the joint age distribution of both age-groups. Standardized rates and CIs were calculated according to the methodology of Fay and Feuer (35), as the occurrences of diabetes are low in different age-groups. The incidences of ADM in the ruptured and unruptured patients were calculated for 10-year age intervals, and the CIs in each age group were calculated as exact central Poisson CIs (36).

Review of the literature

A PubMed search for articles on SAH risk and diabetes was made from 2001 to April 2012 with the following keyword(s): subarachnoid hemorrhage, stroke, diabetes, and case-control. Bibliographies of the retrieved articles were examined for further relevant publications. Cross-checking was continued until no further publications in English were found. Only the studies that reported the number of patients exposed to diabetes, allowing recalculation of the associated SAH risk, were included. Studies restricted to subgroup of patients (e.g., young patients) were excluded. When there were multiple studies from the same cohort, the newest published study was included. A fixed-effects Mantel-Haenszel

Table 3—*Independent risk factors for sIA rupture in the study cohort of 1,542 sIA patients in multivariate binomial regression analysis*

	P	OR	95% CI
Familial sIA	0.001	0.42	0.31–0.56
Location of sIA			
ACoA		1	
Mbif	0.001	0.24	0.17–0.34
BAbif	0.001	0.23	0.13–0.40
Others	0.001	0.38	0.27–0.54
Antihypertension medication	0.011	0.69	0.53–0.92
Antihypercholesterolemic medication	0.001	0.49	0.38–0.63
ADM	0.37	1.21	0.80–1.83

ACoA, anterior communicating artery; BAbif, basilar artery bifurcation; Mbif, middle cerebral artery bifurcation.

method was used in the review of the literature to estimate pooled odds ratios (ORs) and CIs. The appropriateness of fixed-effects model was evaluated by the Cochran Q test, which indicated no heterogeneity of study effects (Q = 3; df = 7; $P = 0.7$).

Ethics

The study was approved by the ethics committee of the KUH. Data fusion from the national registries was performed with the approval from Ministry of Social Affairs and Health of Finland.

RESULTS

Unruptured sIA disease

Of the 1,542 sIA patients, 484 (31%) carried an unruptured sIA disease (Table 2). There were 211 (44%) males and 273 (56%) females, and their median ages at the first diagnosis were 53 and 55 years, respectively. The most frequent sIA location was the middle cerebral artery bifurcation (48%). Two or more sIAs were diagnosed in 127 (26%) patients. Familial sIA disease was found in 123 (25%) patients. Of the 484 patients, 224 underwent microsurgical and 56 endovascular occlusion therapy of sIA(s).

ADM in unruptured sIA patients

During the observation period for drug use—from 1994 to 2008 or death—43 (9%) of the 484 unruptured sIA patients used ADM. The median starting age was 61 years for the 22 males and 66 years for the 21 females. The ADM had been started before the sIA diagnosis in 14 (31%) cases and after the diagnosis in 31 (69%) cases. In multivariate analysis, only the age at diagnosis (OR 1.03 [95% CI 1.012–1.051, $P = 0.01$) independently associated with ADM.

Ruptured sIA disease

There were 1,058 ruptured sIA patients, 451 (43%) of whom were male and 607 (57%) female, with median ages at first rupture of sIA of 51.0 and 56.0 years, respectively (Table 2). The most frequent location of ruptured sIA was the anterior communicating artery at 29%. Two or more sIAs were diagnosed in 298 (28%) patients. Familial sIA disease was carried by 145 (14%) patients.

ADM in ruptured sIA patients

From 1994 to 2008 or death, 90 (9%) of the 1,058 ruptured sIA patients used ADM. The median starting age was 58 years for the 40 (44%) males and 66 years for the 50 (56%) females. The ADM had been started before the rupture in 30 (33%) cases and after the rupture in 60 (67%) cases. In multivariate analysis, the age at rupture (OR 1.05) associated independently with ADM. The cumulative mortality rate at 12 months after the rupture of sIA was 25%.

In multivariate analysis of all 1,542 sIA patients, familial sIA (OR 0.42), sIA in middle cerebral artery bifurcation (0.24), sIA in basilar artery bifurcation (0.23), sIA in "other" location (0.38), antihypercholesterolemic medication (0.49), and antihypertension medication (0.57) independently associated with rupture of sIA, while ADM did not (Table 3).

ADMs used

Between 1994 and 2008, the 133 patients with ADM used 22 different drugs according to the anatomic therapeutic chemical classification. During the study interval, the most frequently used ADMs were as follows: metformin and other oral ADM (n = 96), insulin combined with oral ADM (n = 29), and monotherapy with insulin (n = 7).

Incidence of type 2 diabetes

The age-standardized incidence of type 2 diabetes was 6.36 (4.60–8.63) per 1,000 follow-up years for patients with unruptured sIA and 6.98 (95% CI 5.62–8.59) per 1,000 follow-up years for patients with ruptured sIA. The incidence of type 2 diabetes was highest in the group of 60–70 years, with no significant differences between the ruptured and unruptured patients (Fig. 1*B*).

CONCLUSIONS—We tested the hypothesis that type 2 diabetes would increase the risk of sIA rupture by comparing 1,058 ruptured sIA patients and 484 unruptured sIA patients first diagnosed between 1995 and 2007 in a defined eastern Finnish population. The type 2 diabetic patients were identified by ADM usage between 1994 and 2008, obtained from the Finnish registry of prescribed drug purchases. The ADM usage, 9% in both cohorts, did not associate with the rupture of sIA in multivariate analysis.

Type 2 diabetes is a well-established risk factor for brain infarction and may predispose to intracerebral hemorrhage (17–19). Instead, the association between type 2 diabetes and sIA disease has remained unclear. Unlike our study and the cohort of 329 cases of SAH from sIA published in 1984 (37), three recent studies (20–22) and our present review of the literature from the six published ones suggested that diabetes is a protective factor for SAH (Table 1; Fig. 1). Inagawa hypothesized that the protecting effect of diabetes would be connected to enhanced atherosclerosis in the sIA wall, making it less prone to rupture (21). Atherosclerosis has not been identified as an independent risk factor for saccular aneurysms that form in the branching sites of intracranial extracerebral arteries (3)—unlike in fusiform aneurysms, e.g., in the aorta (38,21). In theory, a genetic link that predisposes to the development of type 2 diabetes and lowers the risk of developing sIAs may exist. Hypercholesterolemia was associated with reduced risk of SAH in three case-control studies (40% risk reduction), with no clear sex difference (3). Another theoretical protective factor in diabetic patients might be more efficient diagnosis and treatment of hypertension—an independent risk factor of the sIA disease (3).

In the present cohort, the median ages for diagnosis of the sIA disease were 54 years for the unruptured cases and 54 years for the ruptured sIA cases. Instead, the median starting age for ADM was 63 and 62 years, respectively. Consequently, the impact of diabetes on arterial walls may manifest so late that it does not show in the sIA disease.

Type 2 diabetes and sIA disease are complex traits with genomic components. The 9p21.3 locus associates with both diseases (6,7,30,31) but not in the same linkage disequilibrium block. To our knowledge, other shared susceptibility loci have not been found, suggesting that type 2 diabetes and sIA disease do not share genomic predisposition.

Unfortunately, the sIA registry does not contain reliable data on BMI, smoking, or drinking habits of the sIA patients. An obvious weakness was also the lack of data on the diagnostic tests used for type 2 diabetes such as fasting glucose levels and oral glucose tolerance tests. On the other hand, we compared the ruptured sIA patients with the unruptured sIA patients, and both had their blood glucose levels studied during the hospitalization for the sIA disease. In ruptured sIA patients, these glucose levels are unreliable because of impact of ruptured sIA and its neurointensive care. Of the 133 ADM users, as many as 81 had started ADM within 12 months after the sIA diagnosis. Still, we may have missed cases of unmedicated diabetes during the period of ADM purchases, and the vascular effects of diabetes may be different in medicated and untreated individuals. In a cross-sectional population-based survey in Finland between October 2004 and January 2005, the total prevalence of both previously diagnosed and screen-detected type 2 diabetes was 16% in men and 11% in women aged 45–74 years (39). Previous studies registered the diabetes status only once, missing diabetes cases presenting after the sIA diagnosis. The strengths of the current study derive from the Finnish health care system. Finland is divided into mutually exclusive catchment areas among the five university hospitals. This system allows the creation of disease cohorts that are unselected and minimally biased. Very accurate population statistics and a stable population ensure that few patients are lost to follow-up.

In conclusion, type 2 diabetes is a risk factor for two forms of stroke, brain infarction and intracerebral hemorrhage (17–19), but our study suggests that type 2 diabetes does not increase the risk of rupture of sIA, which is by far the most frequent cause of nontraumatic SAH.

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A.E.L. collected and analyzed data and wrote the manuscript. M.I.K. analyzed data and edited the manuscript. A.Ri. collected data. T.K., A.Ro., J.R., J.H., J.G.E., J.E.J., and M.v.u.z.F collected data and edited the manuscript. A.E.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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