Atrial fibrillation in aging

Methodological aspects and the relation to dementia and cerebral vascular disease

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Atrial fibrillation in aging- Methodological aspects and the relation to dementia and cerebral vascular disease

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Så gick det lilla knyttet ut på stranden
och fann en snäcka som var stor och vit,

Han satte sig försiktigt ner i sanden
och tänkte, o så skönt att jag kom hit,

och lade vackra stenar i sin hatt
och havet var så lugnt och det blev natt.

-Tove Jansson,
Vem kan trösta knyttet

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ABSTRACT

Emerging evidence suggest an increased risk of dementia in individuals with atrial fibrillation (AF). However, until recently, few studies have investigated the relation between AF and dementia taking both prevalent and incident stroke into account. Therefore, this thesis aims to examine if AF increase the risk of dementia in a sample free from a history of stroke at baseline and incident stroke during follow-up. Further, the mechanisms behind an association between AF and dementia in the absence of symptomatic stroke is not elucidated. Therefore, this thesis also aims to examine if AF is associated to silent brain infarcts (SBIs) and small vessel disease on brain MRI. Since epidemiological studies often are accompanied with biases, we also analyzed differential attrition during follow-up and agreement between self- and proxy-reported diagnoses.

Data were obtained from the Gothenburg H70 Birth Cohort (H70) studies and the Prospective Population Study of Women (PPSW) in Gothenburg. The samples used in this thesis include the cohorts born 1930 (followed from age 70 to 88) and 1944 (examined at age 70). The H70 and PPSW studies are comprehensive population-based studies aiming to be representative of older adults living in Gothenburg, Sweden.

We found that a history of AF at age 70 increased the risk of dementia during follow-up in the 1930 cohort. Further, we found that AF was cross-sectionally associated to symptomatic stroke, SBIs, and lacunes among 70-year-olds in the

1944 cohort. There were no associations between AF and global white matter hyperintensity (WMH) volumes or the presence of any cerebral microbleed. However, among participants with symptomatic stroke, AF was associated with larger WMH volumes. In the 1930 cohort, both AF and dementia were associated with attrition due to death. Further, agreement between self- and proxy-reported diagnoses was substantial for AF, myocardial infarction, angina pectoris, hypertension, and diabetes mellitus, but only fair for heart failure and intermittent claudication.

Further research is needed to investigate the mechanism(s) behind the association between AF and dementia, the optimal treatment regimens for AF in relation to dementia prevention, and possibilities to include brain MRI in treatment guidelines to further personalize anticoagulation treatment in AF patients. In addition, analyzing differential attrition and diagnostic accuracy in epidemiologic research is necessary to evaluate and generalize results.

Keywords: atrial fibrillation, dementia, stroke, silent brain infarcts, white matter hyperintensity, cerebral microbleed, small vessel disease, epidemiology

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SAMMANFATTNING PÅ SVENSKA

Förmaksflimmer (FF) innebär en ökad risk för stroke, vilket i sin tur kan orsaka demens. Forskning har även visat att FF innebär en ökad risk för demens hos personer som inte har haft någon stroke, men fram till nyligen har få studier undersökt sambandet mellan FF och demens där man tagit hänsyn till stroke under hela uppföljningstiden.

Denna avhandling syftar till att undersöka om FF ökar demensrisken även i frånvaro av stroke under hela uppföljningstiden. Mekanismerna bakom ett samband hos personer som inte får någon stroke är inte klarlagda. Därför syftar denna avhandling även till att undersöka om FF är kopplat till tysta infarkter (infarkter som syns på hjärnavbildning men som inte gett typiska strokesymtom) och småkärlssjuka i hjärnan. Eftersom selektivt bortfall kan påverka resultat och generaliserbarhet undersökte vi även om deltagare som föll bort under studiens gång skilde sig från de som stannade kvar i studien. Vi undersökte även hur väl själv- och anhörigrapporterade diagnoser överensstämmer med varandra.

Datan kommer från H70-studierna och kvinnostudien (KVUS) i Göteborg. Deltagarna som inkluderats i denna avhandling är 70-åringar födda 1930 som följts upp till 88 års ålder och 70-åringar födda 1944.

Vi fann att FF ökade risken för demens även i frånvaro av stroke. Vi fann även att FF var kopplat till tysta infarkter och tecken på småkärlssjuka i hjärnan i form av lakuner. Det fanns däremot inget samband mellan FF och andra tecken på småkärlssjuka i hjärnan så som förändringar i den vita substansen. Bland deltagare som haft en stroke var FF däremot kopplat till skador i den vita substansen. Slutligen fann vi att FF var kopplat till bortfall pga död under uppföljningstiden och att överensstämmelsen mellan själv- och anhörigrapporterade diagnoser var betydande för FF, hjärtinfarkt, kärlkramp, hypertoni och diabetes, medan den var dålig för hjärtsvikt och claudicatio.

Ytterligare forskning behövs för att undersöka mekanismer bakom sambandet mellan FF och demens, vilken som är den optimala behandlingen av FF för att förebygga demens och om hjärnavbildning kan inkluderas i guidelines för att ytterligare personifiera behandling med blodförtunnande hos patienter med FF. Att undersöka hur de som försvinner under studiens gång skiljer sig från de som är kvar och hur tillförlitligheten är för olika informationskällor är nödvändigt för att kunna värdera och generalisera resultat.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Rydén L*, Wetterberg H*, Ahlner F, Falk Erhag H, Gudmundsson P, Guo X, Joas E, Johansson L, Kern S, Mellqvist Fässberg M, Najar J, Ribbe M, Sacuiu S, Samuelsson J, Sigström R, Skoog J, Rydberg Sterner T, Waern M, Zettergren A, Skoog I. **Attrition in the Gothenburg H70 Birth Cohort Studies -an 18-year follow-up of the 1930-cohort**. Submitted manuscript. *LR and HW are joint first authors

II. Rydén L, Sigström R, Nilsson J, Sundh V, Falk Erhag H, Kern S, Waern M, Östling S, Wilhelmson K, Skoog I. **Agreement between self-reports, proxy-reports and the National Patient Register regarding diagnoses of cardiovascular disorders and diabetes mellitus in a population-based sample of 80-year-old**s. Age and ageing. 2019:48(4):513-518.

III. Rydén L, Zettergren A, Seidu N M, Guo X, Kern S, Blennow K, Zetterberg H, Sacuiu S, Skoog I. **Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke.** Journal of Internal Medicine. 2019:286(1):101-110.

IV. Rydén L, Sacuiu S, Wetterberg H, Najar J, Guo X, Kern S, Zettergren A, Shams S, Pereira JB, Wahlund LO, Westman E, Skoog I. **Atrial fibrillation, stroke and silent cerebrovascular disease: A population-based MRI study.** Neurology. 2021;97(16):e1608-e1619.

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ABBREVIATIONS

Aβ	Amyloid beta
ADL	Activities of daily living
AF	Atrial fibrillation
APOE	Apolipoprotein E
BBB	Blood-brain barrier
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CMB	Cerebral microbleed
CT	Computed tomography
DALY	Disability-adjusted life year
DSM	Diagnostic and Statistical Manual of Mental Disorders
DOAC	Direct-acting oral anticoagulant
ECG	Electrocardiogram
H70	The Gothenburg H70 Birth Cohort Studies
HR	Hazard ratio
ICD	International Classification of Diseases
ICM	Implanted cardiac monitor
INR	International normalized ratio
K	Kappa

MRI	Magnetic resonance imaging
NPR	National patient register
NPV	Negative predictive value
OR	Odds ratio
PPSW	The Prospective Population Study of Women
PPV	Positive predictive value
RCT	Randomized controlled trial
SBI	Silent brain infarct
TIA	Transitory ischemic attack
TIV	Total intracranial volume
WMH	White matter hyperintensity

1 INTRODUCTION

1.1 ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is characterized by irregular and often fast heartbeats.[1] Symptoms of AF include palpitations, breathlessness, tiredness, chest pain, dizziness, and syncope but AF may also be present without symptoms and therefore remain undiagnosed.[1] The estimated number of individuals living with AF in the world were 59.7 million in year 2019, a doubling compared to 1990.[2] However, after age-standardizing the prevalence, there were no significant differences (0.78% in 1990 vs 0.74% in 2019), suggesting that the increase in absolute numbers mainly are due to an aging population and population growth.[2] Among European adults, the prevalence is estimated to 2% resulting in about 10 million individuals living with AF, a number that is expected to increase to 14-17 million in 2030.[3]

AF becomes more common with higher age, and is present in around 0.14% of individuals <49 years, 4% of individuals 60-70 years, and 10-17% of individuals >80 years.[3] AF is more common among men, with a male/female ratio of 1.2.[3] The highest burden of AF, measured by age-standardized disability-adjusted life years (DAILYs), is seen in high-income North America, Australasia, Central Asia, and Europe, while the lowest DAILYs due to AF are seen in high-income Asia Pacific region, Andean and Central Latin America, the Caribbean, Africa, and the Middle East,[2] see Figure 1.

AF is associated with adverse outcomes such as heart failure, stroke, mortality, and impaired quality of life, and has also been associated with cognitive decline and dementia.[1] AF causes a major burden on health systems, including both hospitalizations and outpatient visits. It has been estimated that AF on average leads to 0.25 hospitalizations and six outpatient visits per AF patient and year.[3] With the increasing number of individuals living with AF, this would mean 3.5-4 million hospitalizations and 100-120 million outpatient visits due to AF per year in Europe in year 2030.[3]

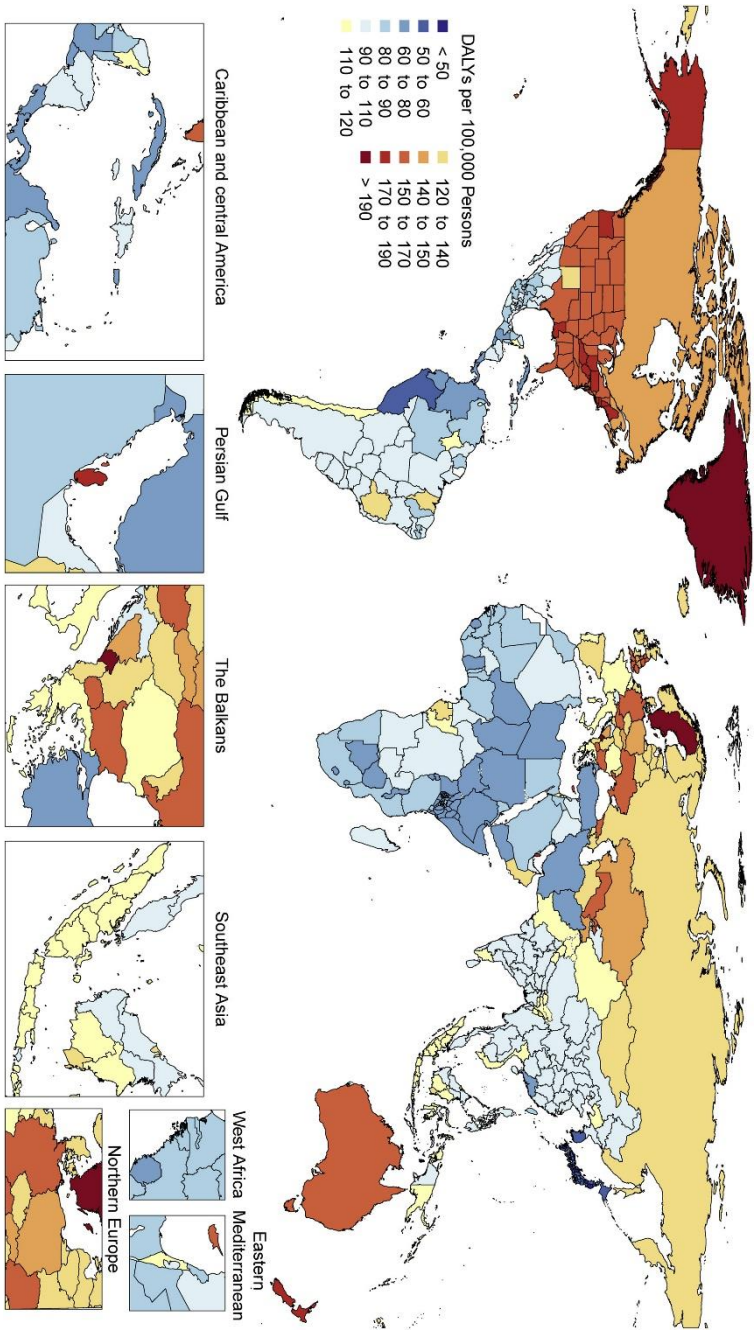

Figure 1. *Map of age-standardized DALYs due to atrial fibrillation and flutter in 2019. Global Burden of Cardiovascular Diseases and Risk Factors*[2] *© Roth at al. (Licensed under CC BY 4.0) https://creativecommons.org/licenses/by/4.0/*

1.1.1 PATHOPHYSIOLOGY

There are several pathophysiological mechanisms for AF, such as atrial structural and electrical remodeling, and changes in the autonomic nervous system.[4] Atrial remodeling can be induced by e.g. other cardiac diseases such as heart failure and myocardial infarction. Thereafter, the arrhythmia itself contributes to the same pathophysiological abnormalities increasing the risk that AF persist or re-occur.[4] When atrial remodeling occurs or the autonomic nerve activation is affected, there is a risk fort re-entry circuits or focal ectopic firing in the atrium, which in turn both induce and maintain AF,[5] see Figure 2.

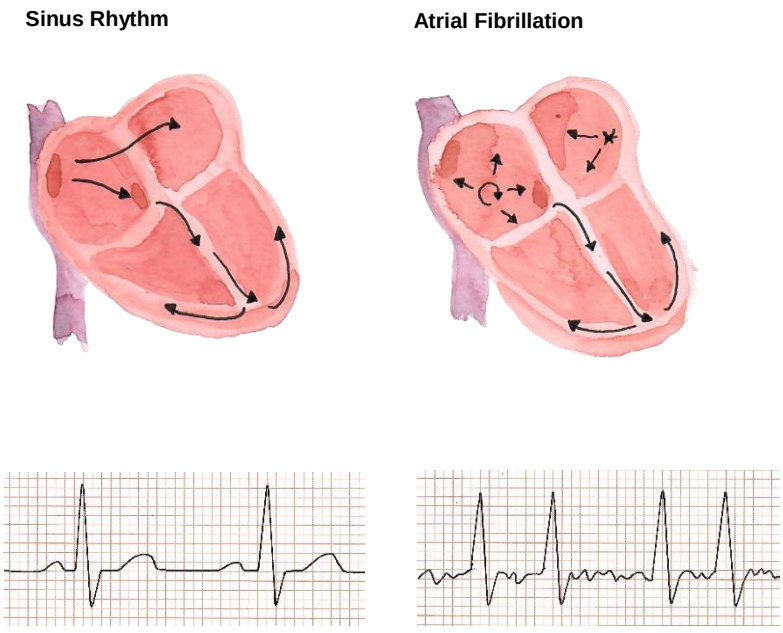

Figure 2. *Sinus rhythm origin from the sinus node with regular ventricular heart beats and atrial fibrillation with re-entry circuit and ectopic firing resulting in irregular ventricular heart beats.*

AF diagnoses are established with electrocardiograms (ECGs) where irregular heartbeats (R-R intervals), lack of distinct repeating p-waves and irregular atrial activation is pathognomonic,[1] see Figure 2.

Since AF may be paroxysmal it may not be detectable with a single ECG. It is therefore often a need for extended monitoring when AF is suspected or when a potential adverse outcome from AF, such as stroke or transient ischemic attack (TIA), has occurred. For example, the American Heart Association (AHA)/ American stroke association recommend long term rhythm monitoring with a mobile cardiac outpatient telemetry, implanted cardiac monitor (ICM), or other long term rhythm monitoring after a stroke or TIA, if no clear etiology has been established.[6]

AF may also be present without symptoms and therefore remain undiagnosed in individuals. There is an ongoing discussion on whether or not a more general screening for AF is beneficial. The European Society of Cardiology (ESC) recommend opportunistic screening (i.e. screening during regular health care visits[7]) for AF by pulse taking or ECG in individuals aged 65 years and older and to consider a systematic screening in individuals aged 75 years and older or those in high risk of stroke.[1] However, the AHA has no recommendations regarding AF screening and there are expert groups that recommend against AF screening due to the lack of evidence.[7]

1.1.2 MANAGEMENT OF AF

The main goals of AF treatment are to reduce AF symptoms through heart rhythm and rate control[8] and to prevent stroke through treatment with oral anticoagulants.[9]

Electrical or medical cardioversion are used to restore sinus rhythm and antiarrhythmic drugs, catheter ablation, or surgical ablation can be used to maintain sinus rhythm.[9] Antiarrhythmic drugs have been shown to double the number of patients who maintain sinus rhythm,[8] while catheter ablation, which aim to isolate the pulmonary veins, has been shown to reduce AF frequency with 70-80%.[10] It has also been found that catheter ablation and antiarrhythmic drugs may have a synergistic effect, where the use of antiarrhythmic drugs after a catheter ablation increased the proportion of patients who maintain sinus rhythm[8]. In smaller studies, catheter ablation has been shown to improve left ventricular function[8] and quality of life,[11] but more research is needed to establish whether rhythm control improves survival and reduce adverse outcomes such as stroke, acute coronary symptoms, and cognitive function in AF patients.[8]

If sinus rhythm cannot be restored, drugs regulating the ventricular heart rate can be used. This may also be the preferred treatment strategy over rhythm control and rate control is sometimes enough to improve AF-related symptoms.

There is however a lack of evidence regarding the optimal heart rate in AF patients treated with rate control.[1] In the Rate Control Efficacy in Permanent Atrial Fibrillation II randomized controlled trial (RCT) there were no differences in major cardiovascular events between those who were assigned to a less strict control strategy (to keep heart rate below 110) and those who were assigned to a strict control strategy (to keep heart rate below 80 at rest and 110 during moderate exercise).[1, 12]

To reduce thromboembolic complications for AF, anticoagulant treatment can be used based on the patients aggregated risk for thromboembolic events versus the risk for major bleeding complications. The CHA_2DS_2-VASc score[1] is one commonly used instrument to assess the future risk of thromboembolic events, see Table 1. According to the ESC guidelines from 2020,[1] individuals with low thrombo-embolic risk (CHA_2DS_2-VASc 0 in men and 0-1 in women) do not need anticoagulant treatment. The individual risk for bleeding complication can be estimated using for example the HAS-BLED-score,[1] see Table 1. A HAS-BLED-score of ≥ 3 points highlights individuals at risk of bleeding complications. Warfarin, which was approved for medical use in 1954, has been the established drug for anticoagulant treatment until recently, reducing ischemic stroke by 68% compared to placebo.[13] In 2009-2013, four RCTs on four direct-acting oral anticoagulants (DOACs), i.e. apixaban, dabigatran, edoxaban, and rivaroxaban, showed noninferior reduction in thromboembolic risk compared to warfarin.[14] In addition, DOACs have been shown to reduce bleeding risk, they are easier to administrate, and have fewer drug-to-drug interactions compared to warfarin[13, 14] and are now generally recommended as first line therapy in AF patients without moderate-to-severe mitral stenosis or a mechanical heart valve.[1, 14]

Table 1. The CHA_2DS_2-VASc and HAS-BLED scores

CHA_2DS_2-VASc score	**HAS-BLED score**
1 point	**1 point**
Congestive heart failure	Hypertension (>160 mmHg systolic)
Hypertension	Renal disease
Age 65-74	Liver disease
Diabetes mellitus	Stroke history
Vascular disease	Prior major bleeding or predisposition to bleeding
Female sex	Labile INR
	Age >65
2 points	Medication usage predisposing to bleeding
Age 75 or above	Alcohol use ≥8 drinks/week
Stroke/TIA/thromboembolism	

1.1.3 RISK FACTORS FOR AF

High age, male sex, white ethnicity, obesity, taller stature, hypertension, diabetes mellitus, obstructive sleep apnea, myocardial infarction, heart failure, smoking, and genetic predisposition are considered well known risk factors for AF.[15] In addition, the annual rates of increase in blood pressure, body weight, and fasting blood glucose has been found to increase AF risk.[16] A meta-analysis regarding the relation between alcohol consumption and AF found that high alcohol consumption was associated with increased risk of AF and that chronic moderate alcohol intake (1-2 standard drinks per day) was associated with a small increased risk of AF in men.[17] Low alcohol consumption (up to 6-7 standard drinks per week) was not associated with an increased risk of AF.[17] Regarding physical activity, moderate physical activity has been suggested to protect against AF, while excessive, especially high-volume endurance exercise increase the risk of AF.[15] For risk factors in AF, see Table 2.

AF share several risk factors, such as high age, smoking, hypertension, diabetes mellitus, and high BMI, with other cardiovascular diseases highlighting the possibility that these risk factors cause manifest cardiovascular diseases that in turn cause AF or vice versa.[18] Other risk factors for cardiovascular diseases (i.e., non-white ethnicity, shorter stature, higher total and LDL cholesterol, and higher diastolic blood pressure) have on the other hand been suggested to be associated with lower risk of developing AF.[18]

Table 2. Risk factors and protective factors for atrial fibrillation

Life-style and health related risk factors	**Biological risk factors**
Obesity	High age
Hypertension	Male sex
Smoking	White ethnicity
High alcohol consumption	Taller stature
Excessive physical activity	Genetic predisposition
Obstructive sleep apnea	
Myocardial infarction	**Protective factors**
Heart failure	Moderate physical activity

1.1.4 COMORBIDITIES AND CONSEQUENCES OF AF

Several conditions often co-occur with AF and the co-occurrence with other conditions is often associated with adverse prognosis and increased mortality.[15] Heart failure may both cause and be directly caused by AF.[15] In addition, AF and heart failure may co-occur due to shared risk factors. One study based on the Framingham heart study showed that 37% of those who developed AF already had a heart failure diagnosis and 57% of those who developed heart failure already had an AF diagnosis.[19] AF has also a bidirectional relationship with myocardial infarction and a study based on the Atherosclerosis Risk in Communities (ARIC) study showed that those with AF had a 63% increased risk of developing myocardial infarction.[20] One trial, screening patients for AF with ICM after an acute myocardial infarction, found that the highest risk of new-onset AF was during the first two month, where 16% developed AF.[21] After one year, 32% had developed AF.[21] Worth to notice is that the vast majority of the AF events were asymptomatic making it possible that AF episodes have occurred before the infarction. Other conditions that seem to have a bidirectional relationship with AF are chronic kidney disease and venous thromboembolism.[15] In addition, cancer often co-occur with AF although this area is not as well studied.[15] One possibility that new AF is more frequently discovered after a cancer diagnosis may be the extensive investigations that are conducted in newly detected cancer patients.[15]

Stroke is a feared consequence of AF and AF has been associated with a 4- to 5- fold increased risk of stroke.[22] However, a systematic review found a substantial variation in the annual stroke rate in AF patients, ranging from 0.5% to 9.3%.[23] The stroke risk was generally higher in patients with higher CHA_2DS_2-VASc score.[23] Strokes in AF patient are also associated with higher mortality and disability compared to strokes due to other causes.[24] Ischemic stroke has several different etiologies and has been classified as (1) large-artery atherosclerosis, (2) cardio embolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology (cryptogenic stroke) according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[25] The main mechanism behind the association between AF and stroke is thought to be cardiac embolism from thrombus formation, often located in the left atrium, especially in the left atrial appendage.[26] The formation of thrombus can be explained by the "Virchow´s triad", since AF has been associated to all the criteria, i.e. hypercoagulability, vessel wall abnormalities (e.g., endothelial injury and structural changes), and abnormal blood flow.[26] However, AF has also been associated to infarcts not typically caused by embolism such as lacunes, which is seen as a marker of

small vessel disease.[27] There is an ongoing debate whether the arrhythmia itself causes stroke or if aging and vascular risk factors contribute to an abnormal atrial substrate that in turn causes both AF and stroke.[28] In addition, there is a possibility that stroke may cause AF since brain injuries affect the autonomic nervous system and trigger a systemic inflammatory response, which both have a role in the pathogenesis of AF.[29]

Other adverse outcomes of AF include dementia, which will be described in detail below.

1.1.5 CHARACTERIZATION OF AF

There are several international consensus documents and AF guidelines addressing single domains, such as symptom severity (e.g the European Heart Rhythm association Symptom severity score),[30] the temporal pattern (e.g first diagnosed, paroxysmal, persistent, longstanding persistent, and permanent)[30], and stroke risk (e.g., CHA_2DS_2-VASc score). A new characterization scheme, the 4S-AF Scheme, has been proposed to better characterize AF and includes four areas, i.e. stroke risk, symptoms, severity of burden, and substrate.[31] In the 4S-AF scheme the severity of AF burden includes not only the temporal pattern of AF, but also the total AF burden which can be measured as for example total time in AF and number of episodes. Substrate considers comorbidities, cardiovascular risk factors, and atrial cardiomyopathy.

1.1.6 SOCIAL DETERMINANTS AND SEX DIFFERENCES IN AF

As mentioned before, AF is more common in men than in women. However, among individuals with AF, anticoagulants have been reported to be underused to a higher degree in women compared to men,[32] women are more often treated with rate control strategies and are less often treated with ablation.[33] In addition, women with AF also report worse health-related quality of life than men[34] and experience a higher risk for adverse outcomes such as increased risk of stroke and mortality.[33] Reasons for the higher age-standardized incidence and prevalence in men are not fully understood but factors such as taller stature and larger heart chambers in men may play a role.[33] On the other hand, women with AF have more atrial fibrosis, which could play a role for the higher risk of adverse outcomes seen in women.[33]

Part of the racial/ethnic differences seen in AF incidence and prevalence worldwide could be explained by different AF detection rates in different settings. However, detection rate and knowledge about the diagnosis cannot solely explain the higher incidence and prevalence seen in white individuals

compared to other races/ethnicities (such as Black, Hispanic, and American/Indian/Alaska Native individuals).[35] For example, the ARIC study found that the risk of developing AF during the 21-year follow-up (using ECG screening) was 1 in 3 in white Americans and 1 in 5 in black Americans.[36] The reason for this racial/ethnic difference in AF frequency is not fully understood and the fact that non-white individuals have higher prevalence of AF risk factors makes this a paradox.[35] Explanations include excess premature death rates in non-white individuals[35] and genetic factors.[37] It has for example been shown that a larger proportion of European ancestry increases the risk of AF in black individuals.[37] However, even though AF is less prevalent in black individuals, management and outcomes have been shown to be in favor of white individuals. For example, white individuals with AF are more often treated with adequate anticoagulant treatment and have a lower risk of stroke and mortality.[35]

Low income, lower education level, and unemployment have all been associated with higher AF incidence.[35] In addition, anticoagulant treatment for AF is under-prescribed in low-income countries and lower socio-economic status has been shown to decrease the likelihood of receiving DOACs compared to warfarin.[35] In addition, adverse outcomes such as mortality, stroke, hospitalization for heart failure, and myocardial infarctions have been reported to be more common in individuals with lower income.[35] Other important factors that need to be further examined in relation to AF are rurality versus urbanity and health literacy, since AF require awareness for both detection and management in order to prevent adverse outcomes.

1.2 COGNITIVE IMPAIRMENT AND DEMENTIA

Dementia is the most severe form of cognitive impairment and consists of loss of cognitive abilities from the prior cognitive function which results in impaired function in activities of daily living (ADL). This cognitive disease affected approximately 47 million individuals worldwide in 2015, a number that is expecting to double every 20 years.[38] Dementia prevalence increases with higher age and affect 24-33% of 85-year-olds and older in the Western world.[39] The most common form is Alzheimer´s dementia, accounting for about 50-60% of all dementia cases.[40] Other forms of dementia include vascular dementia, Lewy body dementia, and frontotemporal dementia.[41] There are also other diseases or conditions that are linked to the development of dementia such as Creutzfeldt-Jakob disease, Parkinson´s disease, Huntington´s disease, alcohol-related encephalopathy, and traumatic brain injury.[42] In addition, there are conditions, sometimes reversible, that cause dementia-like symptoms, for example infections, metabolic disorders, nutritional deficiencies, subdural hematomas, brain tumors, and normal pressure hydrocephalus.[42]

1.2.1 DIAGNOSTIC CRITERIA FOR DEMENTIA

There are two main diagnostic systems for classifying dementia, i.e. the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). The ICD system is used when coding diagnoses within the health system, for example hospital discharge diagnoses, while the DSM system, which has the ability to better capture mild dementia cases, is widely used in research.[43]

The DSM III-R criteria,[44] published in 1987, is widely used in research. For diagnostic criteria see Table 3. Later versions of the DSM-system include e.g. DSM-IV, published in 1994[45] and DSM-V, published in 2013.[46] In research, Alzheimer´s dementia is often classified according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[47] see Table 3. Vascular dementia is often classified according to the National Institute for Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria,[48] see Table 3.

Table 3. Diagnostic criteria for Dementia according to the DSM-III-R, and diagnostic criteria for Alzheimer´s dementia and vascular dementia

Dementia according to the DSM-III-R

A. Impairment in short- and long-term memory
B. Impairment in abstract thinking or judgement or other disturbances of higher cortical functions or personality change
C. Evidence that the cognitive disturbance resulting from criteria (A) and (B) significantly interferes with work or usual social activities or relationship with others
D. Not occurring exclusively during the course of delirium
E. Either evidence of a specific organic factor judged to be etiologically related to the disturbance, or in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder

Alzheimer´s dementia (NINCDS-ADRA criteria)

Probable Alzheimer´s dementia

A. An established dementia diagnosis
B. Deficits in two or more areas of cognition
C. Progressive worsening of memory and other cognitive functions
D. No disturbance of consciousness
E. Onset between ages 40 and 90, most often after age 65
F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

Possible Alzheimer´s dementia

May be made in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variation in onset, in the presentation, or in the clinical course. May also be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.

Vascular dementia (NINDS-AIREN criteria)

Probable vascular dementia

A. An established dementia diagnoses.
B. Cerebrovascular disease (focal neurological signs on examination consistent with stroke (with or without history of stroke) and evidence of relevant cerebrovascular disease by brain imaging)
C. A relationship between A and B, manifest by one or more of: (1) onset of dementia within 3 months following a recognized stroke, (2) abrupt deterioration in cognitive functions or a fluctuating stepwise progression of cognitive deficits

Possible vascular dementia

May be made when brain imaging to confirm definite cerebrovascular disease are missing, in the absence of clear temporal relationship between dementia and stroke, or inpatients with subtle onset and variable course of cognitive deficits and evidence of relevant cerebrovascular disease.

1.2.2 RISK FACTORS FOR DEMENTIA

The Lancet commission has identified 12 modifiable risk factors for dementia, i.e. low education level, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes mellitus, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution.[49] Other risk factors for dementia include high age, the Apolipoprotein E (*APOE*) ε4 allele, diabetes mellitus, cardiovascular disease, and sleep disturbance.[50]

1.2.3 ALZHEIMER'S DEMENTIA

Alzheimer's dementia is the most common dementia type and typical clinical symptoms include impairment in episodic memory and orientation, aphasia, apraxia, agnosia, affected judgment, and decision-making.[40] Alzheimer's dementia is often slowly progressive and can be classified as late (>65 years) or early onset (<65 years).[51] Late onset Alzheimer´s dementia is the most common form that constitute 90-99% of the cases and most cases of late onset Alzheimer´s dementia are sporadic (60%), while the rest (40%) have a positive family history of Alzheimer´s dementia.[51] Alzheimer´s dementia is a neurodegenerative disease with pathological features of senile plaques, neurofibrillary tangles, and degeneration of neurons and synapses in the brain.[40] Several pathogenic mechanisms have been suggested for Alzheimer´s dementia, e.g. amyloid beta (Aβ) aggregation and deposition, tau hyperphosphorylation, neurovascular dysfunction, abnormality in the proteins regulating the cell cycle, inflammatory processes, oxidative stress, and mitochondrial dysfunction affecting the neuronal energy metabolism.[40] The foremost hypothesis for Alzheimer´s dementia is the amyloid cascade hypothesis,[40] where an imbalance between Aβ production and clearance result in Aβ accumulation and the formation of oligomers affecting neuronal and synaptic functions in the brain. Aβ gradually deposits into plaques that activate brain microglia and astrocytes, resulting in an inflammatory response. In addition to the Aβ cascade, tau, an axonal protein, becomes hyperphosphorylated due to an unbalance in kinases and phosphatases.[40] Tau hyperphosphorylation leads to impaired axonal transport which affects synaptic and neuronal function in the brain.[40] The neurovascular hypothesis, on the other hand, suggests that there is an impairment in the delivery of nutrients to brain neurons due to dysfunctional blood vessels and that the blood vessel dysfunction also reduces Aβ clearance.[40] In younger patients with Alzheimer´s dementia, dementia severity corresponds well to the plaque and tangle burden, whereas this is not the case among older patients with Alzheimer´s dementia, indicating that it may not be a homogeneous disease.[52]

1.2.4 VASCULAR DEMENTIA

Vascular dementia is related to vascular injury in the brain and it can be due to both large vessel disease, i.e. large infarcts and haemorrhages, and small vessel disease, for example lacunes and white matter hyperintensities (WMHs).[53] There are also rare familial forms of vascular dementia, such as the cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[54]

Vascular dementia constitute 15-20% of the dementia cases in Europe and North America.[55] However, the number of cases classified as vascular dementia depend on the diagnostic criteria used.

The clinical characteristics of vascular dementia are somewhat different from Alzheimer´s dementia. In Alzheimer´s dementia, the neurodegeneration is expected to continue and hence the symptoms are expected to increase over time. In vascular dementia caused by stroke, the neuropsychological symptoms are often worst during the acute phase and may thereafter improve over time and then stabilize until a new event occurs. There are also differences in symptoms, where vascular dementia has a greater variety since the symptoms highly depend on the location of the lesions.[54] Common symptoms include impairment in executive function, attention, and information processing.[54] In addition, symptoms such as depression and apathy are common in vascular dementia.[54]

1.2.5 MIXED ALZHEIMER'S AND VASCULAR DEMENTIA

Several risk factors for vascular dementia, such as old age, hypertension, AF, carotid or aortic atherosclerosis, coronary artery disease, ventricular dysfunction, diabetes mellitus, high cholesterol, smoking, and the *APOE* ε4 allele, are also known or suggested risk factors for Alzheimer´s disease.[56] In addition, patients with Alzheimer´s dementia often have cerebrovascular pathology, including cerebral infarcts, microinfarcts, and WMHs.[56] Whether cerebrovascular pathology in patients with Alzheimer´s dementia only co-exist due to shared risk factors or is contributing to the pathogenesis of Alzheimer´s dementia is not elucidated.[56] However, studies have shown that cerebrovascular ischemic pathology upregulates the expression of the amyloid precursor protein (APP) leading to Aβ deposition.[40] The coexistence of Alzheimer´s disease and vascular pathology may also cause dementia in cases where only one pathology would not be enough to disturb the cognitive function to the level that allows for a dementia diagnosis to be made.[40, 56]

1.3 AF AND THE RISK OF COGNITIVE IMPAIRMENT AND DEMENTIA

Awareness about cardiac causes of cognitive impairment leading to vascular dementia became evident in the 1970s and was referred to as cardiogenic dementia.[57] In the 1990s, researches suggested that cardiovascular diseases and risk factors could also trigger Alzheimer´s disease.[57] Today, several cardiac diseases, such as heart failure, coronary artery disease, AF, and valvular disease have been suggested to contribute to cognitive impairment and dementia.[57]

In 1997, Ott and colleagues found an association between AF and dementia in the absence of stroke in a cross-sectional study based on the Rotterdam study.[58] Since then, several studies have confirmed these results in longitudinal studies,[59-68] while others have not found an association.[69-72] Although many studies have adjusted for stroke at baseline or excluded participants with stroke history at baseline, until recently, only a few studies took incidence stroke into account.[60-63, 67, 73] A meta-analysis from 2019, only including studies taking incident stroke into account, reported a nearly 30% increased risk of dementia in participants with AF.[74]

There are some longitudinal studies that, in addition to all cause dementia, have found an association between AF and vascular dementia[73] and Alzheimer´s dementia[63, 73] irrespective of symptomatic stroke. However, a study based on the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), found no association between AF and Alzheimer´s dementia.[62]

1.3.1 SOCIAL DETERMINANTS AND SEX DIFFERENCES REGARDING THE ASSOCIATION BETWEEN AF AND DEMENTIA

Little is known about sex, racial/ethnic, and socio-economic differences in the relation between AF and dementia risk. Given the differences in AF prevalence and stroke risk between different groups, it is plausible that these factors also interact with AF in relation to dementia.

Results regarding sex difference in the relation between AF and dementia have been mixed. A study based on SNAC-K found an association between AF and dementia among women only,[62] while a study based on the ARIC study found that the increased risk of dementia was similar between sexes.[60] The ARIC study also reported on racial differences regarding the relation between AF and dementia and found no difference between black and white participants.[60]

1.3.2 MECHANISMS

The mechanisms behind the association between AF and dementia are not elucidated. As described above, AF and dementia share risk factors, such as high age, diabetes mellitus, hypertension, coronary artery disease, and heart failure.[75] Other possible explanations in the absence of symptomatic stroke include silent brain infarcts (SBIs; i.e. infarcts visible on brain imaging but with no corresponding neurological symptoms) altered cerebral blood flow, and inflammation,[75] see Figure 3.

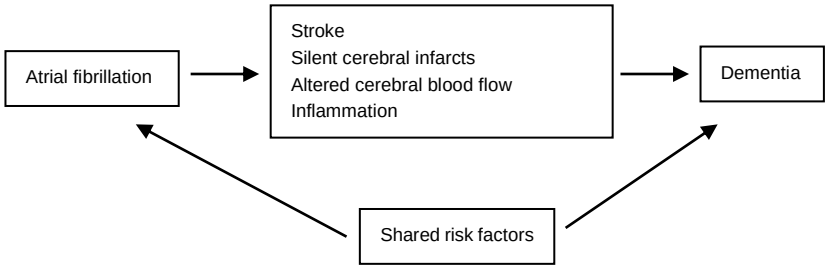

Figure 3. *Mechanisms behind the relation between atrial fibrillation and dementia*

Stroke

AF has been associated with an increased risk of stroke,[76] that in turn is associated with dementia.[77] Even though studies regarding the association between AF and dementia have shown an association in the absence of symptomatic stroke,[74] few longitudinal studies have examined if the association can be explained by SBIs. A study based on the ARIC study found that incident AF in participants free from symptomatic stroke was associated to a greater cognitive decline.[78] However, the association between AF and cognitive decline was only seen in participants with prevalent or incident SBIs, suggesting that the association between AF and cognitive decline was mediated by SBIs. In contrast, a cross-sectional case-control study found that AF was associated with lower function in learning and memory, and attention and executive function in a sample free from symptomatic stroke and SBIs.[79]

Altered cerebral blood flow

The brain consumes around 20% of the available oxygen in the blood and has high metabolic requirements which places demands on the cerebral blood flow.[80]

It has been found that individuals who were fibrillating at the time of the examination had reduced total cerebral blood flow compared to those in sinus rhythm, irrespective of AF history, suggesting that the arrhythmia itself causes reduced cerebral blood flow.[81] This may be due to reduced cardiac output in AF patients since the ventricles are not filled properly due to the absence of normal atrial contractions.[57] In addition, rapid heart rate may also impair ventricle filling and it has been reported that heart rhythm regulation in AF patients with heart failure improve cardiac output.[82]

Under normal conditions, cerebral blood flow is hold constant through regulatory mechanisms.[83] Regulatory mechanisms may be affected by traumatic brain injury, stroke, and Alzheimer´s disease.[84] However, AF has also the potential to affect regulatory mechanisms thorough autonomic disturbances,[85] endothelial damage/dysfunction, and lower bioavailability of endothelial vasodilators.[83, 86]

One computational study, modelling cerebral blood flow during sinus rhythm vs AF found that cerebral blood pressures were slightly reduced during AF.[87] However, mean flow rates were similar during sinus rhythm and AF indicating that when the regulatory systems are working normally, the reduced cerebral blood pressure will be compensated.[87] The main difference between sinus rhythm and AF was the variability in cerebral hemodynamic parameters, where the variability was largest in the distal circulation. AF caused both hyperperfused episodes (mainly in arterioles) and hypertensive events (mainly in capillaries), that in turn might damage the deep white matter.[87]

It has been shown that low cardiac output or hypotension that leads to cerebral hypoperfusion affects memory and attention, and may lead to Alzheimer´s dementia.[57] Cerebral hypoperfusion may cause hypoxia, which can affect the blood-brain barrier (BBB) permeability causing impaired Aβ clearance.[88] In addition, brain hypoperfusion can lead to local acidosis that can alter tau protein functioning causing hyperphosphorylation and formation of tau oligomers.[88]

Inflammation

Both AF and Alzheimer´s disease have been associated with several inflammatory markers and inflammation has been suggested to be both a cause of AF and Alzheimer´s disease and a consequence from the diseases.[88]

Risk factors for arrythmia, such as coronary artery disease, hypertension, obesity, myocardial lesions, and valvular disease can trigger inflammation that can cause cardiac structural and electrical remodeling leading to AF.[88] However, AF also seem to trigger an inflammatory response. It has for example been shown that patient who maintained sinus rhythm after cardioversion or ablation had a gradual decrease in CRP levels, while CRP levels in patients with recurrent AF did not change.[89]

Brain abnormalities as a trigger for AF

Although there are plausible explanations why AF cause dementia, the opposite direction of the relationship is possible. It has for example been shown that that patients with Alzheimer´s dementia have higher Aβ40 and Aβ42 levels in the myocardium compared to age-matched controls, which affect the cell function in the heart.[90] In addition, as mentioned before, there is a possibility that stroke may cause AF since brain injuries may affect the autonomic nervous system and trigger a systemic inflammatory response.[29] For example, infarcts in the insular cortex that is involved in the regulation of cardiac rhythm have been associated with several cardiac arrhythmias, including AF.[91]

1.3.3 AF AND MARKERS OF SMALL VESSEL DISEASE

Markers of small vessel disease (see Figure 4) on brain magnetic resonance imaging (MRI) include recent small subcortical infarcts, lacunes, WMHs, and cerebral microbleeds (CMBs), but also atrophy, perivascular spaces, intracerebral hemorrhages, and superficial cortical siderosis.[27] Markers of small vessel disease that are analyzed in this thesis are described below. The definitions are according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) published in 2013.[27]

Recent small subcortical infarcts

Recent small subcortical infarcts are often called lacunar infarcts and are defined as an infarction that occurred within the previous few weeks in the territory of a perforating arteriole.[27] In the acute phase it can be up to 20 mm on axial sections.[27] Recent small cortical infarcts often turn into lacunes or

WMHs on brain MRI, but MRI images may also be normal or nearly normal in the chronic phase.[27]

Lacunes of presumed vascular origin

Lacunes are round or ovoid fluid-filled cavities (3-15 mm) located in the subcortex.[27] They are often the chronic presentation after a small subcortical infarct but may also be due to small deep haemorrhages.[27] Lacunes are common in older adults and have been associated with increased risk of stroke, gait impairment, and dementia.[27] One study, based on the Rotterdam study, found that most (>90%) SBIs were lacunes.[92, 93] However, not all lacunes are silent and in the Rotterdam study more than half of all symptomatic infarcts were lacunes.[93] High age and hypertension are the most widely accepted risk factors for SBIs.[92] However, in a meta-analysis from 2014, AF was associated with a 2-fold increase in the odds of SBIs.[94] In contrast, a recent longitudinal study from SNAC-K, found no association between AF and annual changes in number of lacunes.[95]

White matter hyperintensities

Many different terms have been used and are still used for WMHs such as leukoaraiosis, white matter lesions, and white matter changes.[27] The term WMHs refers to the hyperperintensities seen on T2-weighted images (e.g., fluid-attenuated inversion recovery (FLAIR) images). The lesions can be of variable size and should be without cavitation.[27] The pathogenesis for WMHs is not fully understood, but plausible mechanisms include brain hypoperfusion, neuroinflammation, and thromboembolism.[96] WMHs have been found to increase the risk of both stroke, dementia, and mortality,[96] as well as depression, gait disturbance, and urinary symptoms.[97] Results on the association between AF and WMHs have been disparate. One study found that AF was associated to WMHs in the deep and subcortical but not in the periventricular white matter,[98] while another study found that AF was associated with WMHs in the periventricular white matter but not in the subcortex[99]. Studies from the Mayo clinic study of aging,[100] the ARIC study,[101, 102] and the Framingham offspring study[103] did not found an independent association between AF and global WMH volumes.

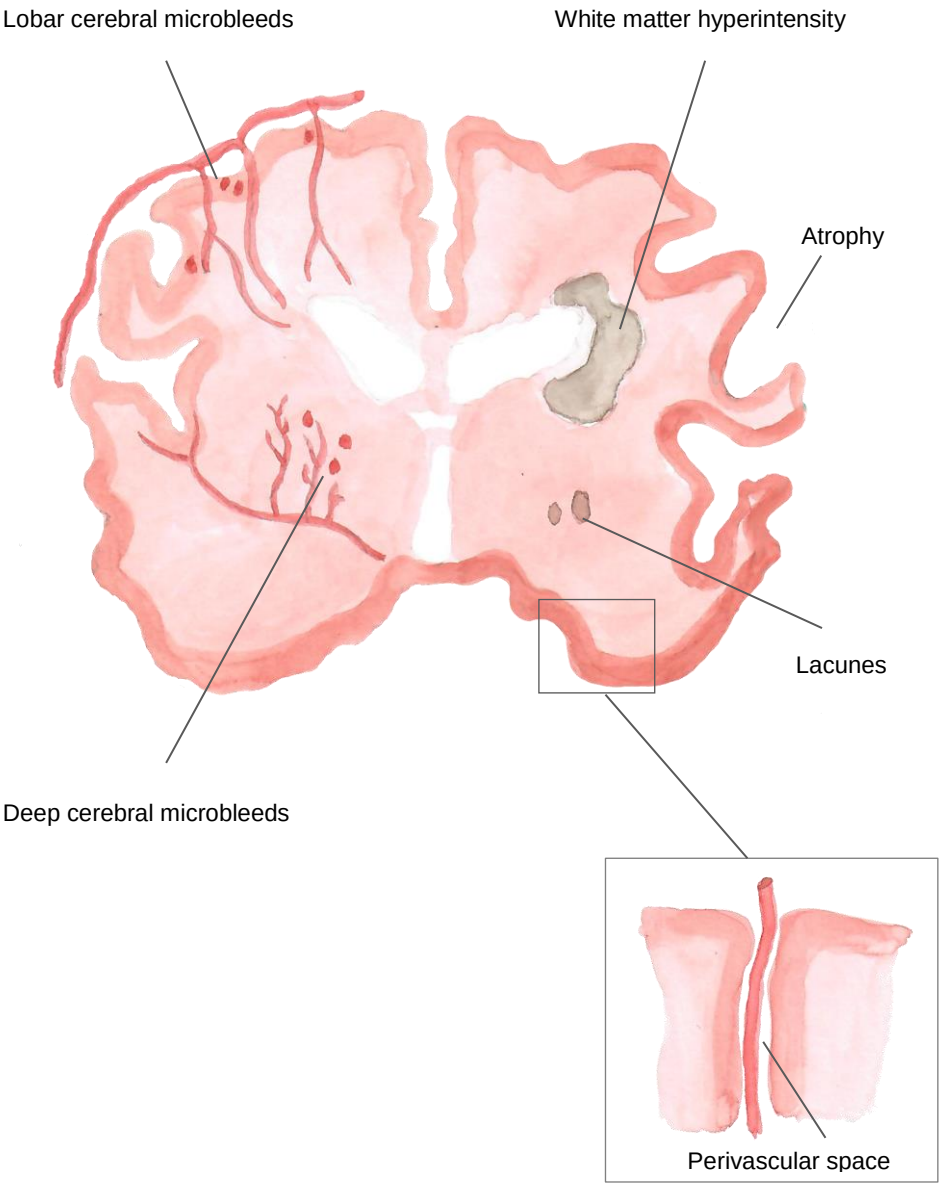

Figure 4. *Small vessel disease*

Cerebral microbleeds

CMBs are small (often 2-5 mm, but sometimes up to 10 mm) lesions that can be seen on T2*-weighted Gradient-Recalled Echo (GRE) or Susceptibility-Weighted (SWI) MR sequences.[27] They consist of focal hemosiderin deposit from minor bleedings.[104] CMBs have been associated with an increased risk of ischemic stroke and intracranial hemorrhage.[105, 106] CMBs located in the deep subcortical or infratentorial areas have been associated to hypertension and vascular risk factors whereas lobar CMBs have been associated to cerebral amyloid angiopathy (CAA).[107] Few studies have reported on the association between AF and CMBs.[108] One cross-sectional case-control study from Japan found that CMBs were more often present in AF patients compared to controls (patients without AF who underwent brain MRI for investigation of any neurologic disorder except symptomatic stroke).[109] However, these were unadjusted analyses and the groups differed regarding sex, cardio vascular risk factors, and anticoagulant treatment.[109] In a meta-analysis from 2019, anticoagulant treatment was associated to prevalent and incident CMBs.[110] When studying the distribution of CMBs, anticoagulants were associated with strictly lobar CMBs only and not with deep/infratentorial.[110]

1.4 ATRIAL FLUTTER

Atrial flutter (AFL) is also a cardiac arrhythmia originating from the cardiac atria. AF and AFL are often combined into one entity in epidemiologic studies.[111] Reasons for combining the two arrhythmias include that AFL is far less common than AF, these arrhythmias can be misclassified by physicians,[111] hospital discharge diagnoses have diagnostic codes including both diagnoses making it impossible to separate AF from AFL,[112] and that AF often develops in AFL patients.[111] The Framingham Heart study found that individuals with AFL had a 5-fold increased risk of developing AF compared to controls. In addition, AF and AFL share several risk factors and both have increased risk of myocardial infarction, heart failure, and stroke.[111] However, differences in outcomes between AF and AFL have been found. For example, one recent register-based study from Taiwan found that patients with AF had an increased risk of ischemic stroke compared those with AFL. In addition, among patients without stroke, patients with AF had higher risk of developing dementia.[113]

1.5 EPIDEMIOLOGICAL STUDIES

Epidemiological studies are used to form policy decisions and to contribute to evidence-based medicine. Epidemiological studies have been defined in many different ways. One example is the definition by Miquel Porta who defined epidemiological studies in "a dictionary of epidemiology"[114] as:

> *"The study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control health problems."*

Hippocrates is described as the first epidemiologist. He started to use a rational perspective of diseases rather than a supernatural and noted that different diseases were present in different areas, for example that malaria and yellow fever often were found in areas that were permanently saturated with water.[115] There are several other known scientists using epidemiological methods before the 20th century, like James Lind (1716-1794) who identified scurvy symptoms and found that lemon and oranges were associated to recovery and John Snow (1813-1858) who studied cholera outbreaks and compared death rates for individuals with different water suppliers.[115] However, in the second half of the 20th century, more systematic principals regarding epidemiological methods, such as how to design and evaluate epidemiological studies, took form.[116]

1.5.1 STUDY DESIGN

Different study design is suitable for different research questions. Descriptive studies describe frequencies and patterns of diseases or health factors. This can be used for statistical purposes and to generate hypotheses. However, to test a hypothesis, analytical epidemiology with the inclusion of a comparison group is essential. Analytical studies can be both experimental, where individuals or communities are exposed in a controlled manner and followed over time, and observational, where researchers observe individuals or communities without interfering.[117, 118] Common study designs for observational studies are case-control, cohort, and cross-sectional studies,[117] see Table 4.

Table 4. Common study designs in epidemiological research

Case-control studies
Case-control studies are retrospective where the cases and a suitable control-group are identified first. Thereafter, information about exposures or risk factors are measured. Case-control studies are for example good when examining rare outcomes.

Cohort studies
In cohort studies, individuals in a defined population who are at risk of the outcome are first identified as exposed or unexposed and thereafter followed until the outcome occur, the participant drop out, or the study ends. Since the exposure is identified before the outcome it is possible to draw conclusions regarding causality.

Cross-sectional studies
In a cross-sectional study, information on both the exposure and the outcome is measured at the same time.

1.5.2 VALIDITY AND PRECISION

To be able to interpret and generalize results from epidemiological studies, the whole research process needs to be considered, from study design and execution to how to carry out analyses. It has been described that "the objective of an epidemiologic study is to obtain a **valid** and **precise** estimate of the frequency of a disease or of the effect of an exposure on the occurrence of a disease in the source population of the study".[116] Validity refers to whether a measurement represent the true value, while precision refers to whether a measure can be reproduced under the same conditions[116], se Figure 5.

Precise but not valid | Not precise and not valid | Valid and precise

Figure 5. *The "Bull´s eye", validity and precision*

1.5.3 BIASES

Errors that occur in research can either be systematic or random, where systematic errors have the highest risk to affect study validity and are often referred to as biases. Two forms of biases are information bias and selection bias.[116]

Information bias are errors in the measurement.[116] For categorical variables, these biases are often called misclassification.[116] For binary variables, such as the presence or absence of a disease, the magnitude of the misclassification can be expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV),[116] see Table 5. Misclassification is differential if for example individuals with the exposure of interest have gone through a more extensive examination and therefore have a higher detection rate of the outcome than the unexposed.[116] One other type of differential misclassification is called recall bias,[116] i.e. that the individuals that have the outcome of interest more often remember or report being exposed than those without the outcome. Nondifferential misclassification means that there is no difference in misclassification between different groups, i.e. that the sensitivity and specificity of an exposure is equal in individuals with and without the outcome.[116] For binary outcomes this often result in an underestimation of an effect.[116] However, there are special circumstances where the effect may be enhanced or even reversed.[116] Worth to mention is that misclassification is also important when it comes to confounders, since misclassification of confounders limit the possibility to fully adjust for the confounding factor.[116]

Table 5. Definition of sensitivity, specificity, positive predictive value, and negative predictive value

Sensitivity The probability that individuals are classified as having a disease in the study when the disease is present
Specificity The probability that individuals are classified as not having a disease in the study when no disease is present
Positive Predictive Value The probability that individuals truly have a disease if classified as having a disease in the study
Negative Predictive Value The probability that individuals truly do not have a disease if classified as not having a disease in the study

Selection bias occurs when there are differences among those who participate and those who do not participate in the study.[116] This could be due to self-selection[116] if for example participants volunteer to participate and to stay in a study or not. Self-selection can also occur before study start. One example is the healthy-worker effect,[116] where individuals in good physical health are able to work in physical demanding jobs, whereas those with poor physical health choose other jobs or are not able to work at all. This will bias studies investigating for example the relation between different jobs and mortality.

1.5.4 GENERALIZABILITY

In addition to reach valid study results, it is important to be able to generalize results to other populations. This is often referred to as external validity.[116] One key question is whether different populations or societies possess different characteristics that affect the frequencies of disorders or associations between an exposure and an outcome or if there are biological similarities that make the results possible to generalize despite differences between populations.[116]

2 AIM

Studies have shown that AF is associated to incident dementia and cognitive decline in the absence of symptomatic stroke. However, longitudinal population-based studies taking symptomatic stroke into account during follow-up have been scarce. In addition, the mechanisms behind the association between AF and dementia are not elucidated.

This thesis aims to investigate if AF increases the risk of incident dementia after excluding participants with a history of symptomatic stroke at baseline and incident stroke during follow-up (paper III in this thesis). Further, it aims to investigate if AF is associated to SBIs and small vessel disease on brain MRI (paper IV).

Epidemiological studies are often affected by selection bias. Therefore, in paper I, we aimed to describe the longitudinal sample of the 1930-cohort of the Gothenburg H70 Birth Cohort (H70) Studies (used in paper III) and to examine if different types of attrition were associated with certain participant characteristics. This is important in order to both evaluate and to be able to generalize the results.

In addition, epidemiological studies are highly dependent on the information sources. Many studies depend solely on medical registers, while other include self- or proxy-reports in combination with physical examinations and biomarkers. For the study on AF and incident dementia (paper III) we had access to proxy-reports, the national patient register (NPR), and ECGs to diagnose AF, but not self-reports. Therefore, in paper II, we aimed to investigate the agreement between different sources of information (self-report, proxy-report, and the NPR) for AF, and other cardiovascular diagnoses and diabetes mellitus.

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3 PARTICIPANTS AND METHODS

3.1 PARTICIPANTS

Data were derived from the H70-studies and the Prospective study of women (PPSW) in Gothenburg, Sweden. The H70-studies are multidisciplinary longitudinal studies of residents aged 70 years and older in Gothenburg. The first 70-year-olds were examined in 1971 and since then, five additional cohorts with baseline at age 70 years have been examined. The present study includes two of the H70 cohorts, those born 1930 and 1944. Paper I, II, and III are using samples from the 1930-cohort and paper IV is based on the 1944-cohort. All samples are systematically selected based on birth date in order to yield representative samples of older adults in Gothenburg. Exclusion criteria were death or emigration before study start, inability to speak Swedish, and contact failure. The sampled individuals were first contacted by mail, including information about the studies and a consent form. Thereafter, the invited individuals were contacted by telephone and asked about participation. Examinations were conducted at an outpatient clinic or in the participants home if the participant did not have the possibility to come to the outpatient clinic.

In 2000, the H70 studies were merged with the PPSW. Women in the PPSW study were first examined in 1968-69 and followed up in 1974-75, 1980-81, and 1992-94, before the study was merged with the H70-study.

Participants in both the H70 and the PPSW studies were residents in Gothenburg at the time of inclusion. At follow-up, all previous participants were invited even though they had moved out of Gothenburg. Paper II and III include all individuals examined the specific year and therefore, also individuals who lived outside of Gothenburg at the time of the examination were included.

3.1.1 THE 1930-COHORT

The longitudinal sample of the 1930-cohort is described in detail in paper I. The 1930-cohort was first examined at age 70 in year 2000-02, and followed up at age 75 (in year 2005-07), age 79 (in year 2009-11), age 85 (in 2015-16), and age 88 (in year 2018-19).

In paper I, the samples with baseline in 2000-02 and 2005-07 were used, see figure 6. In 2000-02 a total of 524 individuals participated (response rate 70%). In 2005-07 the sample was extended in order to yield a larger sample. Therefore, in 2005-07, a total of 767 individuals participated (response rate 64%).

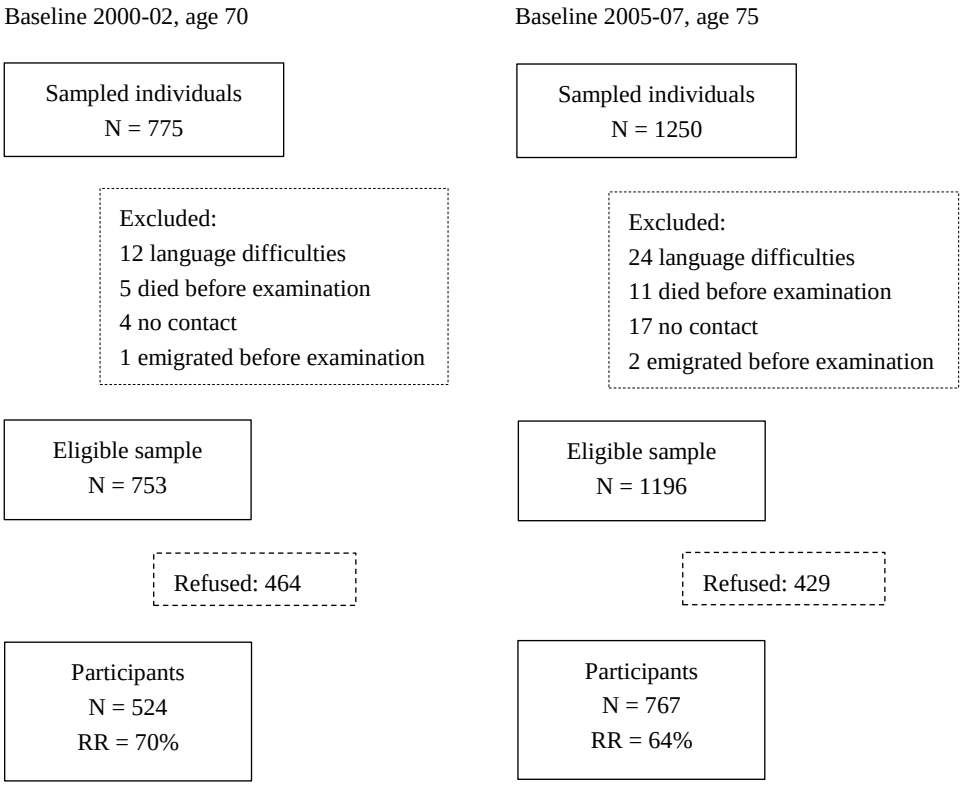


Figure 6. *Flow chart paper I, baseline in 2000-02 and 2005-07*

In paper II, individuals who participated in 2009-11 in the H70-study or the PPSW study were included, see Figure 7. In total, 662 individuals participated (response rate 62%). Of these, 475 (72%) had data from both self- and proxy-reports. Individuals with dementia (n = 42) and those whose self-reports included additional information from medical records, relatives or other sources (n = 14) were excluded, leaving 419 participants.

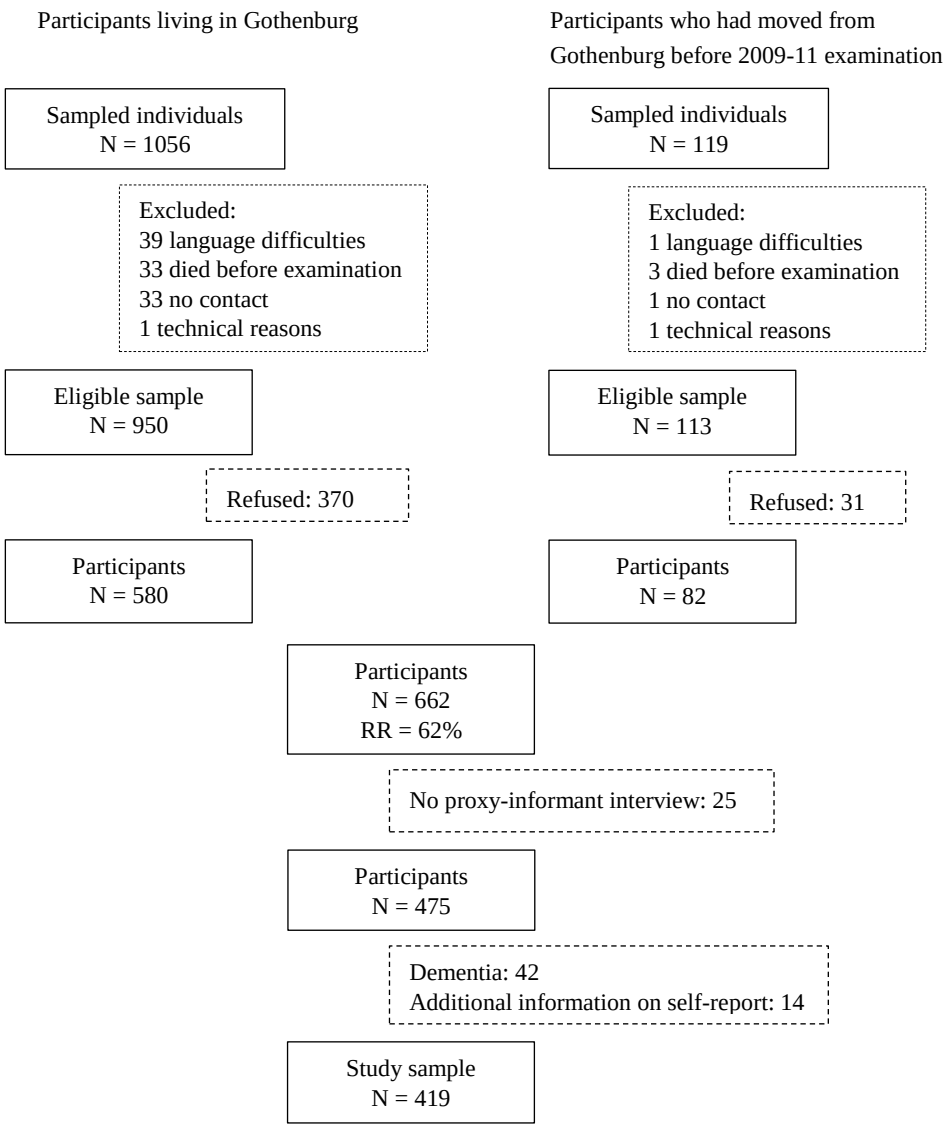


Figure 7. *Flow chart paper II, examination in 2009-11*

In paper III, individuals who participated in 2000-02 in the H70-study or the PPSW study were included, see Figure 8. A total number of 604 individuals participated (response rate 71%) and 579 individuals took part in the psychiatric examination. All individuals with dementia at baseline (n = 16), or missing information on AF (n = 2) were excluded, leaving 561 individuals for analyses. Of the 561 individuals examined at age 70, 433 individuals participated at the follow-up examination at age 75 (response rate amongst survivors: 80%) and 364 individuals participated at the follow-up examination at age 79 (response rate amongst survivors: 77%).

3.1.2 THE 1944-COHORT

The 1944-cohort was first examined at age 70 in 2014-16 and the first follow-up examination at age 75 was started in 2020 and is still ongoing. An extensive description of the sample and examination is found in Rydberg Sterner and Ahlner et al.[119]

In paper IV, individuals participating in 2014-16 in the H70-study were included, see Figure 9. A total number of 1203 individuals participated (response rate 72%) and 791 individuals took part in the brain MRI examination. All individuals with multiple sclerosis, normal pressure hydrocephalus, Parkinson disease, or valvular disease (n = 15) were excluded, leaving 776 individuals for analyses of stroke/infarcts and CMBs. A total of 13 individuals had invalid automated WMH segmentation, leaving 763 individuals for analyses of WMH volumes.

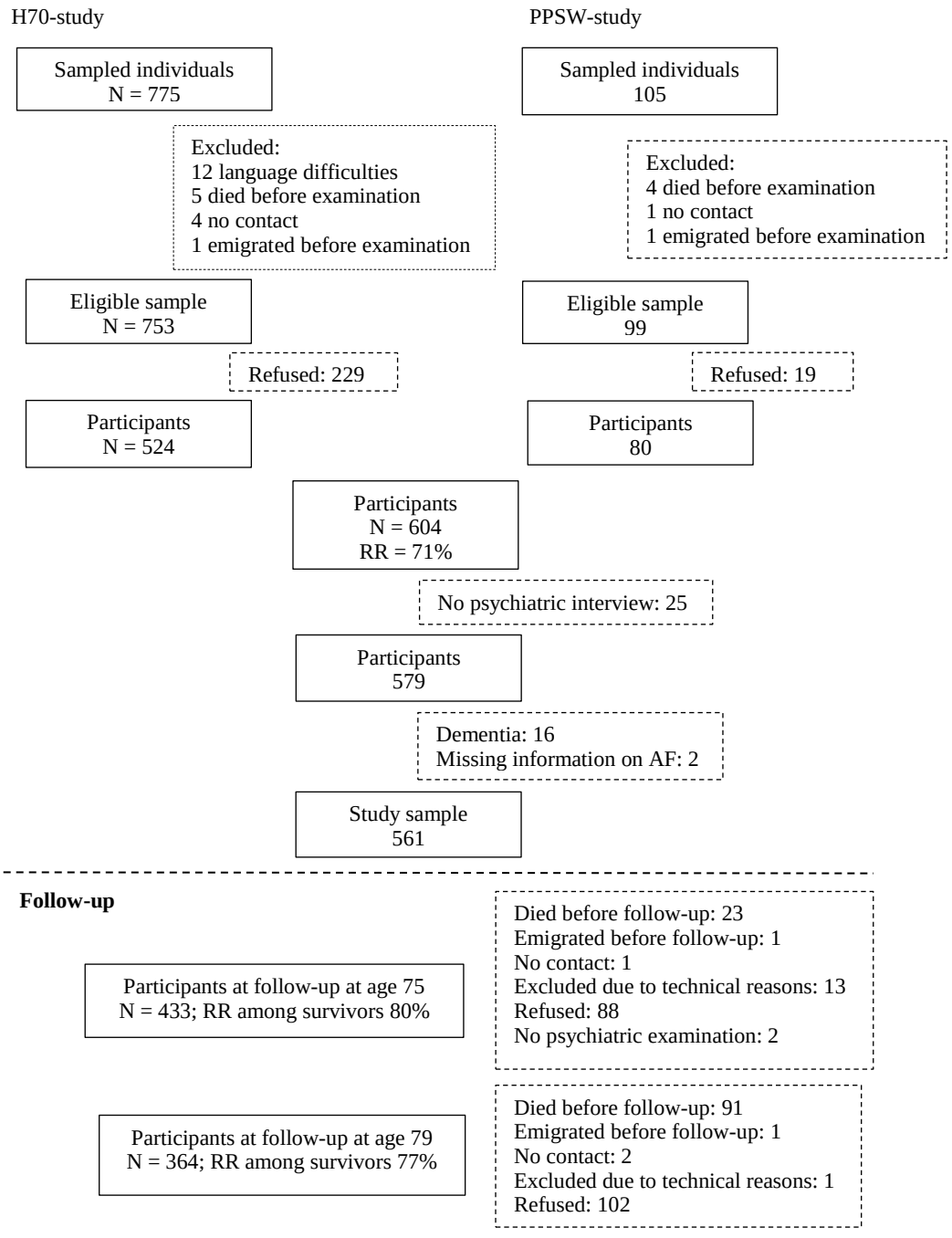
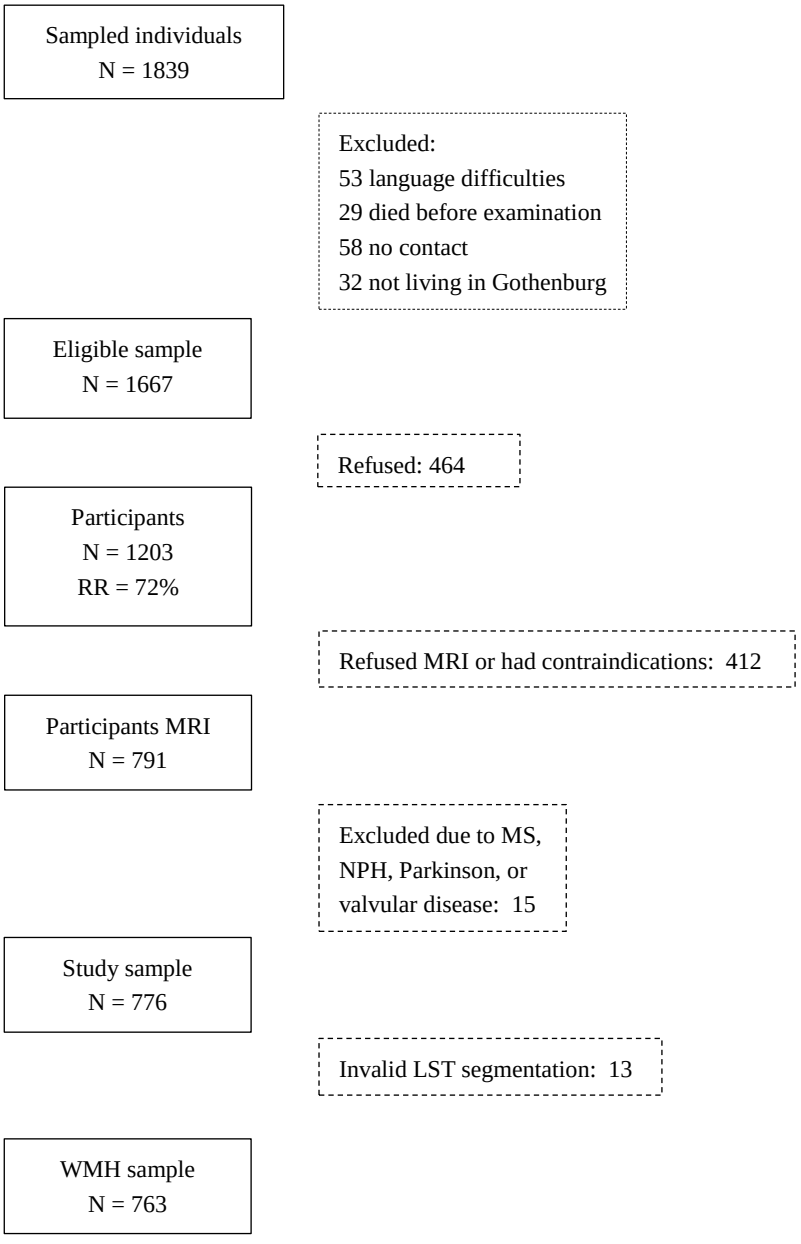


Figure 8. *Flow chart paper III, baseline in 2000-02 and follow-ups in 2005-07 and 2009-11*



LST, lesion segmentation tool; MRI, magnetic resonance imaging; MS, multiple sclerosis; NPH, normal pressure hydrocephalus; WMH, with matter hyperintensity

Figure 9. *Flow chart paper IV, examined in 2014-16*

3.2 DATA COLLECTION

The examinations included semi-structured interviews about somatic and psychiatric disorders and symptoms, medications, social factors, life-style factors, and ADL. Psychometric tests and physical examinations (e.g., anthropometry, blood pressure, ECG, lung function, and blood sampling) were performed. Examinations of physical fitness was performed and included for example gait speed, grip strength, and chair stand. Thereafter, the participants were invited to additional examinations such as computed tomography (CT) and MRI of the brain, lumbar puncture, and body composition. All participants were asked to provide contact information to a proxy informant who were asked to participate in an interview by telephone.

Hospital discharge diagnoses were obtained from the inpatient part of the NPR coded according to the ICD system. All Swedish citizens have access to the health care system and are therefore included in the register if in need of inpatient care. The NPR received national coverage in 1978. Death dates were obtained from the Swedish Tax Agency.

3.3 DEFINITION OF AF AND DEMENTIA

In paper I and III, AF diagnoses were based on proxy-informant interviews, the NPR (ICD8-SE 427.92; ICD9-SE 427D; ICD10-SE I48), and ECGs coded according to the Minnesota Code (MC 8-3). In paper IV, AF was diagnosed based on self-reports, the NPR (ICD10-SE I48), and ECGs (MC 8-3).

In all included papers, dementia diagnoses were based on the DSM-III-R criteria[44] using information from psychometric tests and proxy-informant interviews. However, in the DSM-III-R criteria it is mandatory with impairment in both short- and long-term memory, while the H70-studies include cognitive impairment in short- or long-term memory. In paper III, Alzheimer´s dementia was based on the NINCDS-ADRDA criteria[47] and vascular dementia was diagnosed similar to the NINDS–AIREN criteria for possible vascular dementia, except that a temporal relation between the neurological symptoms and dementia within 1 year was mandatory in the H70-studies.[48]

3.4 DATA ANALYSES

Paper I. Logistic regression was used to examine associations between characteristics at baseline and attrition at follow-up.

Paper II. McNemar´s test was used to examine differences in prevalence between different information sources. Overall agreement, positive agreement, negative agreement, and Cohen´s Kappa were calculated to examine agreement between different information sources. Kappa values were interpreted as slight between 0 and 0.20, fair between 0.21 and 0.40, moderate between 0.41 and 0.60, substantial between 0.61 and 0.80, and almost perfect between 0.81 and 1.0.[120] Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were used to study validity between different information sources.

Paper III. Fisher´s exact test was used to examine differences in proportions and independent sample T-test was used to examine differences in mean values. Cox regression analyses were used to examine if a history of AF at baseline increased the risk of incident dementia during follow-up. Participants were censored at the time of death, emigration, dementia onset, or at the end of the study in 2012. Additional cox regression analyses were performed after excluding individuals with history of stroke at baseline or incident stroke during follow-up. Interactions for AF and sex, and AF and the presence of the *APOE* ε4 allele were examined in relation to incident dementia.

Paper IV. Fisher´s exact test or Pearson´s Chi-square test was used to examine differences in proportions and independent sample T-test was used to examine differences in mean values for sample characteristics. Logistic regression was used to examine the association between AF and stroke/infarcts/CMBs. Individuals with symptomatic stroke were excluded in analyses of SBIs. Linear regression was used to examine the association between AF and WMH volume. WMH volumes were logaritmized due to non-normal distribution of the residuals. Sensitivity analyses were performed after excluding individuals with dementia (and TIA in analyses including SBIs). Interactions for AF and sex were examined in relation to stroke/infarcts and WMH volume. Interactions for AF and stroke/infarcts were examined in relation to WMH volumes.

3.5 ETHICAL CONSIDERATIONS

All studies have been approved by the Regional Ethical Review Board in Gothenburg. Informed consent was obtained from all participants or their relatives in cases when it was not possible to obtain informed consent from the participant, i.e. for participants with dementia or other cognitive difficulties. Participants were informed that they could redraw their consent at any time and get all individual data deleted.

This thesis utilizes data from interviews, blood samples, physical examinations, ECG, CT and MRI brain imaging, and the NPR. CT brain imaging exposes the participant to radiation. However, the radiation from one CT scan was calculated to corresponded to one-year background radiation and was not assessed to pose a risk in this age group. For brain MRI imaging, the same safety protocol was used as in the regular health system.

The interviews and examinations included in the H70-studies and the PPSW were time consuming and could be tiering. The general examination took about one day. After that, the participants were asked to take part in additional examinations such as imaging. For the general examination, home visits and examinations divided into several days were offered to facilitate for participants who had difficulties coming to the outpatient clinic or did not manage the examination in one day. The examinations were in some cases also adapted to the individual, for example in individuals with dementia.

In cases were lab tests or examinations (e.g., blood pressure, ECG, and brain imaging) were pathological, the participants were informed and referred to the regular health system, often the primary health center. If the participant approved, the results were also sent to the ordinary health care provider.

4 RESULTS

4.1 PAPER I

Rydén L*, Wetterberg H*, Ahlner F, Falk Erhag H, Gudmundsson P, Guo X, Joas E, Johansson L, Kern S, Mellqvist Fässberg M, Najar J, Ribbe M, Sacuiu S, Samuelsson J, Sigström R, Skoog J, Rydberg Sterner T, Waern M, Zettergren A, Skoog I. Attrition in the Gothenburg H70 Birth Cohort Studies - an 18-year follow-up of the 1930-cohort. *(Submitted manuscript)*. *LR and HW are joint first authors

Paper I describes the longitudinal sample of the 5th cohort of 70-year-olds in the H70-studies. The response rates at baseline were 70% (in 2000-02 at age 70) and 64% (in 2005-07 at age 75). The response rates among survivors were between 70 and 80 % at all follow-ups except at age 88 where the response rate among survivors were just below 60 %.

When analysing characteristics associated with different types of attrition, we found that the main characteristics associated with refusal were lower education and cognitive level, and higher blood-pressure. Several socio-demographic and health related factors were associated to attrition due to death, such as male sex, lower education level, cardiovascular diseases (e.g., atrial fibrillation and heart failure), stroke, dementia, and lower cognitive level. Thus, over time, the sample became more and more selected due to both refusal and attrition due to death.

4.2 PAPER II

Rydén, L., Sigström, R., Nilsson, J., et al. (2019). Agreement between self-reports, proxy-reports and the National Patient Register regarding diagnoses of cardiovascular disorders and diabetes mellitus in a population-based sample of 80-year-olds. *Age and Ageing*, *48*(4), 513-518. doi:10.1093/ageing/afz033.[121]

In this cross-sectional study, we found a substantial agreement between self- and proxy-reported diagnoses of myocardial infarction, angina pectoris, AF, hypertension, and diabetes mellitus, see Table 6. The agreement between self- and proxy-reported diagnoses of intermittent claudication and heart failure were on the other hand fair. In addition, specificity was high for proxy-reports compared to self-reports regarding all diagnoses, while sensitivity varied considerably among the different diagnoses, see Table 6.

Table 6. Sensitivity, Specificity, and Kappa-values for proxy- and self-reported diagnoses, using self-reports as gold standard

	Sensitivity	**Specificity**	**Kappa**
Myocardial infarction	73 (56–86)	98 (97–99)	0.75 (0.63–0.87)
Angina pectoris	69 (55–81)	98 (96–99)	0.73 (0.62–0.83)
Intermittent claudication	35 (14–62)	98 (96–99)	0.38 (0.15–0.60)
Heart failure	45 (27–64)	95 (92–97)	0.40 (0.23–0.56)
Atrial fibrillation	63 (50–75)	95 (92–97)	0.61 (0.50–0.72)
Hypertension	73 (67–79)	94 (88–97)	0.62 (0.54–0.69)
Diabetes mellitus	78 (64–89)	98 (96–99)	0.79 (0.69–0.88)

A large proportion of the hospital discharge diagnoses in the NPR were captured by both self- and proxy-reports. I.e., sensitivity was above 70% for both self- and proxy-reports compared with the NPR, except for self-reported heart failure where sensitivity was 67% and proxy-reported angina pectoris and AF where sensitivity was 64% and 69% respectively.

In addition, prevalence figures varied between different information sources with significantly lower prevalence figures according to the NPR compared to self-reports for all diagnoses except angina pectoris and myocardial infarction. When comparing self- and proxy-reported diagnoses, prevalence figures differed for hypertension only, with higher prevalence figures according to self-reports.

4.3 PAPER III

Rydén, L., Zettergren, A., Seidu, N. M, et al. (2019). Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke. *Journal of Internal Medicine, 286*(1), 101-110. doi:10.1111/joim.12902.[122]

In this longitudinal study, we found that AF increased the risk of developing dementia (HR 2.8; 95% CI 1.3–5.7; P = 0.004), see Table 7. The increased risk remained after exclusion of participants with a history of symptomatic stroke at baseline and incident stroke during follow-up. After stratifying by sex, the increased risk of dementia was only seen among men (p=0.047 for the interaction between AF and sex in relation to dementia in the total sample and p=0.091 in the subsample free from symptomatic stroke). In addition, after stratifying by the *APOE* ε4 allele, an increased risk was only seen among non-carriers of the *APOE* ε4 allele (p=0.128 for the interaction between AF and *APOE* ε4 status in relation to dementia in the total sample and p=0.354 in the subsample free from symptomatic stroke).

We also found that AF increased the risk of developing Alzheimer´s dementia (HR 2.7; 95% CI 1.1–6.6; P = 0.032). The increased risk remained after exclusion of individuals with symptomatic stroke. There were too few individuals who developed vascular dementia during follow-up to analyze vascular dementia separately.

Table 7. *Atrial fibrillation (AF) and the risk of incident dementia in the total group, among men, and among non-carriers of the APOE ε4 allele*

	HR (95% CI) adjusted*	**P-value**
Total sample		
AF	2.8 (1.3–5.7)	0.004
AF (men)	4.6 (1.9–11.2)	<0.001
AF (APOE ε4 non-carriers)	4.2 (1.8–9.7)	<0.001
Stroke-free sample		
AF	2.9 (1.2–6.8)	0.013
AF (men)	6.7 (2.3–19.7)	<0.001
AF (*APOE* ε4 non-carriers)	4.2 (1.4–12.0)	0.007

*Sex, education, smoking, BMI, myocardial infarction, heart failure, hypertension, diabetes mellitus, *APOE* ε4 status, and ACE rs1799752 status at baseline were considered as possible covariates

4.4 PAPER IV

Rydén L, Sacuiu S, Wetterberg H, Najar J, Guo X, Kern S, Zettergren A, Shams S, Pereira JB, Wahlund LO, Westman E, Skoog I. Atrial fibrillation, stroke and silent cerebrovascular disease: A population-based MRI study. Neurology 2021;97(16):e1608-e1619.[123]

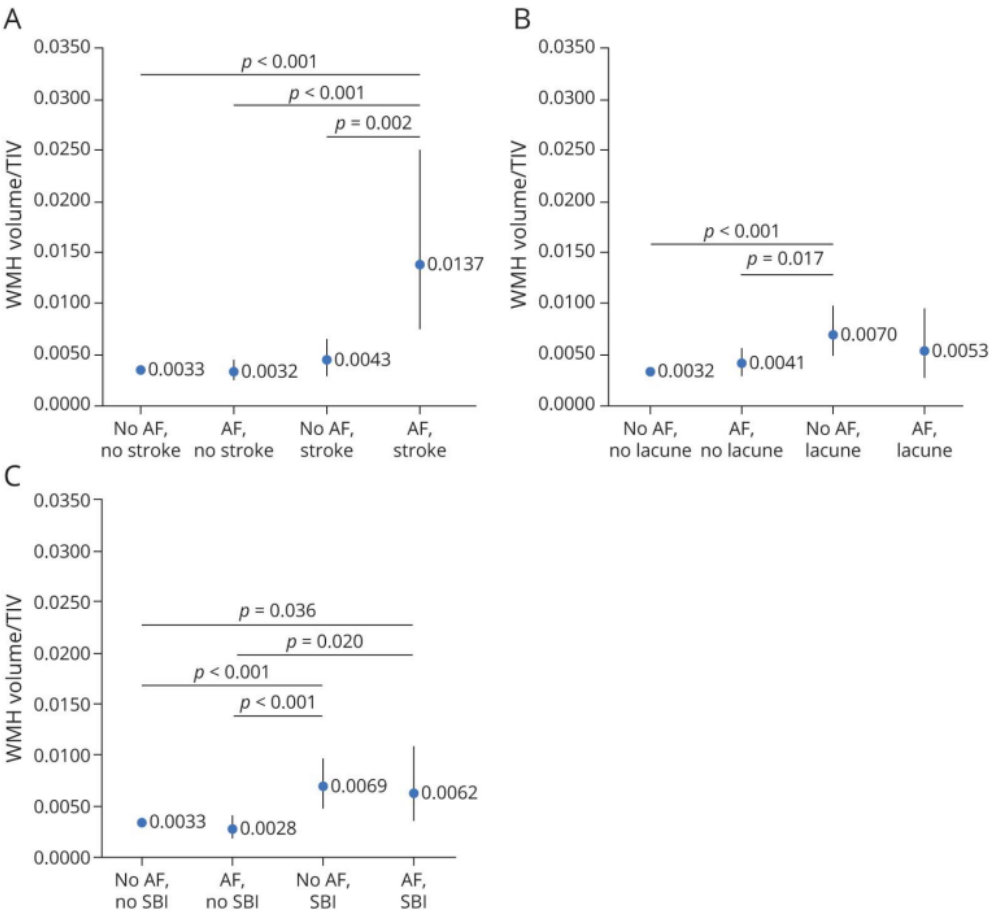
In this cross-sectional study, AF was associated with symptomatic stroke, large infarcts, lacunes, and SBIs, see Table 8. AF was not associated with global WMH volume in the total sample. However, among those with symptomatic stroke, individuals with AF had larger WMH volumes than those without AF, see Figure 10. AF was not associated with WMH volume among those without symptomatic stroke. In addition, AF was not associated with CMBs except in the frontal lobe.

Table 8. *Atrial fibrillation (AF) and the association with symptomatic stroke and cerebral infarcts*

	OR (95% CI) Adjusted**	**P-value**
Symptomatic stroke	4.5 (2.1-9.5)	<0.001
Large infarcts	5.0 (1.5-15.9)	0.007
Lacunes	2.7 (1.2-5.6)	0.008
Silent brain infarcts*	3.5 (1.6-7.4)	0.001

* Individuals with a history of symptomatic stroke (N=44) were excluded

** Sex, education, smoking, alcohol risk consumption, heart disease, hypertension, diabetes mellitus, hypercholesterolemia, *APOE* ε4, and BMI where considered as potential covariates.



AF, atrial fibrillation; SBI, silent brain infarct; TIV, total intracranial volume; WMH, white matter hyperintensity

Sex, education, smoking, alcohol risk consumption, heart disease, hypertension, diabetes mellitus, hypercholesterolemia, APOE, and body mass index were included as potential covariates. Values of $p < 0.008$ is considered statistically significant after Bonferroni correction.

Atrial fibrillation, stroke and silent cerebrovascular disease: A population-based MRI study.[123]

Figure 10. *Estimated WMH Volume as a Fraction of TIV By AF and Stroke Status*

5 DISCUSSION

5.1 THE RELATION BETWEEN AF AND DEMENTIA, SILENT BRAIN INFARCTS, AND SMALL VESSEL DISEASE

This thesis suggests that AF increases the risk of incident dementia irrespective of symptomatic stroke, which is supported by studies from other longitudinal population-based cohorts from the Northern and Western Europe and the USA (i.e., the Rotterdam study,[61] the Whitehall II study,[67] SNAC-K,[62] Adult Changes in Thought (ACT) study,[63] and the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)[60]). In addition, we found an interaction between AF and sex in relation to incident dementia. After stratifying by sex, the association between AF and dementia were only seen among men. That there was no association between AF and dementia among women needs to be interpreted with caution since there were few women with AF. In contrast to our study, the SNAC-K study found an association between AF and dementia among women but not among men[62] and the ARIC-NCS study found that the increased risk of dementia were similar between sexes.[60]

The mechanism(s) behind the association between AF and dementia in the absence of symptomatic stroke is not elucidated, but explanations include SBIs, altered cerebral blood flow, and inflammation.[75] To increase the knowledge of how AF affects the brain we analyzed if AF was associated with SBIs and markers of small vessel disease on brain MRI. We found that AF was associated to SBIs and lacunes, but not to global WMH volume and the presence of CMBs, except in the frontal lobe.

The association between AF and SBIs is supported by other studies. For example, a meta-analysis found that AF was associated with a 2-fold increase in the odds of SBIs.[94] In contrast to our result, a longitudinal study from SNAC-K, found no association between AF and annual changes in number of lacunes.[95] An association between AF and SBIs opens for the possibility that SBIs mediate the association between AF and dementia in the absence of symptomatic stroke. Traditionally, the mechanism behind cerebral infarcts in AF patients is thought to be cardiac embolism.[26] However, since we also found an association between AF and lacunes, which is viewed as a marker of small vessel disease[27], it is possible that other pathophysiologic mechanisms than cardiac embolism play a role. Alternatively, lacunes might, at least in some cases, be caused by cardiac embolism. That lacunes may be caused by cardiac

embolism have been suggested before since they have been associated with different cardiac procedures and diseases.[92, 124] Further support of the possibility that SBIs act as a mediator in the relationship between AF and dementia is a study reporting that cognitive decline only was present in AF patients with SBIs and not in those without SBIs.[78] However, it has also been reported that AF patients had lower cognitive function in a sample free from both symptomatic stroke and SBIs,[79] making it possible that other mechanisms than symptomatic stroke and SBIs also play a role.

We did not find an association between AF and global WMH volume, which is in consistence with previous cross-sectional population-based studies from Europe and the USA (i.e., the Age, Gene/ Environment Susceptibility-Reykjavik (AGES-Reykjavik) study, Mayo clinic study of aging, and the ARIC study).[100-102, 125] In paper III we found that AF at age 70 was associated with incident dementia during follow-up, but since paper IV (investigating the association between AF brain MRI lesions) included 70-year-olds only it is possible that WMHs will develop at higher ages, still being a potential mediator in the relationship between AF and dementia. The other cross-sectional studies from Europe and the USA mentioned above did however not find an association between AF and global WMHs, even though they included older participants and had a mean age between 73 and 78 years.[100-102, 125] In contrast to our results and the above-mentioned cross-sectional studies, one recent longitudinal and population-based study from Sweden (SNAC-K), with a mean age of 70 years at baseline and a 6-year follow up, found that AF was associated with an increase in global WMH volumes.[95] Worth to mention is that this study excluded participants with cerebral infarcts at both baseline and at follow-up.[95] Even though most studies have not found an association between AF and global WMHs, it is possible that AF is associated to regional WMHs. For example, one cross-sectional study found an association between AF and periventricular WMHs but not between AF and deep WMHs.[99] In contrast, another cross-sectional study found an association between AF and deep WMHs but not with periventricular WMHs.[98]

One interesting study on different WMH patterns in patients with embolic stroke found an association between AF and a pattern of anterior subcortical WMH patches but not with multiple subcortical spots.[126] Therefore, the authors conclude that this "challenges the view that chronic embolism accounts for AF-related WMH because preferential embolism into the anterior subcortical white matter is unlikely".[98, 99, 126] Other plausible mechanisms for WMHs in the absence of embolism include hypoperfusion, neuroinflammation, and thrombosis.[96]

Even though we did not find an association between AF and WMH volume in the total sample, we found an association between AF and WMH volume in participants with a history of symptomatic stroke. Although this does not explain the association between AF and dementia in the absence of symptomatic stroke, it might shed light on the reported association between AF and lower cognitive level in patients with a history of stroke.[127] One explanation might be that a brain affected by a stroke might be more vulnerable to alterations in cerebral blood flow caused by AF, leading to WMHs and cognitive difficulties. However, stroke is also associated with WMHs[128] and one explanation behind the association between AF and WMHs in patients with symptomatic stroke might be that embolic strokes caused by AF are more severe than other stroke ethiologies.[24]

That we did not find an association between AF and the presence of lobar or deep/infratentorial CMBs need to be interpreted cautiously due to few individuals with CMBs in the sample. However, we found an association between AF and the presence of CMBs in the frontal lobe, opening for the possibility that there might be a relation between AF and a regional distribution of CMBs. A lobar distribution of CMBs have been associated to CAA.[107] However, it has been suggested that CAA mainly has a posterior distribution of lobar CMBs and not typically a frontal distribution.[129, 130] Population-based studies examining the relation between AF and CMBs are scarce[108] but there are a number of studies that have investigated the relation between anticoagulant treatment and CMBs. One meta-analysis from 2019, including 47 studies, found an increased risk of CMBs in patients treated with anticoagulants compared to those without anticoagulants.[110] CMBs have been associated with an increased risk of ischemic stroke and intracranial hemorrhages, at least in samples with ischemic stroke and TIA[106] and neurodegeneration.[105] There are also studies reporting an association between CMBs and cognitive decline independent of other markers of small vessel disease such as WMHs and lacunes.[105]

5.2 PREVENTING DEMENTIA IN INDIVIDUALS WITH AF

Even though current treatment guidelines for AF focus on stroke prevention through anticoagulant treatment and on reducing AF symptoms through rhythm and rate control, these treatment regimens have the potential to reduce the risk of cognitive decline and dementia. Anticoagulants has the potential to decrease dementia risk in AF patients by preventing both symptomatic stroke and SBIs.[13] Rhythm control may also decrease the risk of stroke since it reduces AF burden.[131] In addition, both rate and rhythm control have the potential to prevent dementia since irregular and a fast heart rhythm may lead to left ventricular dysfunction,[132] which may lead to brain hypoperfusion.[133]

5.2.1 ANTICOAGULATION

There are studies supporting a positive effect of anticoagulant treatment in AF patient in relation to dementia. For example, one meta-analysis, including nine prospective studies[62, 134-141], reported that anticoagulant treatment was associated with a reduction in dementia incidence in AF patients.[142] The favorable effect of anticoagulant treatment on cognition in these studies might be due to reduction of symptomatic stroke. However, one study excluding patients with a history of stroke/TIA and censoring patients at the time of a subsequent stroke/TIA found that AF patients treated with anticoagulants had no increased risk of dementia compared to those without AF, while AF patients who were not on anticoagulants had an increased dementia risk compared to patients without AF.[136] This suggests that anticoagulants may reduce dementia risk in patients with AF, not only by preventing symptomatic stroke, but also by preventing SBIs. It is also possible that anticoagulants reduce the risk of dementia through other mechanisms than preventing symptomatic and silent cardiac embolism or that prescriptions of anticoagulants are associated with other protective factors for dementia that has not been adjusted for.

One possible bias in studying anticoagulant treatment in relation to dementia prevention is that prescription of anticoagulants might be more common among patients with higher cognitive ability, i.e. confounding by indication. To reduce this potential error, one meta-analysis included studies utilizing an observational window (varying from 6 month to 4 years) where patient who developed dementia within that time frame were excluded, decreasing the risk that cognitive level affected the choice of initiating anticoagulant treatment.[142] When only including studies with an observational window, there were no difference in dementia risk between patients with and without anticoagulants.[142]

Whether treatment with warfarin or DOAC is favorable for dementia prevention in AF patients is not elucidated. One meta-analysis, including six RCTs[143-148] and two observational studies,[137, 149] found a tendency towards a lower risk of cognitive impairment in patients on DOAC compared with warfarin or acetylsalicylic acid.[150] In addition, a recent study found a 16% reduction of dementia cases in patient treated with DOAC compared to warfarin.[151] Adequate stroke prevention in AF patients treated with warfarin depend on the time spent in the therapeutic range (TTR) and it has been reported that AF patients on warfarin with high TTR (>70%) had a 27% decreased dementia risk compared to patients with low TTR (<50%).[151]

5.2.2 RHYTHM AND RATE CONTROL

Both the irregular heart rhythm and non-optimal heart rate have the potential to affect cognitive abilities. It has for example been suggested that low or high ventricular heart rate (>90 or <50 beats per minute) increase the risk of dementia in patients with longstanding AF (>1 year) and cognitive impairment.[152] In addition, cardioversion has been found to increase brain perfusion in AF patients[153] and catheter ablation has been reported to be beneficial for AF patients in relation to cognition.[154-156] Even though there is an increased risk of symptomatic stroke and SBIs during and short after cardiac ablation procedures[157] it has been shown that stroke rates 1 and 3 years after the procedure are lower in ablated AF patients compared to patients who have not underwent ablation,[156] suggesting a favorable effect of lowering AF burden.

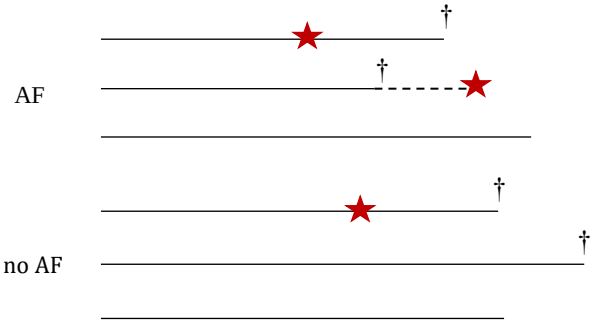
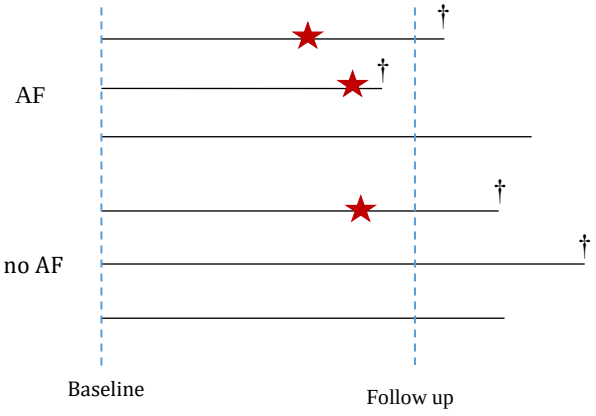


Figure 11. a) Illustration of when death occur before a conceivably dementia case



b) Illustration of when death occur before follow-up

★ = dementia † = death

5.3 METHODOLOGICAL CHALLENGES IN EPIDEMIOLOGICAL STUDIES

Common biases in epidemiologic studies include selection and information bias. Therefore, in paper I, we investigated attrition in the 1930 cohort and in paper II, we investigated agreement of cardiovascular diagnoses and diabetes mellitus between different information sources.

5.3.1 ATTRITION

In paper I, we found that attrition due to refusal was mainly associated with lower education and cognitive level, and higher blood pressure, while attrition due to death was associated to several sociodemographic and health related factors. Differential attrition has the potential to affect both representativeness and bias results. In the 1930 cohort, where we found that AF at baseline (at age 70) increased the risk of dementia during follow-up, we also found that both AF and dementia were associated with attrition due to death. Thus, in paper III, both the exposure (AF) and the outcome (dementia) were associated to attrition due to death, which risk to affect the results. One study, investigating the association between smoking and cognitive decline, which both are associated with mortality, used inverse-probability-of-attrition weights to account for the differential attrition.[158] They found that the differential attrition lead to an underestimation of the effect of smoking on cognitive decline. However, this approach has been criticized since it measures the probability of cognitive decline under the condition that there had been no mortality during the study period.[159] Chaix et al.[159] express this in a commentary to the article: "In replacing dead participants by cloning the living, IPW [inverse-probability-weights] generates a sample in which participants are not allowed to die." Figure 11a shows a theoretical example where participants with AF die before they develop the outcome.[158] It is also possible that individuals who get dementia die before they are followed up and will therefore be classified as non-demented at the time they are censored, see Figure 11b. Neither AF nor dementia were associated with refusal at follow-up at age 75 and 79, which were the follow-ups included in paper III.

5.3.2 AGREEMENT BETWEEN DIFFERENT INFORMATION SOURCES

All sources of information include a risk of misclassification. Self-reported information is a common information source in epidemiological studies, but when asking about disease history or events in the past there is a risk of recall bias. For studies including individuals with cognitive difficulties, the risk of

misclassifications is especially high. To be able to include participants with cognitive difficulties, additional information from proxy informants, such as relatives or close friends, can be used. Another common source of information is registers, which has the advantage of including many participants at a low cost. In addition, registers can be used to capture individuals lost to follow-up. However, medical registers only include those who have sought medical care and registers based on hospital discharge diagnoses, such as the inpatient part of the NPR, only include individuals who have been hospitalized, missing individuals with milder diseases and diseases not requiring inpatient care.

To evaluate information sources utilized in this thesis, we compared self-reports, proxy-reports, and register-based diagnoses in paper II. We found that prevalence figures differed between the information sources, with lower prevalence figures according to the NPR compared to self-reports for AF, heart failure, hypertension, intermittent claudication, and diabetes mellitus. This is important to consider when using register data only. Prevalence figures for myocardial infarction and angina pectoris did not differ between the NPR and self-reports. These results were expected since patients with myocardial infarction and angina pectoris are more likely to need inpatient care than patients with for example hypertension and intermittent claudication.

Prevalence figures for proxy-reports did not differ from self-reports except for hypertension. Agreement between self- and proxy-reports varied with the studied diagnosis, with the highest agreement for myocardial infarction, angina pectoris, and diabetes mellitus and the lowest agreement for heart failure and intermittent claudication. For heart failure and intermittent claudication, less than half of the self-reported diagnoses were also reported by the proxy informant and less than half of the proxy-reported diagnoses were confirmed by self-reports. This shows that proxy-reports are poor predictors for self-reports regarding these diagnoses.

In paper III, the AF diagnosis was based on proxy-reports, the NPR, and ECGs. Since there were no questions about AF in the participant interviews in the H70-studies in 2000-02, we compared proxy-reported diagnoses with self-reports in 2009-11 when both information sources were present. The agreement for proxy- and self-reported AF diagnoses was substantial. However, 37% of all self-reported AF diagnoses was not reported by the proxy-informant and 29% of all proxy-reported AF was not confirmed by self-reports. By also including the NPR and ECGs we increased the detection rate of AF, even though some cases were probably still missed due to the lack of self-reported information. On the other hand, by including several sources, the risk of false positive cases also increased since we classified cases as present

if any of the included sources report a diagnosis. These misclassification errors may lead to an underestimation of the effect.

Misclassification of covariables may also bias the results. For example, heart failure often co-exists with AF and has also been associated to cognitive impairment.[160] In paper III, the diagnosis of heart failure was based on the NPR only, since we had no self- or proxy-reported heart failure, and therefore milder cases or cases that did not need inpatient care were missed. This is illustrated by the findings in paper II where the prevalence of heart failure was 7.9% when self-reported compared to 3.0% according to the NPR. This limits the possibility to appropriately adjust for heart failure. On the other hand, by only including diagnoses from the NPR we adjusted for the most severe cases, which can be a desirable approach. For the other diseases used as covariates, for example myocardial infarction and diabetes mellitus, we had multiple information sources, including self-reports and register data, getting a higher detection rate. The agreement between different information sources was also higher for these diseases than for heart failure, suggesting that these diagnoses are more accurate.

5.4 ADDITIONAL METHODOLOGICAL DISCUSSION

Beside the methodological challenges raised in paper I and II, there are other methodological aspects to discuss. Two of the included papers (paper I and III) were prospective cohort studies, which increases the possibility to draw conclusions regarding causality. Cohort studies also decrease the risk of differential recall bias compared to case-control studies since information about the exposure is collected before the outcome occur. Paper IV was a cross-sectional study, which limits the possibility to draw conclusions regarding causality and a longitudinal design would have improved the study. Paper III was also a cross-sectional study, but in this case, the cross-sectional design was the most appropriate since paper III analyzes prevalence and agreement between information sources.

All participants in this thesis were aged 70 or older. Therefore, differential survival before study start affects the samples. Individuals surviving to this age might have specific characteristics, why generalizability to other age groups is limited. In addition, refusal at baseline also play a role. In paper III and IV, response rate was above 70% and even though these response rates are fairly high, how responders differ from non-responders and the target population might be even more important. For example, in the 2014-16 study, there was no difference in the proportion of women between the participants and target population (70-year-olds living in Gothenburg). However, participants had higher education level than the target population.[161] Differential participation can bias the results in association studies if the association between the exposure and outcome differ among those who participate and those who do not participate in the study.

In paper IV, not all participants in the general examination took part in the additional brain MRI examination. Participants in the brain MRI examination had higher education level and higher MMSE scores than non-participants.[123] Thus, it is possible that non-participants had more brain pathologies than participants, since cognitive impairment and dementia have been associated with several brain pathologies, such as infarcts and small vessel disease.[162, 163] Regarding AF diagnoses, 11.4% had AF among non-participants in the brain MRI examination compared to 8.7% among participants. This difference was however not significant.[123] If non-participation has a relation to both the exposure (AF) and the outcome (brain MRI pathologies) the results risk to be biased.

Another problem with misclassification, beside the before mentioned problems with detection rate and false positive cases, is when diseases remain undiagnosed. AF may be present in individuals without symptoms and therefore remain undiagnosed. AF can also remain undetected when screened for since AF often has a paroxysmal pattern. Repeated ECGs will yield a higher detection rate than a single one and continuous screening for the same period will increase the detection rate further.[7] As an example, in the Crystal AF trial, AF was detected in 8.9% of all patients with ICM after six months compared to 1.4% in the control group who only underwent ECG monitoring at follow-up visits.[164] In the H70- and PPSW-studies, a single ECG was included, making it possible to detect undiagnosed AF. However, if repeated or continues screening had been used, detection rate had most likely increased.

Regarding dementia diagnoses, we utilized standard criteria, i.e. DSM-III-R[44] for any dementia, NINCDS-ADRDA[47] for Alzheimer´s dementia, and criteria similar to NINDS-AIREN[48] for vascular dementia. Dementia prevalence highly depend on the criteria used. For example, a previous paper from the H70 studies found that dementia prevalence was 9.6% according to DSM-IV, 6.3% according to DSM-III-R, and 3.1% according to ICD-10.[165] The agreement between these diagnostic systems, measured with Kappa values, varied from 0.47 to 0.76.[165] The main reasons for low agreement was that DSM-III-R require both impaired short- and long-term memory and the differential inclusion of behavior or personality changes.[165] Paper III in this thesis diagnose dementia according to the DSM-III-R criteria based on the examinations. However, these diagnoses did not require impairment in both short- and long-term memory, making the diagnoses less strict and more similar to the DSM-IV criteria. We also utilized diagnoses from the NPR, which is based on the ICD-10 criteria. As mentioned above, the diagnostic criteria used will yield different prevalence and incidence figures, but results in association studies may also be affected. Therefore, when comparing results from different studies, the diagnostic criteria used is important to consider.

The Alzheimer´s dementia diagnosis was based on the NINCDS-ADRDA criteria.[47] However, we did not include biological markers (i.e., cerebrospinal fluid, EEG, or brain imaging), which can be used to support a probable Alzheimer´s dementia diagnosis. The inclusion of biological markers or histopathology (which is included in the definite Alzheimer´s dementia criteria)[47] have the potential to increase diagnosis accuracy. Likewise, for vascular dementia diagnosed according to the NINDS-AIREN criteria,[48] a probable vascular dementia diagnosis require evidence on brain imaging. We did not include brain imaging since only a subsample participated the in brain imaging examinations. In addition, we included a temporal relationship

between stroke and dementia of one year in our diagnostic criteria, while the probable NINDS-AIREN criteria uses a time frame of 3 months.[48] A possible dementia diagnosis according to the NINDS-AIREN criteria can however be made in the absence of neuroimaging and a clear temporal relationship.[48] Evidence of cerebrovascular disease on brain imaging and a temporal relation within 3 month would have made the criteria for vascular dementia stricter.

5.5 STRENGTHS

Among the strengths of this thesis is the inclusion of papers regarding both consequences of AF and methodologic aspects of epidemiologic studies. Further, this thesis utilize data from prospective population-based studies aiming to be representative of same aged individuals in Gothenburg, Sweden. The examinations and interviews were performed by health professionals and included comprehensive assessment of both somatic and psychiatric health, and the inclusion of biomarkers.

Paper I is a description of the H70 1930-cohort (the sample that is utilized in paper II and III). Describing the study sample is essential in order to evaluate the quality of the studies and to be able to generalize study results to other populations. In addition, attrition analyses were performed, identifying characteristics that were associated with different types of attrition. Analyzing different types of attrition separately is important since non-death attrition and attrition due to death may affect study results and representativeness differently.

Paper II investigate agreement between information sources. All sources of information have a risk of information bias, i.e. measurement errors affecting study results. Studying agreement between different information sources can shed light on the magnitude of the information biases.

In paper III, we investigated if AF at baseline increased the risk of developing dementia during follow-up. Among the strength of this study is the possibility to exclude individuals with a history of symptomatic stroke at baseline and incident stroke during follow-up. Further, to diagnose individuals with dementia, we used information from both the examinations and register data. Most diagnoses were based on the examinations, where multiple sources were assessed, i.e. psychometric tests and proxy informant interviews. However, by also including register data we could capture diagnoses for participants lost to follow-up and extend the follow-up time.

In paper IV, we utilized a large population-based sample of brain MRI to study the association between AF and SBIs and markers of small vessel disease. Among the strengths of paper IV are the inclusion of different markers of small vessel disease and that we investigated the co-occurrence of AF and stroke/infarcts in relation to WMHs. The measurement of WMH volumes were calculated using an automatic segmentation tool and a quality control was performed for all images. In addition, an experienced radiologist blinded to clinical data assessed all MRI images for infarcts, intracerebral hemorrhages, lacunes, and CMBs.

5.6 LIMITATIONS

There are also several limitations that needs to be considered. Even though the H70-studies are large population-based studies, sample size limits the power of the studies, especially for subgroup analyses. For example, in paper III and IV, the prevalence of AF was higher among men, leaving few women with AF. This may in part explain that some findings were only present among men. In addition, in paper IV, there was a limited number of participants with CMBs and with both AF and stroke/infarcts. Therefore, these results need to be interpreted with caution.

Since AF may be paroxysmal and go without symptoms, there is a risk for underdiagnosis of AF. Even though we screened all participants with an ECG, screening repeatedly or during a longer time period have been shown to increase the number of identified AF cases further.[7] In addition, since ICD-codes often contain both AF and AFL, we might have included some patients with AFL only. However, since AFL is far less common and AF often co-exist in AFL patients[111], we do not believe that this is a major problem. No known AFL diagnoses are included.

Paper III was a longitudinal study, where differential attrition during follow-up may affect study results. Attrition due to death is especially important in studies among older adults were death rates are high. As mentioned before, we used register data from the NPR to capture individuals who developed dementia that were lost to follow-up. However, all individuals who develop dementia will not be captured in the in-patient part of the NPR since not everyone living with dementia will end up in hospital. It is also possible that dementia diagnoses will not be registered in individuals that are hospitalized for other reasons. In addition, AF diagnoses and the possible confounders included in paper III were reported at baseline, making it possible that individuals develop diseases during follow-up, which has not been accounted for.

Paper IV is a cross-sectional study, which limits the possibilities to draw conclusions regarding causality. Further, even though everyone participating in the general examination was invited to an additional brain MRI examination, only 67% of all individuals participated. Those who did not participate in the MRI examination had more often lower education level, lower MMSE scores and more often dementia.[123]

Paper III and IV investigated AF history up to age 70, limiting generalizability to other age groups. Further, only individuals who were able to speak Swedish were included in the in the H70- and PPSW- studies, making the samples homogeneous which may affect generalizability.

Finally, we have not investigated the potential beneficial effect of AF treatment on the increased dementia risk in AF patients, which would have been valuable. Reasons for not including treatment were that participants with both present and past AF were included and we had no information on treatment history. Further, some participants were diagnosed with AF for the first time during the examination and thereafter referred to the regular health system for further care. These individuals might have been prescribed treatment for AF after the baseline examination. In addition, we had not the possibility to differentiate between paroxysmal and persistent/permanent AF or to investigate AF burden, which would have strengthened the studies.

6 CONCLUSION

We found that AF increases the risk of dementia also in the absence of symptomatic stroke, which is supported by an increasing body of evidence. In addition, we found that AF was associated with SBIs, which is a possible mediator in the relation between AF and dementia. One possible pathophysiologic mechanism behind the association between AF and SBIs is cardiac embolism. However, we also found a relation between AF and lacunes, which is a marker of small vessel disease, opening for the possibility that there are additional mechanisms behind the association between AF and infarcts than embolism, including altered cerebral blood flow, inflammation, and shared risk factors. Alternatively, lacunes might in some cases be caused by cardiac embolism. We did not find an association between AF and other markers of small vessel disease, i.e. CMBs (except in the frontal lobe) and global WMH volume. However, the number of AF participants with CMBs were low, why this needs to be investigated further. In addition, it is possible that AF is associated with regional WMHs, which has been suggested by other studies. Finally, among participants with symptomatic stroke, those with AF had larger WMH volumes than those without AF. In addition, both SBIs and lacunes were associated to larger WMH volumes, but AF did not affect these associations. This suggests that a brain hit by a stroke, large enough to cause symptoms, is more vulnerable to the hemodynamic consequences of AF. Alternatively, strokes caused by AF might be more severe, leading to larger WMH volumes.

When evaluating potential biases in the included studies, we found that both AF and dementia were associated with attrition due to death. When both the exposure and the outcome are associated with increased mortality, there is a risk of biased results. In addition, we found that agreement between self- and proxy-reported AF was substantial. However, the overlap between the different information sources was not perfect, indicating a risk of misclassification. In addition, when combining different information sources (proxy- or self-reports, register data, and ECGs) as we did, more diagnoses will be captured, while the risk of false positive cases increase. These potential misclassifications of AF diagnoses most likely increased the risk of underestimating the effect.

7 FUTURE PERSPECTIVES

An increasing body of evidence suggests an increased risk of dementia in AF patients. However, to further examine potential mechanisms behind the association between AF and dementia, longitudinal studies including SBIs, lacunes, WMHs, CMBs, and atrophy as potential meditators are needed. Studies exploring the mediating effect of cardiac output, brain hypoperfusion, and inflammatory markers can further increase the knowledge regarding potential mechanisms behind the association between AF and dementia.

There are several comorbidities that have a bidirectional relationship to AF. Therefore, interactions between diseases are needed to be assessed. Especially AF in combination with heart failure and brain lesions have the potential to severely affect the brain. For example, a brain affected by large infarcts or small vessel disease might have impaired regulatory mechanisms and therefore not be able to compensate for reduced cardiac output or variable blood flow leading to both hypoperfusion and hypertensive events.

Further research is also needed in order to optimize and personalize treatment in AF patients to prevent cognitive decline and dementia. The success or failure of different treatment regimens can also provide information regarding the mechanisms behind the association between AF and dementia. Future studies on the effect of anticoagulants in samples free from (1) symptomatic stroke (both at baseline and during follow-up) and (2) symptomatic stroke and SBIs are warranted. In addition, studies investigating the effect of DOAC compared to optimized treatment with warfarin (i.e. high TTR) in relation to dementia risk are scarce. In addition, more research is needed regarding the beneficial effect of rate versus rhythm control in AF patients in relation to cognitive decline and dementia.

So far, anticoagulant treatment and rhythm control, especially cardiac ablation, show promising potential to reduce dementia risk in AF patients. However, observational studies on treatment effect risk to be confounded by indication, i.e. that individuals with the highest cognitive ability or other patient characteristics form the treatment decision of anticoagulants and ablation. RCTs have the potential to overcome this problem and there are some ongoing and upcoming RCTs in AF patients investigating different treatment regimens in relation to cognition and dementia. For example, the Cognitive Decline and Dementia in Atrial Fibrillation Patients (CAF) trial (ClinicalTrials.gov Identifier: NCT03061006) aim to study if treatment with DOAC differ from treatment with warfarin in relation to incident dementia and cognitive decline,

but also in relation to cerebral macro- and micro infarcts.[166] The blinded randomized trial of anticoagulation to prevent ischemic stroke and neurocognitive impairment (BRAIN) AF trial (ClinicalTrials.gov NCT02387229) aim to study if treatment with DOAC differ from standard treatment in relation to cognitive decline in AF patients with low stroke risk. One ongoing RCT regarding the effect of rate versus rhythm control include the "Comparison of Brain Perfusion in Rhythm Control and Rate Control of Persistent Atrial Fibrillation: Prospective Randomized Trial" (ClinicalTrials.gov Identifier: NCT02633774) where patients with persistent AF will be randomized to rate or rhythm control to investigate changes in cognitive function and brain perfusion.

Finally, brain imaging has the potential to further personalize treatment in AF patients. Current treatment guidelines for anticoagulants in AF patients are based on for example the CHA_2DS_2-VASc and HASBLED scores, where brain imaging is not included. For example, SBIs have been shown to increase future risk of ischemic stroke and cognitive decline, WMHs have been associated to increased risk of ischemic stroke, intracranial hemorrhages and cognitive decline, and CMBs have been associated with increased risk of ischemic stroke and intracranial hemorrhages.[167] However, the current evidence for including brain imaging to further personalize treatment in AF patients is not sufficient why more research is needed.

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42(5):373-498.
2. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;76(25):2982-3021.
3. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;6:213-220.
4. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol* 2014;63(22):2335-2345.
5. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol* 2008;1(1):62-73.
6. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;52(7).
7. Engdahl J, Rosenqvist M. Large-scale screening studies for atrial fibrillation - is it worth the effort? *J Intern Med* 2021.
8. Willems S, Meyer C, de Bono J, et al. Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation. *Eur Heart J* 2019;40(46):3793-3799c.
9. Kraft M, Büscher A, Wiedmann F, et al. Current Drug Treatment Strategies for Atrial Fibrillation and TASK-1 Inhibition as an Emerging Novel Therapy Option. *Front Pharmacol* 2021;12:638445.
10. Zimetbaum P. An Argument for Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation. *Circulation* 2005;111(23):3150-3156.
11. Mark DB, Anstrom KJ, Sheng S, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;321(13):1275-1285.

12. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;362(15):1363-1373.
13. Katsanos AH, Kamel H, Healey JS, Hart RG. Stroke Prevention in Atrial Fibrillation: Looking Forward. *Circulation* 2020;142(24):2371-2388.
14. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;52(7):e364-e467.
15. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res* 2020;127(1):4-20.
16. Johnson LS, Juhlin T, Engström G, Nilsson PM. Risk factor changes and incident atrial fibrillation among middle-aged men in the Malmö Preventive Project cohort. *Eur Heart J Cardiovasc Pharmacother* 2016;2(2):81-87.
17. Gallagher C, Hendriks JML, Elliott AD, et al. Alcohol and incident atrial fibrillation - A systematic review and meta-analysis. *Int J Cardiol* 2017;246:46-52.
18. Allan V, Honarbakhsh S, Casas JP, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost* 2017;117(5):837-850.
19. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. *Circulation* 2016;133(5):484-492.
20. Soliman EZ, Lopez F, O'Neal WT, et al. Atrial Fibrillation and Risk of ST-Segment-Elevation Versus Non-ST-Segment-Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2015;131(21):1843-1850.
21. Jons C, Jacobsen UG, Joergensen RM, et al. The incidence and prognostic significance of new-onset atrial fibrillation in patients with acute myocardial infarction and left ventricular systolic dysfunction: a CARISMA substudy. *Heart Rhythm* 2011;8(3):342-348.
22. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation* 2020;141(9):e139-e596.
23. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide Variation in Reported Rates of Stroke Across Cohorts of Patients With Atrial Fibrillation. *Circulation* 2017;135(3):208-219.

24. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke* 1996;27(10):1765-1769.
25. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24(1):35-41.
26. Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart* 2020;106(19):1463-1468.
27. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12(8):822-838.
28. Singleton MJ, Imtiaz-Ahmad M, Kamel H, et al. Association of Atrial Fibrillation Without Cardiovascular Comorbidities and Stroke Risk: From the REGARDS Study. *J Am Heart Assoc* 2020;9(12):e016380.
29. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. *Stroke* 2016;47(3):895-900.
30. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With EACTS. *Rev Esp Cardiol (Engl Ed)* 2017;70(1):50.
31. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF Scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): A Novel Approach to In-Depth Characterization (Rather than Classification) of Atrial Fibrillation. *Thromb Haemost* 2021;121(3):270-278.
32. Bah A, Nuotio I, Palomäki A, et al. Inadequate oral anticoagulation with warfarin in women with cerebrovascular event and history of atrial fibrillation: the FibStroke study. *Ann Med* 2021;53(1):287-294.
33. Volgman AS, Benjamin EJ, Curtis AB, et al. Women and atrial fibrillation. *J Cardiovasc Electrophysiol* 2021;32(10):2793-2807.
34. Silva RL, Guhl EN, Althouse AD, et al. Sex differences in atrial fibrillation: patient-reported outcomes and the persistent toll on women. *Am J Prev Cardiol* 2021;8:100252.
35. Essien UR, Kornej J, Johnson AE, Schulson LB, Benjamin EJ, Magnani JW. Social determinants of atrial fibrillation. *Nat Rev Cardiol* 2021.
36. Mou L, Norby FL, Chen LY, et al. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol* 2018;11(7):e006350.
37. Marcus GM, Alonso A, Peralta CA, et al. European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation* 2010;122(20):2009-2015.

38. Prince MW, A; Guerchet, M; Ali, G-C; Wu, Y-T; Prina, M. World Alzheimer Report 2015. London2015.
39. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366(9503):2112-2117.
40. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006;368(9533):387-403.
41. Emmady PD, Tadi P. Dementia. StatPearls. Treasure Island (FL): StatPearls Publishing, 2021.
42. Clinic M. Dementia. Accessed October 20, 2021. https://www.mayoclinic.org/diseases-conditions/dementia/symptoms-causes/syc-20352013.
43. Sacuiu SF. Dementias. In: Aminoff MJ, Boller F, Swaab DF, eds. Handbook of Clinical Neurology 3rd Series, Neuroepidemiology: Elsevier, 2016.
44. American Psychiatric A. Diagnostic and statistical manual of mental disorders ; revised (DSM-III-R). *Washington DG* 1987.
45. Association AP. Diagnostic and Statistical Manual of Mental Disorders, 4 ed ed. Washington, DC: APA Press, 1994.
46. Association AP. Diagnostic and Statistical Manual of Mental Disorders, 5 ed ed. Arlington, VA: American Psychiatric Association, 2013.
47. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939-944.
48. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43(2):250-260.
49. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;396(10248):413-446.
50. Kuo CY, Stachiv I, Nikolai T. Association of Late Life Depression, (Non-) Modifiable Risk and Protective Factors with Dementia and Alzheimer's Disease: Literature Review on Current Evidences, Preventive Interventions and Possible Future Trends in Prevention and Treatment of Dementia. *Int J Environ Res Public Health* 2020;17(20).
51. Nardini E, Hogan R, Flamier A, Bernier G. Alzheimer's disease: a tale of two diseases? *Neural Regen Res* 2021;16(10):1958-1964.
52. Prohovnik I, Perl DP, Davis KL, Libow L, Lesser G, Haroutunian V. Dissociation of neuropathology from severity of dementia in late-onset Alzheimer disease. *Neurology* 2006;66(1):49-55.
53. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE. Emerging Concepts in Vascular Dementia: A Review. *J Stroke Cerebrovasc Dis* 2021;30(8):105864.

54. O'Brien JT, Thomas A. Vascular Dementia. *Focus (Am Psychiatr Publ)* 2017;15(1):101-109.
55. Wolters FJ, Ikram MA. Epidemiology of Vascular Dementia. *Arterioscler Thromb Vasc Biol* 2019;39(8):1542-1549.
56. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. *Neurobiol Aging* 2000;21(2):321-330.
57. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* 2012;2012:367516.
58. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;28(2):316-321.
59. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010;7(4):433-437.
60. Chen LY, Norby FL, Gottesman RF, et al. Association of Atrial Fibrillation With Cognitive Decline and Dementia Over 20 Years: The ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). *Journal of the American Heart Association* 2018;7(6).
61. de Bruijn RF, Heeringa J, Wolters FJ, et al. Association Between Atrial Fibrillation and Dementia in the General Population. *JAMA Neurol* 2015;72(11):1288-1294.
62. Ding MZ, Fratiglioni L, Johnell K, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging A population-based study. *Neurology* 2018;91(19):E1732-E1740.
63. Dublin S, Anderson ML, Haneuse SJ, et al. Atrial fibrillation and risk of dementia: a prospective cohort study. *J Am Geriatr Soc* 2011;59(8):1369-1375.
64. Liao JN, Chao TF, Liu CJ, et al. Risk and prediction of dementia in patients with atrial fibrillation--a nationwide population-based cohort study. *Int J Cardiol* 2015;199:25-30.
65. Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ* 2012;184(6):E329-336.
66. Rusanen M, Kivipelto M, Levälahti E, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis* 2014;42(1):183-191.
67. Singh-Manoux A, Fayosse A, Sabia S, et al. Atrial fibrillation as a risk factor for cognitive decline and dementia. *Eur Heart J* 2017;38(34):2612-2618.
68. Tilvis RS, Kähönen-Väre MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci* 2004;59(3):268-274.

69. Forti P, Maioli F, Pisacane N, Rietti E, Montesi F, Ravaglia G. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment (MCI). *Arch Gerontol Geriatr* 2007;44 Suppl 1:155-165.
70. Marengoni A, Qiu C, Winblad B, Fratiglioni L. Atrial fibrillation, stroke and dementia in the very old: a population-based study. *Neurobiol Aging* 2011;32(7):1336-1337.
71. Peters R, Poulter R, Beckett N, et al. Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. *J Hypertens* 2009;27(10):2055-2062.
72. Rastas S, Verkkoniemi A, Polvikoski T, et al. Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. *Stroke* 2007;38(5):1454-1460.
73. Kim D, Yang PS, Lip GYH, Joung B. Atrial Fibrillation Increases the Risk of Early-Onset Dementia in the General Population: Data from a Population-Based Cohort. *J Clin Med* 2020;9(11).
74. Saglietto A, Matta M, Gaita F, Jacobs V, Bunch TJ, Anselmino M. Stroke-independent contribution of atrial fibrillation to dementia: a meta-analysis. *Open Heart* 2019;6(1).
75. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? *Europace* 2018;20(3):408-419.
76. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8):983-988.
77. Guo X, Östling S, Kern S, Johansson L, Skoog I. Increased risk for dementia both before and after stroke: A population-based study in women followed over 44 years. *Alzheimers Dement* 2018;14(10):1253-1260.
78. Chen LY, Lopez FL, Gottesman RF, et al. Atrial Fibrillation and Cognitive Decline-The Role of Subclinical Cerebral Infarcts The Atherosclerosis Risk in Communities Study. *Stroke* 2014;45(9):2568-+.
79. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;29(17):2125-2132.
80. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev* 2021;101(4):1487-1559.
81. Gardarsdottir M, Sigurdsson S, Aspelund T, et al. Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. *Europace* 2018;20(8):1252-1258.
82. Tian H, Li Y, Zhang J, Cheng C. The effect of controlling the heart rate on the heart failure index and on heart function in heart failure patients with atrial fibrillation. *Am J Transl Res* 2021;13(4):3487-3493.

83. Junejo RT, Lip GYH, Fisher JP. Cerebrovascular Dysfunction in Atrial Fibrillation. *Front Physiol* 2020;11:1066.
84. Junejo RT, Braz ID, Lucas SJ, et al. Neurovascular coupling and cerebral autoregulation in atrial fibrillation. *J Cereb Blood Flow Metab* 2020;40(8):1647-1657.
85. Linz D, Elliott AD, Hohl M, et al. Role of autonomic nervous system in atrial fibrillation. *Int J Cardiol* 2019;287:181-188.
86. Freestone B, Chong AY, Nuttall S, Lip GY. Impaired flow mediated dilatation as evidence of endothelial dysfunction in chronic atrial fibrillation: relationship to plasma von Willebrand factor and soluble E-selectin levels. *Thromb Res* 2008;122(1):85-90.
87. Anselmino M, Scarsoglio S, Saglietto A, Gaita F, Ridolfi L. Transient cerebral hypoperfusion and hypertensive events during atrial fibrillation: a plausible mechanism for cognitive impairment. *Sci Rep* 2016;6:28635.
88. Martins GL, Duarte RCF, Mukhamedyarov MA, Palotás A, Ferreira CN, Reis HJ. Inflammatory and Infectious Processes Serve as Links between Atrial Fibrillation and Alzheimer's Disease. *Int J Mol Sci* 2020;21(9).
89. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015;12(4):230-243.
90. Troncone L, Luciani M, Coggins M, et al. Aβ Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease: Mind the Heart. *J Am Coll Cardiol* 2016;68(22):2395-2407.
91. D'Souza A, Butcher KS, Buck BH. The Multiple Causes of Stroke in Atrial Fibrillation: Thinking Broadly. *Can J Cardiol* 2018;34(11):1503-1511.
92. Bang OY. Silent brain infarction: a quiet predictor of future stroke. *Precision and Future Medicine* 2018;2(4):167-174.
93. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2002;33(1):21-25.
94. Kalantarian S, Ay H, Gollub RL, et al. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis. *Ann Intern Med* 2014;161(9):650-658.
95. Ding M, Wang R, Kalpouzos G, et al. Cerebral Small Vessel Disease Associated With Atrial Fibrillation Among Older Adults: A Population-Based Study. *Stroke* 2021;52(8):2685-2689.
96. Moroni F, Ammirati E, Rocca MA, Filippi M, Magnoni M, Camici PG. Cardiovascular disease and brain health: Focus on white matter hyperintensities. *Int J Cardiol Heart Vasc* 2018;19:63-69.
97. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9(7):689-701.

98. Kobayashi A, Iguchi M, Shimizu S, Uchiyama S. Silent cerebral infarcts and cerebral white matter lesions in patients with nonvalvular atrial fibrillation. *J Stroke Cerebrovasc Dis* 2012;21(4):310-317.
99. de Leeuw FE, de Groot JC, Oudkerk M, et al. Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* 2000;54(9):1795-1800.
100. Graff-Radford J, Madhavan M, Vemuri P, et al. Atrial fibrillation, cognitive impairment, and neuroimaging. *Alzheimers Dement* 2016;12(4):391-398.
101. Berman JP, Norby FL, Mosley T, et al. Atrial Fibrillation and Brain Magnetic Resonance Imaging Abnormalities. *Stroke* 2019;50(4):783-788.
102. Moazzami K, Shao IY, Chen LY, et al. Atrial Fibrillation, Brain Volumes, and Subclinical Cerebrovascular Disease (from the Atherosclerosis Risk in Communities Neurocognitive Study [ARIC-NCS]). *Am J Cardiol* 2020;125(2):222-228.
103. Piers RJ, Nishtala A, Preis SR, et al. Association between atrial fibrillation and volumetric magnetic resonance imaging brain measures: Framingham Offspring Study. *Heart Rhythm* 2016;13(10):2020-2024.
104. Fazekas F, Kleinert R, Roob G, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol* 1999;20(4):637-642.
105. Fiford CM, Sudre CH, Young AL, et al. Presumed small vessel disease, imaging and cognition markers in the Alzheimer's Disease Neuroimaging Initiative. *Brain Commun* 2021;3(4):fcab226.
106. Wilson D, Charidimou A, Ambler G, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: A meta-analysis. *Neurology* 2016;87(14):1501-1510.
107. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology* 2008;70(14):1208-1214.
108. Selim M, Diener HC. Atrial Fibrillation and Microbleeds. *Stroke* 2017;48(10):2660-2664.
109. Saito T, Kawamura Y, Tanabe Y, et al. Cerebral microbleeds and asymptomatic cerebral infarctions in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis* 2014;23(6):1616-1622.
110. Cheng Y, Wang Y, Song Q, Qiu K, Liu M. Use of anticoagulant therapy and cerebral microbleeds: a systematic review and meta-analysis. *J Neurol* 2021;268(5):1666-1679.
111. Rahman F, Wang N, Yin X, et al. Atrial flutter: Clinical risk factors and adverse outcomes in the Framingham Heart Study. *Heart Rhythm* 2016;13(1):233-240.

112. Internationell statistisk klassifikation av sjukdomar och relaterade hälsoproblem; systematisk förteckning, Svensk version 2021, 10th ed: Socialstyrelsen, 2021.
113. Wang HT, Chen YL, Lin YS, et al. Differential Risk of Dementia Between Patients With Atrial Flutter and Atrial Fibrillation: A National Cohort Study. *Front Cardiovasc Med* 2021;8:787866.
114. M P. Dictionary of epidemiology, 5 ed. ed. New York: Oxford University Press, 2008.
115. Merrill RM. Introduction to Epidemiology, 5 ed. Sudbury, USA: Jones and Bartlett Publishers, 2010.
116. Kenneth J. Rothman SG, and Timothy L. Lash. Modern Epidemiology. Philadelphia, USA: Lippincott Williams and Wilkins, 2008.
117. D.S. T. Epidemiology, a basis for public health and disease prevention, 1st ed: Glyendal Norsk Forlag, 2015.
118. Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg* 2010;126(6):2234-2242.
119. Rydberg Sterner T, Ahlner F, Blennow K, et al. The Gothenburg H70 Birth cohort study 2014–16: design, methods and study population. *Eur J Epidemiol* 2019;34(2):191-209.
120. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-174.
121. Rydén L, Sigström R, Nilsson J, et al. Agreement between self-reports, proxy-reports and the National Patient Register regarding diagnoses of cardiovascular disorders and diabetes mellitus in a population-based sample of 80-year-olds. *Age Ageing* 2019;48(4):513-518.
122. Rydén L, Zettergren A, Seidu NM, et al. Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke. *J Intern Med* 2019;286(1):101-110.
123. Rydén L, Sacuiu S, Wetterberg H, et al. Atrial Fibrillation, Stroke, and Silent Cerebrovascular Disease: A Population-Based MRI Study. *Neurology* 2021.
124. Hassell ME, Nijveldt R, Roos YB, et al. Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol* 2013;10(12):696-706.
125. Stefansdottir H, Arnar DO, Aspelund T, et al. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. *Stroke* 2013;44(4):1020-1025.
126. Mayasi Y, Helenius J, McManus DD, et al. Atrial fibrillation is associated with anterior predominant white matter lesions in patients presenting with embolic stroke. *J Neurol Neurosurg Psychiatry* 2018;89(1):6-13.

127. Kokkinidis DG, Zareifopoulos N, Theochari CA, et al. Association Between Atrial Fibrillation and Cognitive Impairment in Individuals With Prior Stroke: A Meta-Analysis and Meta-Regression Analysis. *Stroke* 2020;51(6):1662-1666.
128. Schmidt R, Scheltens P, Erkinjuntti T, et al. White matter lesion progression: a surrogate endpoint for trials in cerebral small-vessel disease. *Neurology* 2004;63(1):139-144.
129. Rosand J, Muzikansky A, Kumar A, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. *Ann Neurol* 2005;58(3):459-462.
130. Yates PA, Villemagne VL, Ellis KA, Desmond PM, Masters CL, Rowe CC. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. *Front Neurol* 2014;4:205.
131. Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Heart Rhythm* 2017;14(1):e3-e40.
132. Iwasaki YK, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: implications for management. *Circulation* 2011;124(20):2264-2274.
133. Lie SL, Hisdal J, Høiseth L. Cerebral blood flow velocity during simultaneous changes in mean arterial pressure and cardiac output in healthy volunteers. *Eur J Appl Physiol* 2021;121(8):2207-2217.
134. Barber M, Tait RC, Scott J, Rumley A, Lowe GDO, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004;2(11):1873-1878.
135. Bunch TJ, May HT, Bair TL, et al. Atrial Fibrillation Patients Treated With Long-Term Warfarin Anticoagulation Have Higher Rates of All Dementia Types Compared With Patients Receiving Long-Term Warfarin for Other Indications. *J Am Heart Assoc* 2016;5(7).
136. Field TS, Weijs B, Curcio A, et al. Incident Atrial Fibrillation, Dementia and the Role of Anticoagulation: A Population-Based Cohort Study. *Thromb Haemost* 2019;119(6):981-991.
137. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J* 2019;40(28):2327-2335.
138. Madhavan M, Hu TY, Gersh BJ, et al. Efficacy of Warfarin Anticoagulation and Incident Dementia in a Community-Based Cohort of Atrial Fibrillation. *Mayo Clin Proc* 2018;93(2):145-154.
139. Nah MA, Lee KS, Hwang TY. Association Between Atrial Fibrillation and the Risk of Dementia in the Korean Elderly: A 10-Year Nationwide Cohort Study. *J Prev Med Public Health* 2020;53(1):56-63.

140. Krawczyk M, Fridman S, Cheng Y, Fang J, Saposnik G, Sposato LA. Atrial fibrillation diagnosed after stroke and dementia risk: cohort study of first-ever ischaemic stroke patients aged 65 or older. *Europace* 2019;21(12):1793-1801.
141. Marzona I, Baviera M, Vannini T, et al. Risk of dementia and death in patients with atrial fibrillation: A competing risk analysis of a population-based cohort. *Int J Cardiol* 2016;220:440-444.
142. Lin M, Han W, Zhong J, Wu L. A systematic review and meta-analysis to determine the effect of oral anticoagulants on incidence of dementia in patients with atrial fibrillation. *Int J Clin Pract* 2021;75(10):e14269.
143. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364(9):806-817.
144. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981-992.
145. Kirchhof P, Haeusler KG, Blank B, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J* 2018;39(32):2942-2955.
146. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139-1151.
147. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093-2104.
148. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883-891.
149. Jacobs V, May HT, Bair TL, et al. Long-Term Population-Based Cerebral Ischemic Event and Cognitive Outcomes of Direct Oral Anticoagulants Compared With Warfarin Among Long-term Anticoagulated Patients for Atrial Fibrillation. *Am J Cardiol* 2016;118(2):210-214.
150. Zhang C, Gu ZC, Shen L, et al. Non-vitamin K Antagonist Oral Anticoagulants and Cognitive Impairment in Atrial Fibrillation: Insights From the Meta-Analysis of Over 90,000 Patients of Randomized Controlled Trials and Real-World Studies. *Front Aging Neurosci* 2018;10:258.
151. Cadogan SL, Powell E, Wing K, Wong AY, Smeeth L, Warren-Gash C. Anticoagulant prescribing for atrial fibrillation and risk of incident dementia. *Heart* 2021.
152. Cacciatore F, Testa G, Langellotto A, et al. Role of ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: a 10-year study. *Dement Geriatr Cogn Disord* 2012;34(3-4):143-148.

153. Gardarsdottir M, Sigurdsson S, Aspelund T, et al. Improved brain perfusion after electrical cardioversion of atrial fibrillation. *Europace* 2020;22(4):530-537.
154. Jin MN, Kim TH, Kang KW, et al. Atrial Fibrillation Catheter Ablation Improves 1-Year Follow-Up Cognitive Function, Especially in Patients With Impaired Cognitive Function. *Circ Arrhythm Electrophysiol* 2019;12(7):e007197.
155. Kim D, Yang PS, Sung JH, et al. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2020;41(47):4483-4493.
156. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;22(8):839-845.
157. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke* 2012;43(1):265-270.
158. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology* 2012;23(1):119-128.
159. Chaix B, Evans D, Merlo J, Suzuki E. Commentary: Weighing up the dead and missing: reflections on inverse-probability weighting and principal stratification to address truncation by death. *Epidemiology* 2012;23(1):129-131; discussion 132-127.
160. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: A systematic review of the literature. *Eur J Heart Fail* 2007;9(5):440-449.
161. Rydberg Sterner T. Depression amongSwedish 70-year-olds: sex difference from a gender prospective. Borås: Stema specialtryck AB, 2020.
162. Salvadori E, Brambilla M, Cova I, Pomati S, Pantoni L. Cognitive evaluation in cerebral small vessel disease: towards an evidence-based identification of the reference standards. Part 1. A systematic review and qualitative data synthesis. *J Neurol* 2021;268(12):4563-4572.
163. Yang Y, Fuh J, Mok VCT. Vascular Contribution to Cognition in Stroke and Alzheimer's Disease. *Brain Science Advances* 2018;4(1):39-48.
164. Tsai CF, Anderson N, Thomas B, Sudlow CL. Comparing Risk Factor Profiles between Intracerebral Hemorrhage and Ischemic Stroke in Chinese and White Populations: Systematic Review and Meta-Analysis. *PLoS One* 2016;11(3):e0151743.
165. Wancata J, Börjesson-Hanson A, Ostling S, Sjögren K, Skoog I. Diagnostic criteria influence dementia prevalence. *Am J Geriatr Psychiatry* 2007;15(12):1034-1045.

166. Bunch TJ, Jacobs V, May H, et al. Rationale and design of the impact of anticoagulation therapy on the Cognitive Decline and Dementia in Patients with Nonvalvular Atrial Fibrillation (CAF) Trial: A Vanguard study. *Clin Cardiol* 2019;42(5):506-512.
167. Haeusler KG, Wilson D, Fiebach JB, Kirchhof P, Werring DJ. Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives. *Heart* 2014;100(18):1408-1413.