Atrial Fibrillation and Socioeconomic Inequality

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DOI (link to publication from Publisher):
10.54337/aau466210963

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

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BY
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DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

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Thesis submitted 2021

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ISSN (online): 2246-1302
ISBN (online): 978-87-7573-999-8

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2022

ENGLISH SUMMARY

Atrial fibrillation (AF) is the most common supraventricular arrythmia worldwide and it can cause serious complications such as stroke and heart failure. The association between low socioeconomic position (SEP) and the risk of ischemic heart diseases is well described in prior literature. However, prior studies on SEP and AF have shown inconsistent results. The aim of this PhD-thesis was to examine socioeconomic inequality in the risk and treatment of AF and if there were social consequences associated with AF.

This PhD-thesis was based on three studies using nationwide registers from the entire Danish population.

The first study examined the association between different levels of socioeconomic factors (SEFs) and the risk of incident hospital diagnosed AF with baseline age of 35 years old, 50 years old, 65 years old and 80 years old. We found that low education was associated with higher hazard rate ratios (HRs) of AF but that the association was weakened with increasing age and even opposite for the eldest age cohort. Comparable results were seen for income; however, opposite results were seen for men aged 35 years old at baseline. Risk difference (RD), however, was small among the youngest because the absolute risk of AF in this age group is low.

The second study examined the association between SEFs and oral anticoagulation (OAC) initiation according to guidelines in AF patients with high risk of stroke. We found that patients with low levels of education, low levels of income or living alone had a higher risk of not being initiated with OAC when compared with patients with high levels of education, high levels of income or living together, respectively. The unadjusted inequality in education and cohabiting status for overall OAC treatment initiation was reduced with time. Thus, the inequality in novel OAC (NOAC) initiation increased with time.

The third study examined the association between incident AF and social consequences in terms of increased risk of permanent work disability. We found that patients with AF had three times the risk of work disability within 15 months after incident AF compared to individuals in the general population. The absolute risk of work disability was most prominent in strata with low levels of education, low levels of income and living alone.

Overall, this PhD-thesis highlights the socioeconomic inequality in the burden of AF. In combination with supplemental research in the field, this PhD-thesis might contribute to reduce the socioeconomic inequality in the risk and treatment of AF and the social consequences associated with AF.

DANSK RESUMÉ

Atrieflimren (AF) er den hyppigst forekommende hjerterytmeforstyrrelse på verdensplan og kan medføre alvorlige konsekvenser som apopleksi og hjertesvigt. Associationen mellem lav socioøkonomisk position (SEP) og øget risiko for iskæmisk hjertekarsygdom er velbeskrevet i litteraturen. Tidligere studier der har undersøgt sammenhængen mellem SEP og AF har dog vist inkonsistente resultater. Formålet med ph.d.-afhandlingen var at undersøge om der var social ulighed i risikoen for AF, behandling af AF, og om der var sociale konsekvenser associeret med AF.

Afhandlingen bygger på tre studier baseret på nationale danske registre.

Det første studie undersøgte sammenhængen mellem socioøkonomiske faktorer (SEF) og risikoen for at blive diagnosticeret med AF i aldersgrupperne 35 år, 50 år, 65 år og 80 år. Vi fandt at lav uddannelse var associeret med højere hazard rate ratioer (HR) for AF, men at associationen blev svækket, og delvist reverseret, med stigende alder. Sammenlignelige resultater blev set for indkomst, dog havde 35-årige mænd med høj indkomst en højere risiko for AF sammenlignet med mænd med lav indkomst. Risikodifferencen var dog lille blandt de yngste pga. en lav absolut risiko for AF.

Det andet studie undersøgte sammenhængen mellem SEF og initiering af oral antikoagulerende (OAC) medicin i henhold til retningslinjer hos patienter med AF med høj risiko for stroke. Vi fandt at patienter med lav indkomst, lav uddannelse eller som boede alene havde en højere risiko for ikke at få OAC-behandling sammenlignet med patienter der havde høj indkomst, høj uddannelse eller som ikke boede alene. Den ikke-justerede ulighed i OAC-initiering for uddannelse og samboerstatus blev reduceret over tid. Ulighed i behandling med nye OAC (NOAC) blev dog øget over tid.

Det tredje studie undersøgte sammenhængen mellem incident AF og sociale konsekvenser ved at undersøge risikoen for at miste arbejdsevnen. Vi fandt at personer med AF havde tre gange så høj risiko for at miste arbejdsevnen indenfor 15 måneder sammenlignet med den generelle befolkning. Den absolutte risiko for at miste arbejdsevnen var størst i strata med lav uddannelse, lav indkomst og de der boede alene.

Overordnet set bidrager denne ph.d.-afhandling til at belyse sammenhængen mellem socioøkonomisk ulighed og AF. I kombination med supplerende forskning på området, kan denne afhandling være med til at pege på relevante sundhedspolitiske interventioner som kan reducere den socioøkonomiske ulighed i risikoen for AF og behandling af AF samt de sociale konsekvenser associeret med AF.

ACKNOWLEDGEMENTS

First, a special thanks to my main supervisor Sam Riahi. You believed in me and gave me the opportunity and confidence to go through with this PhD. I had lots of independency and responsibility; however, you always took the time to guide and support me whenever I needed. Your solution-oriented way of guiding me has helped to ensure a continuous progress in my PhD. I feel very privileged to have had you as my main supervisor, and your guidance, support and opinions are very valued.

Kirsten Fonager, thank you for sharing your knowledge, especially in the field of epidemiology and social medicine. You have taught me many valuable things which I have used throughout my PhD. You feedback is always sharp and spot-on which truly have improved the quality of the papers and my understanding of many things. Thank you for all your help throughout the years. I am very grateful for it.

Albert Marni Joensen, you were my supervisor during my master thesis during medical school and you were involved in initiating this PhD where you continued as a co-supervisor. You have a great knowledge regarding AF and other clinical aspects but also the possibilities and limitations of our data. Your office door was always open, and you have helped me with minor and major issues during my PhD which I have appreciated a lot.

Mogens Lytken Larsen, thank you for sharing your great knowledge in the field of cardiology and your sensible view of things in general. Also, thank you for believing in me and for being part of making this project possible. Doing a PhD can be challenging at times, however, you always encouraged me when the progress was slow, and you gave me a pat on the back when things went well. This has meant a lot.

Søren Lundbye-Christensen, thank you for being my statistical supervisor. You have taught me more than I thought I was capable of and your way of explaining things are exceptional. Our statistical sessions have meant a lot to me, not only because it has been invaluable help, but also because of your good personality and great humour. Our meetings have been a great motivation throughout the project.

Furthermore, thank you to Søren Paaske Johnsen for many valuable epidemiological inputs which I have learned a lot from, and which have improved the quality of our papers. Martin Nygård Johansen, thank you for helping with data management, helpful discussions regarding statistical issues, and for useful feedback on Study 1. Thank you to Gregory Y.H. Lip for valuable inputs on Study 2 and for giving me the opportunity to come to Liverpool for a foreign stay. Unfortunately, the latter has not been possible due to the COVID-19 pandemic. Thank you to Erik Berg Schmidt, you

were my supervisor during my bachelor thesis of medical school back in 2014 and you connected me with my current PhD supervisors which made this PhD possible. Thank you, Britt Mejer Christensen, for helping with all kinds of practical issues and to Kirstine Rasmussen for helping with project management and fundraising.

I must admit, due to the COVID-19 pandemic, doing a register-based PhD in 2020 and 2021 was in periods quite lonely. Yet, it reminded me about how important good colleagues are; thank you to former and current fellows at the PhD office for great times with lots of fun and for many good conversations about scientific matters and life in general. Also, thanks to colleagues at the Lipid Clinic for conversations and morning coffee breaks.

I would also like to thank The Karen Elise Jensen Foundation, Karl G Andersen (Anderson) Foundation, Region Nordjyllands Sundhedsvidenskabelige forskningsfond, the Aase Ejnar Danielsen Foundation, The Obel Family Foundation, Department of Social Medicine, Aalborg University hospital and Department of Cardiology, Aalborg University hospital for financial support.

Finally, thanks to friends, my family and family-in-law for love and support. A special thanks to my partner Morten and our daughter Nova and all the happiness and love you give me.

Elin Danielsen Lunde, MD
October 2021

LIST OF PAPERS

This PhD-thesis is based on the following studies:

Study 1
Lunde, E. D., Joensen, A. M., Lundbye-Christensen, S., Fonager, K., Paaske Johnsen, S., Larsen, M. L., Berg Johansen, M., & Riahi, S. (2020). Socioeconomic position and risk of atrial fibrillation: a nationwide Danish cohort study. Journal of Epidemiology and Community Health, 74(1), 7-13.

Study 2
Lunde, E. D., Joensen, A. M., Fonager, K., Lundbye-Christensen, S., Johnsen, S. P., Larsen, M. L., YH Lip, G., & Riahi, S. (2021). Socioeconomic inequality in oral anticoagulation therapy initiation in patients with atrial fibrillation with high risk of stroke: a register-based observational study. BMJ Open, 11(5), [e048839].

Study 3
Lunde, E. D., Fonager, K., Joensen, A. M., Johnsen, S. P., Lundbye-Christensen, S., Larsen, M. L., & Riahi, S. The association between newly diagnosed atrial fibrillation and work disability: a nationwide Danish cohort study. Submitted (in review).

ABBREVIATIONS

AF	Atrial fibrillation
DM	Diabetes mellitus
DNPR	The Danish National Patient Register
ECG	Electrocardiogram
GLM	Generalized linear model
HR	Hazard rate ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
MI	Myocardial infarction
NOAC	Novel oral anticoagulant
OAC	Oral anticoagulation
OR	Odds ratio
PAD	Peripheral artery disease
RD	Risk difference
RR	Relative Risk
SEF	Socioeconomic factor
SEP	Socioeconomic position
SES	Socioeconomic status
WPS	Work participation score
95% CI	95% Confidence intervals

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CHAPTER 1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical importance (1) and it is considered a major public health burden related to both health issues and health care costs. In 2014, the prevalence of AF was estimated to be 2 %, doubled from what was reported the previous decade (2). Similarly, results from the Framingham Heart Study reported in 2004 a lifetime risk of AF of one in four for people aged 40 years old or older (3). However, those results were updated 14 years later to a lifetime risk of more than one in three (37%) for patients aged 55 years old or older after including the third generation cohort (4). It is often reported that both the prevalence and incidence of AF are increasing worldwide (1,5). Yet, a recent European study did not find a general trend of rise or fall of AF incidence across different European countries from 1990 to 2017 (6). The cause of the increasing prevalence and possibly increasing incidence are probably multifactorial but better opportunities to detect AF and increasing prevalence of factors predisposing to AF such as comorbidity and advanced age are important factors (5,7). AF is associated with mortality and morbidity such as stroke and heart failure (1) and socioeconomic problems like cognitive disturbance and permanent disability (2).

The association between socioeconomic position (SEP) and cardiovascular diseases has been studied before and it is well known that low SEP is associated with higher incidence and prevalence of cardiovascular diseases such as ischemic heart disease, less access to several treatment modalities like angiography and bypass grafts (8) and higher risk of detachment from work after incident myocardial infarction (9). The last three decades, a growing amount of literature regarding SEP and AF has emerged. However, the results are inconsistent and there are still many unknown aspects of how SEP is associated with AF (10). It is crucial to understand the association in order to identify possible vulnerable groups and potentially reduce the socioeconomic inequalities in the risk, treatment and social consequences of AF.

The aim of this thesis was to examine if there was socioeconomic inequality in the risk of being diagnosed with AF, in oral anticoagulation initiation for AF and if there were social consequences in terms of work disability and low work participation associated with AF.

CHAPTER 2. BACKGROUND

2.1. ATRIAL FIBRILLATION

AF is a supraventricular arrhythmia characterized by uncoordinated activation of the atria with consequent ineffective atrial contractions (7,11). AF can be diagnosed on an electrocardiogram (ECG) by no visible repeating P-waves and irregular RR intervals (when atrioventricular conduction is intact). An episode should last at least 30 seconds on a single-lead ECG tracing or be present on a conventional 12-lead ECG recording to be diagnosed. Various classifications of AF have been suggested. It is, however, often classified into five categories based on presentation, duration and termination: First diagnosed AF, paroxysmal (terminated within 7 days of onset), persistent (sustained ≥7 days), long-standing persistent AF (continuous AF >one year and a rhythm control strategy is chosen) and permanent (AF is accepted and rhythm control strategy is not chosen) (7). Patients with AF may experience symptoms including dyspnoea, palpations, fatigue and chest pain, while approximately 15% to 30% are asymptomatic (12). Also, AF related outcome include a higher risk of death, stroke, heart failure, cognitive decline, depression, impaired quality of life and hospitalizations as summarized in European Society of Cardiology (ESC) guidelines for AF 2020 (7).

Well established risk factors for AF include age, valvular heart disease, heart failure (7,13–15), male sex, hypertension, diabetes and ischemic heart disease/myocardial infarction (7,13,14). Furthermore, less validated triggers such as alcohol, coffee/caffeine, high-level endurance training/vigorous exercise and psychosocial factors may also influence the risk of AF (14,16). It is suggested that more than 50 % of AF burden could be avoided by optimizing cardiovascular risk factors (17). However, traditional risk factors cannot explain all cases of AF and some risk factors remain unexplained (18). Additionally, many factors may have a cumulative effect on the risk of AF (14) which makes it difficult to estimate the specific impact of a given risk factor as several different risk factors may be present in each individual patient. Furthermore, the influence of each risk factor may vary with age as, for example, genetic factors and endurance sport may have a larger role in younger patients than the oldest, while other factors are more important in elderly (19).

The pathophysiology of AF is complex and not fully understood (20). The mechanism involves local ectopic firing and reentrant circuits (21,22), where paroxysmal AF have predominance of local triggers around the pulmonary veins whereas persistent and permanent AF have more reentry substrates (22). Electrical, structural and autonomic remodelling are involved in the development and progression of the atrial substrate and consequently AF (22).

Treatment of AF involves several aspects, including treatment of underlying cardiovascular conditions, oral anticoagulants (OACs) which can reduce the risk of stroke, antiarrhythmic drugs, cardioversion or ablation are among initiatives, which may improve e.g. symptoms and quality of life (7). Despite treatment guidelines, difference in treatment for AF seems to exist for various reasons. For example, although OAC is recommended for patients with high risk of stroke, underuse of OAC for patients with high risk of stroke seems to be present (23).

Atrial flutter is another common supraventricular arrhythmia, which often coexists with AF. The two conditions have a well-established clinical relationship (24) and atrial flutter is often combined with AF in both clinical trials on treatment and in large epidemiological studies (25) such as Framingham Heart Study (3), Atherosclerosis Risk in Communities (17) and Rotterdam Study (26).

2.2. SOCIOECONOMIC FACTORS

A variety of terms to measure and monitor socioeconomic inequalities exists, for example social class, socioeconomic position (SEP) or socioeconomic status (SES). Many do not distinguish between the terms while others argue that there are different theoretical bases behind them and prefer SEP over SES (27–29). The reason SEP might be preferred over SES is that it also reflects the resources a person have, for example an educational degree or income, and not only the status, which refers to the rank- or prestige-related characteristics a person have (28). Hence, in this PhD-thesis, the term SEP has been used instead of SES when talking about socioeconomic inequality in general terms. However, when possible and appropriate, the specific SEF referring to have been used, for example, income, education or occupation. Although there are similarities between the SEFs, they cannot be used interchangeably as each indicator captures a distinct aspect of SEP (30) and there may be different causal mechanisms behind them (31).

Education is a common indicator of SEP (8,27,30,32), and for good reasons as it has several advantages. It is normally easy to measure (27,30), is often predictive of higher income and better jobs, is quite stable throughout life (except early adulthood) and is normally accomplished in early adulthood before poor health and diseases occur, and consequently, the likelihood of reverse causation is small (30). However, the value of education as an indicator of SEP may vary between subgroups (8) and birth cohorts (8,27). Furthermore, the social meaning and consequences of education varies with different periods (30), and a study with participants of different ages may be biased if birth cohorts are not accounted for as older birth cohorts will be over-represented among the lowest educated (27).

Income is another common indicator of SEP, and contrary to education, it is a more direct measure of material resources (27). In some countries, income may provide direct access to medical care (8), but in Denmark, where health care services are free,

income might have a more indirect association with health, for example through buying high quality, healthy food (33), and other quality resources. A high income may also foster self-esteem (27) which in turn might be linked to better health (34). Some disadvantages with income are that it is an unstable measure, and reverse causality may be an issue as income can be influenced by health status. Furthermore, age is important when income is an indicator, as it is probably a more reliable indicator during the prime earning years and less sensitive for younger and older adults (27).

Generally, cohabiting status is not the most used indicator of SEP, however, marital status is sometimes referred to as an item that can be used to measure SEP (35). Moreover, it is well known that social relationships are important health determinants, and that loneliness and social isolation are linked to higher risk of mortality. Cohabiting status can not tell us if a person is e.g. lonely or have a poor social network. However, it might, to some degree and among other things, serve as a marker of social isolation if a person is e.g. living alone (36).

Otherwise, SEP is a complex term and a variety of items other than income, education and cohabiting status may be used to measure components of it (29,35), for example wealth, occupation, contextual variables such as neighbourhoods (30) or other SEP items such as demographic information such as residency (35).

In summary, SEP is not universally defined, and several factors might influence the SEP of a person.

2.3. SOCIOECONOMIC INEQUALITY IN HEALTH

Health inequality is defined as the difference in health between groups or individuals. However, it does not tell if the inequalities are unjust and avoidable. For example; it is quite natural and unavoidable that most people in their 20s have a better health than people in their 60s. Hence, the latter example illustrates a life stage difference and a natural cases of health inequalities. The term *health inequities*, however, are defined as systematic differences in health which is unjust and avoidable. Social inequality in health is, in general, considered health inequities as they are unfair and avoidable (37,38).

Social inequalities are killing people prematurely on a large scale and it is a major problem worldwide. For example, life expectancy in Sweden is more than 80 years whereas it is less than 50 years in many African country (39). Furthermore, social inequality is not only a problem of injustice. It is also a public economic problem because social inequality negatively impacts several aspects of the welfare state such as economic growth and employment. Finally, it is a public health problem as the health potential of populations are not fulfilled (40).

Social inequality in life expectancy and health is not just an issue in-between country, but also within countries with any levels of income. Hence, poor health follows a social gradient; the lower SEP, the poorer health (39). Consequently, social inequities in health are also a problem in a welfare society such as Denmark. In 2020, the Danish Health Authority published a report where they focus on social inequality in health in Denmark (41). A scientific understanding of the association between social factors and health outcomes are important for political intervention (40).

2.4. SOCIOECONOMIC INEQUALITY AND ATRIAL FIBRILLATION

It has been known for decades that SEFs are strong predictors of mortality and morbidity and that it is extending across numerous diseases (32) such as ischemic heart disease (8), heart failure (42) and stroke (43). Furthermore, low levels of SEFs are also associated with several cardiovascular risk factors such as hypertension, high body mass index and smoking (8).

The literature regarding SEFs and AF have previously been sparser but it has, in line with other AF related research (44), increased during the last two decades (10). Despite that, no consistent association between SEFs and the risk of AF seems to be established as studies have found contradicting results (10). Several factors could explain those conflicting result, for example, the use of different SEFs, various study design, confounding variables (10), overadjustment of mediators and potential effect modification by e.g. sex and age.

There is an abundance of studies indicating that low level of SEFs are associated with a lower risk of receiving NOAC (10,45,46). When looking at warfarin or OAC in general, however, several studies suggest no significant socioeconomic difference in treatment (10,47–49), although some studies indicate an association between high levels of SEFs and more prescribed warfarin (50,51). However, there is lack of studies focusing on changes over time and if there is an indication of OAC initiation.

It is well known that conditions such as myocardial infarction and cardiac arrest are associated with detachment from employment (9,52). Regarding AF, the clinical symptoms and sequalae may range from not present at all to severe disability. Yet, a United States (US) study found that AF placed a significant burden on employers related to both costs, absence and productivity (53). Hence, if and how much AF contributes to permanent work disability is not known.

CHAPTER 3. AIMS AND HYPOTHESES

The overall aim of this thesis was to examine socioeconomic inequality in the risk of AF, probability of OAC initiation in patients with AF, and the social consequence in terms of permanent work disability and work participation following AF. The anticipation was that there was socioeconomic inequality in the risk of AF, OAC initiation in patients with AF and social consequences associated with AF.

More specifically, following aims and hypotheses were explored in the three studies of which this thesis was based:

Study 1
Aim: To examine socioeconomic inequality measured by income and education and the risk of an AF diagnosis stratified on different age categories and sex in the Danish population.
Hypothesis: That low income or low education were associated with an increased risk of an AF diagnosis and that the associations varied with age and sex.

Study 2
Aim: To examine socioeconomic inequality measured by education, income, cohabiting status and OAC initiation treatment in AF patients with high risk of stroke according to guidelines the year of inclusion.
Hypothesis: That AF patients with high risk of stroke with low income, low education or living alone had a higher risk of not being initiated with OAC according to guidelines. We also hypothesized that the inequality was diminished over time when more clear and detailed guidelines were implemented in clinical practice.

Study 3
Aim: To examine the association between AF and risk of permanent work disability and poor work participation, and if there was socioeconomic inequality in the risk of work disability and work participation in terms of effect modification by income, education and cohabiting status.
Hypothesis: That patients with AF had a high risk of work disability and poor work participation, especially AF patients with low income, low education and patients living alone.

CHAPTER 4. METHODS

4.1. DATA SOURCE

The three studies of this PhD-thesis were based on Danish, nationwide registers. All individuals living in Denmark have a unique personal identification number (CPR-number) which was used to link individuals across different registers as illustrated in Figure 1 (54,55). All registers were used in Study 1-3, except "the register for social benefits and other transfer payments" (the DREAM database) (56) which was only used in Study 3. A short description of the registers is presented in the following section whereas a more detailed description of the pros and cons of the registers are discussed in "Chapter 6.4. Methodological considerations".

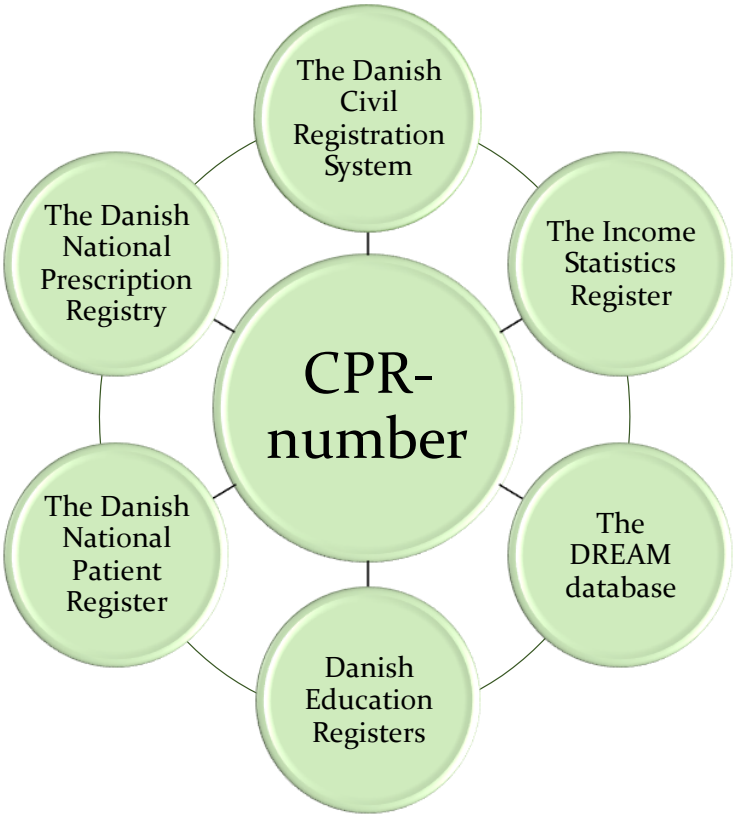

Figure 1. The different registers used and how they can be linked together with individual personal identification numbers (also called CPR-number) (54,55).

The Danish Civil Registration System

Since 1968, the Danish Civil Registration System has recorded information on Danish residents, which include variables such as gender, age, vital status, place of residence and the unique personal identification number (57).

The Danish National Patient Register

The Danish National Patient Register (DNPR) was originally established in 1977 and it keeps information about, for example, diagnoses and surgical procedures performed at hospitals (58). Until end of 1993, diagnoses were coded according to International Classification of Diseases (ICD) edition 8, and from 1994 according to ICD edition 10 (ICD-10). Surgeries were coded according to Danish Classification of Surgical Procedures and Therapies until 1996, and hereafter Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (59). The register is an important tool for epidemiological (59), public health and biomedical research (58). Yet, possible fallacies must be noticed and taken into account when using the register (58) such as varying validity of clinical data (59).

The Danish National Prescription Registry

The Danish National Prescription Register administered by Statistics Denmark is a sub-register of the Register of Medicinal Products Statistics by the Danish Medicines Agency. It is a unique register as it provides information on all dispensed prescriptions in the entire nation of Denmark since 1994 on an individual level. Each drug has an Anatomical Therapeutic Chemical classification (ATC) code. Only few studies have examined the validity of the register, however, several factors indicate high validity, for example, the sold prescription drugs are defined by a barcode and not dependent on physicians recording it (60).

There is some lack of completeness in the DNPR partly because certain diseases are treated by general practitioners and therefore not registered in the DNPR (only patients with contact to the hospital are registered in the DNPR) (59). To compensate this, the Danish National Prescription Registry (60) can be used to identify some incompletely registered conditions. For example, patients with diabetes mellitus can be identified with an ICD-code of diabetes mellitus in the DNPR and/or a disease-specific prescriptions of insulin and/or other antidiabetic drugs in the Danish National Prescription Register (59).

Danish Education registers

Denmark has a long tradition of gathering data on education; individual-level marks were administered by the Danish Ministry of Education since 1910. Today, Danish Ministry of Education and Statistics Denmark collaborate on the generation of Danish

education registers. Several education registers are available, for example, the Student Register and the Population's Education Register. The latter are known to have high validity, and of persons born between 1945-1990, 97% had non missing information. There might be more limited information on immigrants (61) and older people (61,62).

The Income Statistics Register

The Income Statistics Register, available since 1970, describes the income of the Danish population, including wages but also private pension and public transfer payments. The income data is assumed to be of high quality, however undeclared work and erroneous reports to tax authorities will not be registered (63).

Register for social benefits and other transfer payments (DREAM)

The DREAM database contains information on all public transfer payments such as sickness benefits, disability pension and early retirement for Danish citizens on a weekly basis. The variables make it possible to look at the social consequences of AF and other diseases such as exclusion from the labour market. Hjollund et al. concluded that the DREAM database was feasible to use for follow-up of e.g. social consequences of disease (56). This register was only used for Study 3.

4.2. EXPOSURE: SOCIOECONOMIC FACTORS AND ATRIAL FIBRILLATION

In Study 1 and Study 2, SEFs were used as exposure. In Study 3, the results were stratified on SEFs; however, AF was exposure. Income and education were used in all three studies, whereas cohabiting status were used in Study 2 and Study 3.

Education

Information about the highest attained educational level was originally organized into no education/unknown, primary education, lower secondary education, general upper secondary, vocational education and training, short-cycle tertiary education/academy profession programmes, bachelors or similar level, master or similar level or PhD degree or similar level (62,64–66). The specific division into low, medium and high were based on birth cohorts in the population to account for over representation of older people in low educated levels. For example, in 1920, probably less than 5% of a 7^{th} grade continued further school education (67). compared to 94.5% of all 18-30 years old finished 9^{th} grade in 2012 (68). Accordingly, the meaning of education has changed with birth cohort and educational status is not comparable for a 30-year-old versus an 80-year-old in e.g. year 2000. Hence, education was divided into low, medium and high based on birth cohort. The specific cut-off points that were chosen

were based on educational attainment in the general population as described in the individual studies (Study 1-3).

Income

We used household income as proxy for income, which is the equivalized family income calculated with the following formula as described at Statistics Denmark web page:

Disposable household income / (0.5 + (0.5 × number of persons above 14 years) + (0.3 × number of persons below 15 years)) (69).

By doing so, we were able to compare different families with different living conditions (69). For example, two families with the same income will have different resources if they are a family of three versus a family of ten. Furthermore, it is not appropriate to compare the income of a 30-years-old versus a 50-years-old, as a 50-years-old in most cases have a longer career and seniority with consequently a higher salary. Hence, the income gap between a 30- versus 50-year-old does not necessarily indicate a different social level. Furthermore, it is important to keep in mind, that factors such as the general increase in salary and inflation effects income, and it makes it problematic to compare incomes over time. This is the reason we have split the household into age- and year specific terciles and hereby accounted for those problems (70–72).

Cohabiting status

Marital status is sometimes used as an item to measure SEP (35); however, we used cohabiting status instead of marital status as many Danish couples are not married but live together. Cohabiting status was categorized into living alone or not living alone.

Atrial fibrillation

AF was exposure in Study 3. We used the ICD-10 code I48 to identify incident cases of AF or atrial flutter in the DNPR. Rix and colleagues concluded that the ICD-code of AF/atrial flutter diagnosis obtained from the DNPR was of high validity and that it was suitable for register-based research (positive predictive value [PPV] was 92%) (73).

4.3. STATISTICAL METHODS

In this PhD-thesis, many different statistical methods have been used. For descriptive statistics, standard methods such as frequency and percentage for categorical variables and means and standard deviation (SD) for continuous variables were used. For main analysis, however, we used various methods depending on type of data and aim of the

study. In order to better understand the rationale behind choice of methods, a general description of some of the methods and in which situation they can be used, will be presented in the follow in section.

Linear regression

In Study 3 we wanted to analyse the continuous variable work participation score (WPS) (74) between AF cohort versus matched reference cohort. Hence, it was possible to simply use multivariable linear regression to make adjusted analysis of the binary exposure (AF cohort vs. matched reference cohort) and various confounding variable (75). To avoid floor and ceiling effect (76) of the WPS variable (many with 0% and 100% and fewer in between), it was equipped with bootstrap calculation of standard errors (77).

The Generalized linear model

In Study 2 we compared "risk" of initiation of OAC after -30 to +90 days after index date (incident AF) between low levels of SEFs versus high levels of SEFs. In Study 3, we compared risk of permanent work disability within 15 months between AF cohort and reference cohort. In both studies, outcome variable was binary. Logistic regression is often used in analyses where outcome is binary. However, the measure of association in logistic regression is odds ratio (OR), and OR is not necessarily an easy measure to interpret (78). As an alternative, a generalized linear model (GLM) (79) can present measure of association in risk difference (RD) or relative risk (RR), which many find easier to interpret. The GLM consist of three parts. First, a regression part where exposure, adjusted variables and regression form are specified. Second, outcome variable is described as e.g. binary or continuous. Finally, a link function which decides whether measure of association is e.g. RD or RR (80).

The Cox proportional hazards regression model

In Study 1, we compared incidence of AF in a population in different age groups, thus, the data was censored time-to-event data. Censored data means that some individuals do not reach the event but instead reaches end of the study, dies or emigrates (81). Comparison of risk between levels of SEFs, could be shown with a Kaplan-Meier estimator, or in case of competing risks, Aalen-Johansen estimator. However, it is generally not possible to make adjusted comparisons on those methods. Alternatively, Cox regression can be used to crude and adjusted comparisons of incidences (82). In medical literature, the Cox model is the most used regression model for time-to-event data (83). In lay terms, the hazard rate can be looked at as the probability that the event will occur in the next time interval, given that the event has not already occurred (81,84). Assuming that the hazard function over time between two individuals are proportional, the measure of association from the Cox regression model is Hazard Rate Ratio (HR). HR compares hazard rates between the groups (81). Also, the Cox

model gives the opportunity to handle competing risks by calculating the cause-specific hazards. The cause-specific hazard is calculated by censoring the competing event, which usually is death (85). The assumption of proportional hazards must be checked when using the Cox model (81).

As discussed above, the Cox model is an appropriate method in many situations, but it has limitations. Methods to express the results of censored data in absolute risks and at the same time adjust for variables have been limited (82).

The Pseudo-observation method

In Study 1, comparisons of AF incidences between levels of SEFs were supplied with comparisons of risk of AF in a period of 15 years. Those analyses are made using the pseudo-observation method. This is a relatively new method which allows, contrary to the Cox model, calculation of both crude and adjusted relative risks or absolute risks of time-to-event-data (82). Another difference from the Cox model is that the time-window must be predefined when the risk is calculated. In brief, the methods consist of two parts. First, the time-to-event data is transformed into pseudo-observations which has the property that the average pseudo-observation corresponds to the cumulated incidence in the given time window. Second, a GLM can be fitted to the pseudo-observations (86), where after we can make regression models for RD or RR as described in the section “Generalized linear models” (80). Overall, the pseudo-observation method might seem straightforward to use. However, it is important to mention that several assumptions in the data must be met in order to correctly estimate the risks (82). Yet, it is beyond the scope of this thesis to describe.

CHAPTER 5. STUDIES

5.1. STUDY 1

Study 1 was published in *Journal of Epidemiology and Community Health* and was authored by Elin Danielsen Lunde, Albert Marni Joensen, Søren Lundbye-Christensen, Kirsten Fonager, Søren Paaske Johnsen, Mogens Lytken Larsen, Martin Berg Johansen and Sam Riahi (70).

Aim

To investigate the association between level of education, level of income and the risk of being diagnosed with AF in a population of Danish residents included in the period January 1, 1996 to December 31, 2005 at the age 35, 50, 65 and 80 years old at date of inclusion.

Our hypothesis was that there would be an association between low level of education, low level of income and the risk of AF and that the association would vary with age and sex.

Methods

The study design was register-based cohort study. We included all Danish residents aged 35, 50, 65 or 80 years old from 1996 to end of 2005. Exposure was income and education. Outcome was hospital diagnosed incident AF.

We used Cox proportional hazard model regression (87) in order to estimate the cause-specific HRs and 95% confidence intervals (95% CI) with age as time scale. The participants were followed from age of entry until AF, emigration, death or end of study (December 31, 2015). We also calculated the absolute risk and RDs with 95% CI calculated over a 15-year period starting at baseline age (for example from 35 years to 50 years) by using the pseudo-observation method (86). The results were stratified according to sex and age cohort at baseline. Choice of confounders to adjusted for were determined apriori and are presented in Table 1.

Table 1. Confounders adjusted for in different models by education and income.		
	Income	**Education**
Model 1 Crude	None	None
Model 2 Sociodemographic factors	Education, cohabiting status and place of residence.	Income, cohabiting status and place of residence.
Model 3 Model 2 + Comorbidity	Model 3a: DM, alcoholism, hyperthyroidism, obesity, VHD, CHF, congenital heart disease, hypertension, COPD, IHD, PAD and renal disease.	Model 3b: DM, obesity, hyperthyroidism, congenital heart disease, alcoholism.

Abbreviations: DM, diabetes mellitus; VHD, valvular heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; PAD, peripheral artery disease.

Main results

In total, 2,173,857 persons in the predefined age cohorts were included in the study, and 151,340 cases of AF or atrial flutter occurred during follow-up (median follow-up time was 13.6 years).

For the 35 years old, sex distribution was approximately equal (men 50.6% and women 49.4%) whereas there were more women in the cohort of 80 years old individuals (men 38.7% women 61.3%). Hypertension was the most common condition in all age groups with a baseline prevalence of 26.0% for the 80 years old.

The crude and adjusted HRs showed the same pattern; however, the adjusted results were weaker. Figure 2 shows HRs for the fully adjusted model (model 3a and 3b). Women with medium education and high education had a statistically significant lower HRs of AF compared to women with low education; however, the association was stepwise weakened with increasing age group, and even reversed for the 80 years old. A similar pattern of results was seen for men. Women with medium income and high income had lower HR of AF compared to women with the lowest income, most significant in 50-year-old women at baseline and the association was subsequently weakened with increasing age group. Men with medium and high income in the age 35 and 80 at baseline had higher HRs of AF than men with low income whereas men in the age of 50 and 65 had a lower HR.

RDs showed a similar trend as HRs, yet, a smaller association among the youngest, reflecting that incidence of AF are low in this group. For example, RD for medium educated women was -0.3% (95% CI -0.4 to -0.1) (whereas the HR were 0.62 (95%

CI 0.50 to 0.77)) and for medium educated men -0.2% (95% CI -0.4 to -0.0) (HR was 0.85 (0.76 to 0.96).

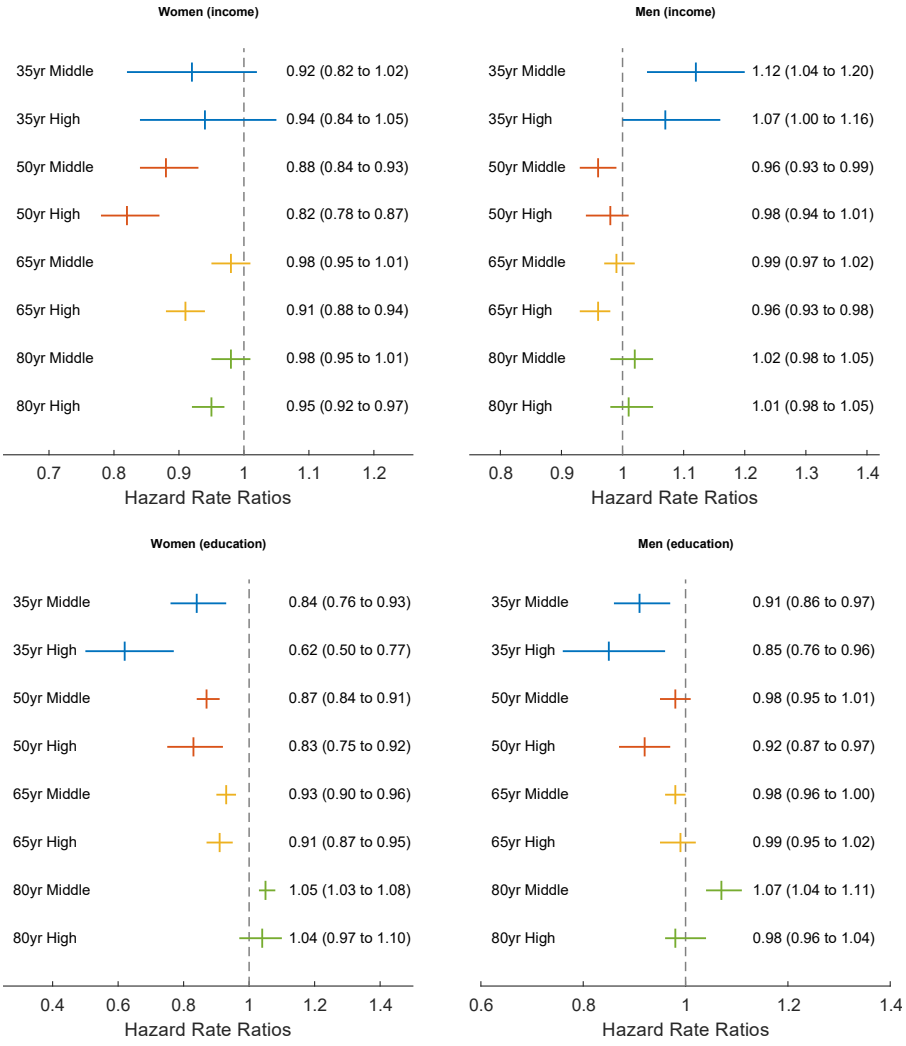

Figure 2. *Hazard Rate Ratios (HRs) for AF stratified on education, income and sex. Adjusted for Model 3a (income) and 3b (education). Reference (1) is the lowest educational and income level. This figure is reused with permission from Study 1: Lunde ED, Joensen AM, Lundbye-Christensen S, Fonager K, Paaske Johnsen S, Larsen ML, et al. Socioeconomic position and risk of atrial fibrillation: A nationwide Danish cohort study. J Epidemiol Community Health. 2019;(5):7–13.*

Conclusion

Overall, there was an association between individuals with low education and low income and the risk of being diagnosed with AF; however, the association varied with age, sex, socioeconomic factors and measure of association. Individuals with low education were associated with increased HRs of AF for the youngest age cohort but the association was reduced with increasing age and partly reversed for the eldest age cohort. Comparable but weaker associations were seen for income except that men in the youngest age cohort with high income had higher HRs of AF compered to men with low income. The absolute risk difference, however, was small for the youngest cohort as AF is a rare disease in young individuals.

5.2. STUDY 2

Study 2 was published in *BMJ Open* and was authored by Elin Danielsen Lunde, Albert Marni Joensen, Kirsten Fonager, Søren Lundbye-Christensen, Søren Paaske Johnsen, Mogens Lytken Larsen, Gregory YH Lip and Sam Riahi (71).

Aim

To investigate the association between different levels of education, income and cohabiting status and initiation of oral anticoagulation (OAC) therapy in the period 1999 to 2016 in a Danish population of patients with AF.

Methods

The study design was register-based observational study. We included all Danish residents 30 years old or older with a registered diagnosis of AF or atrial flutter at a hospital and with high risk of stroke according to applicable guidelines at the time of inclusion between May 1, 1999 to October 2, 2015.

Exposure was cohabiting status, education and income.

Outcome was initiation of OAC defined as a prescription of novel oral anticoagulation (NOAC) or vitamin K antagonist (VKA) within 30 days before to 90 days after incident AF (index date) (88,89).

As outcome-status at 90 days are known for all patients, a generalized linear model (GLM) (79) was used to obtain the results as absolute risks and risk difference (RD). We adjusted for potential confounders in four steps; a crude model, model 1 (age), model 2 (model 1 and sociodemographic factors) and model 3 (model 2 and comorbidity) as shown in Table 2.

Table 2. Overview of confounders adjusted for in different models.		
	Income/Cohabiting status	**Education**
Crude	None	None
Model 1 Age	Age	Age
Model 2 Model 1 + Sociodemographic factors:	Age, education, residence and cohabiting status.	Age, income, residence and cohabiting status.
Model 3 Model 2 + Comorbidity:	Model 3a 1999-2002: Model 2, ischemic stroke, systemic embolism, TIA, DM, hypertension, CHF, MI, VTE, hip/knee arthroplasty and antiplatelet drug. 2002-2007: As 1999-2002, + thyrotoxicosis. 2007-2011: As 2002-2007 and IHD. 2011-2013 and 2013-2016 As 1999-2002 + PAD, bleeding, renal disease, liver disease, and NSAID.	Model 3b 1999-2002: Model 2, VTE and DM. 2002-2007: As 1999-2002, + thyrotoxicosis. 2007-2011: As 2002-2007. 2011-2013 and 2013-2016 As 1999-2002 + alcoholism and NSAID.

Abbreviations: TIA, transient ischemic attack; DM, diabetes mellitus; MI, myocardial infarction; CHF, congestive heart failure; VTE, venous thromboembolism; IHD, ischemic heart disease; PAD, peripheral artery disease; NSAID, nonsteroidal anti-inflammatory drug.

Main results

In total, 154,448 patients with AF and with high risk of stroke were included in the study and 74,551 (48.3%) of the patients redeemed a prescription of an OAC drug in the period of -30 to +90 days of incident AF. Overall, 47.3% were men and mean age was 78.2 years (Standard Deviation 9.7). As the study included a population with high risk of stroke, comorbidity was frequent; 66.9% had hypertension, 11.2% heart failure and 18.2% diabetes mellitus. A total of 18,899 (12.2%) individuals died during follow-up.

Trends in initiation of OAC stratified on socioeconomic factors

Figure 3 shows time trends in initiation of OAC stratified on SEFs for patients with AF and with high risk of stroke. It shows that use of OAC increased over time and

was almost doubled from the beginning of the period to the end of the period. Also, the crude results indicated that patients with low education, low income and living alone received less OAC compared to patients with high education, high income and not living alone. The crude inequality for education and cohabiting status seem to be smaller from around 2011. After adjusting for age (the figure shows the percentage for a person aged 78 years old), the observed inequality was attenuated and more constant over the entire period.

From 2011, VKA was less used in all socioeconomic strata even though initiation of OAC (NOAC + VKA) increased.

Crude risk differences in initiation of OAC or NOAC

Crude RD for OAC initiation in education (lowest versus highest education) was reduced from e.g. 11.1% (95% CI 5.3 to 16.9) in 1999-2002 to 4.5% (2.4 to 6.7) in 2013-2016 for women. The corresponding results for men were 12.9% (9.0 to 16.8) to 5.6% (3.5 to 7.7). Crude RD for cohabiting status (living alone versus not alone) was 8.6% (6.6 to 10.6) in 1999-2002 and 10.8% (9.1 to 12.4) in 2007-2011 and 7.8% (6.4 to 9.2) in 2013-2016 for women. Similar results were seen for men; 8.5% (6.2 to 10.8), 7.8% (5.9 to 9.7) and 7.9% (6.3 to 9.4), respectively. Crude RD for income (lowest versus highest income) was more constant over time; for women it was e.g. −1.3% (−3.9 to 1.2) in 1999-2002 and 1.7% (−0.0 to 3.4) in 2013-2016. For men, there was inequality, however more constant with time; 5.1% in 1999-2002 (3.6 to 6.6) and 5.8% (4.1 to 7.6) in 2013-2016.

Women and men with high income, high education and not living alone had a higher likelihood of receiving NOAC compared to low educated, low income and living alone, and the RD increased with time, e.g. women with low education in 2011-2013 was 5.6% (3.5 to 7.8) and 8.6% (6.4 to 10.9) in 2013-2016.

Adjusted risk difference in initiation of OAC or NOAC

Figure 4, Figure 5 and Figure 6 show adjusted RDs for OAC or NOAC (Model 3) in women and men with different levels of education, cohabiting status and different levels of income, respectively. They show a trend that men and women with higher levels of education, not living alone and higher levels of income had a higher likelihood of receiving OAC, however, compared with the crude results, the associations were attenuated and more constant over time.

For NOAC, adjusted RDs showed the same association even though the RDs were attenuated after adjusting for potential confounders.

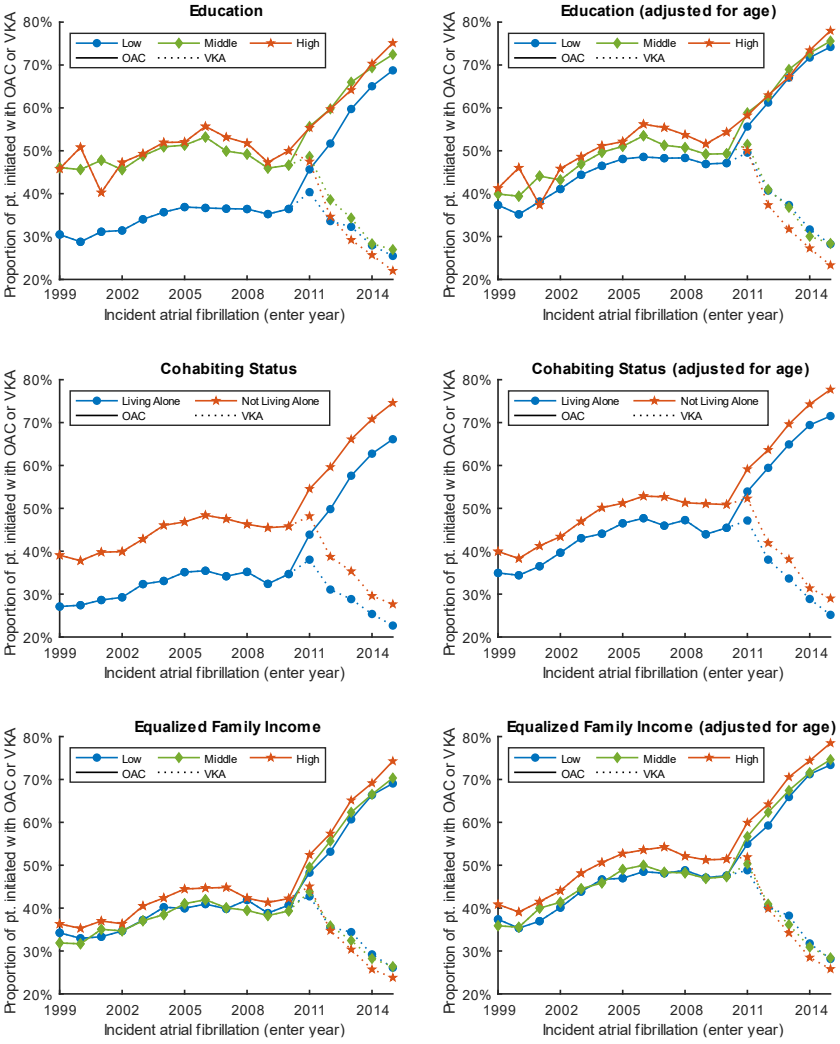

Figure 3. *To the left is percentage of men and women with AF and high risk of stroke (and therefore an indication for OAC therapy) being initiated with OAC drug (NOAC or VKA) or VKA alone showing patients with different levels of SEFs. In the right frame is the same graph, however, adjusted for age showing patients with mean age 78 years old. The figure is reused with permission from Study 2: Lunde, E. D., Joensen, A. M., Fonager, K., Lundbye-Christensen, S., Johnsen, S. P., Larsen, M. L., Lip, G.Y.H., & Riahi, S. (2021). Socioeconomic inequality in oral anticoagulation therapy initiation in patients with atrial fibrillation with high risk of stroke: a register-based observational study. BMJ Open, 11(5), [e048839].*

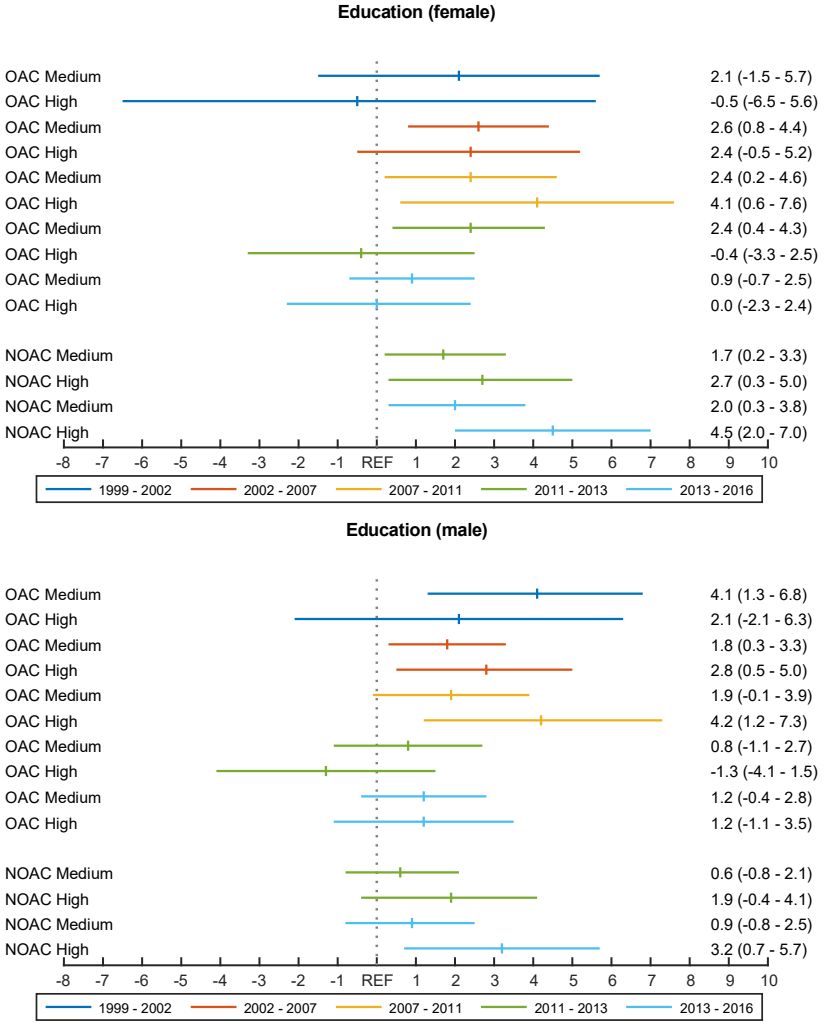

Figure 4. *Adjusted RDs (Model 3) for OAC or NOAC initiation for women and men with different levels of education (reference was low education).*

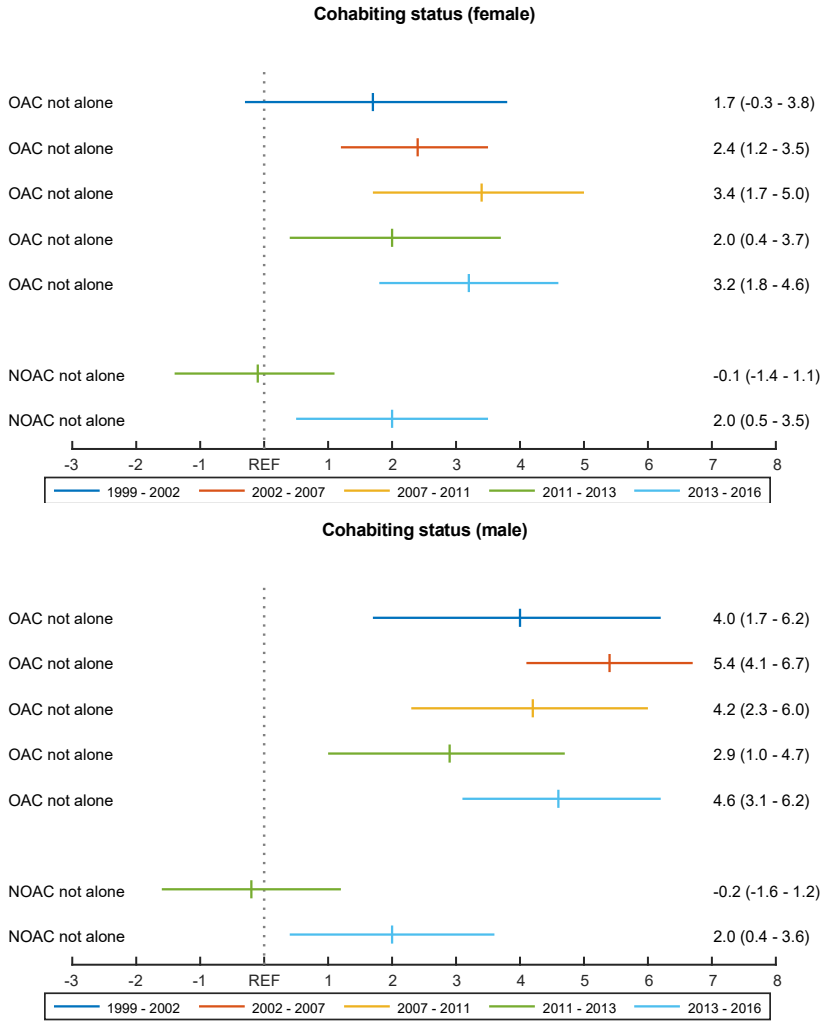

***Figure 5**. Adjusted RDs (Model 3) for OAC or NOAC initiation for women and men living alone versus not living alone (reference was living alone).*

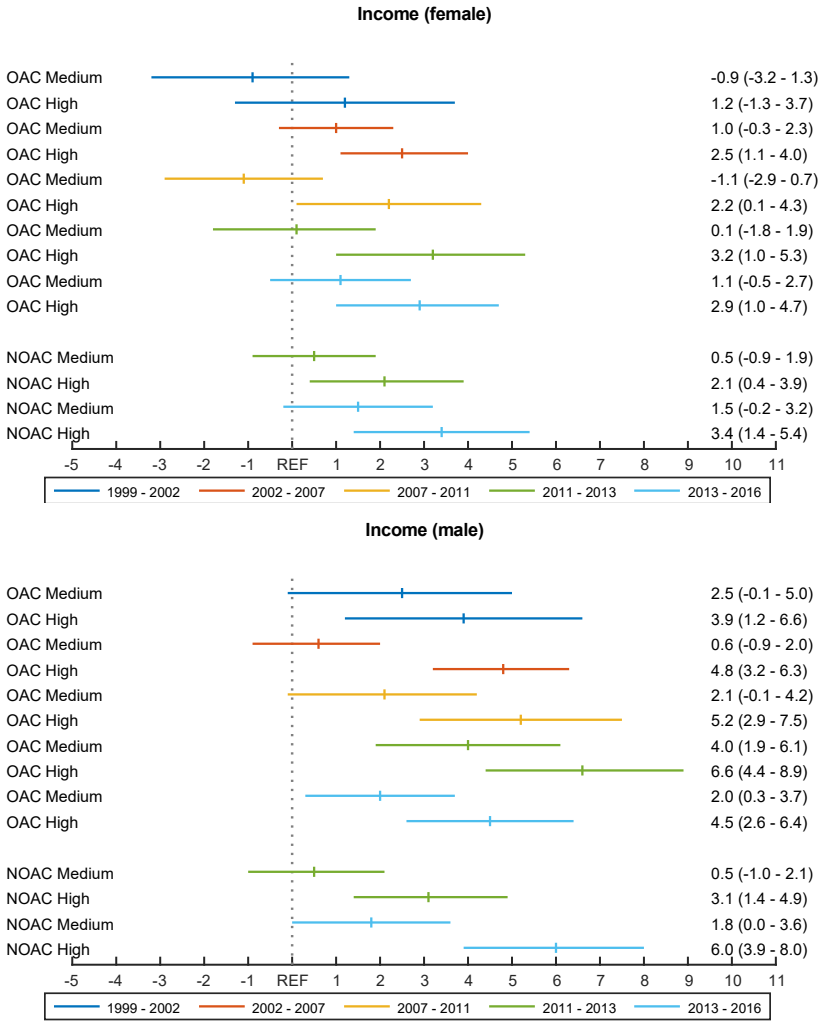

***Figure 6**. Adjusted RDs (Model 3) for OAC or NOAC initiation for women and men with different levels of income (reference was low income)*

Conclusion

Overall, patients with AF and with low education, low income and living alone and with high risk of stroke had lower likelihood of receiving OAC (VKA and NOAC) and NOAC in the period 1999-2016. Around 2011, around the same time when new and specific guidelines were available, the crude inequality for initiation of OAC was reduced for education and to some degree for cohabiting status. After adjusting for age and other potential confounding variables, the association was still present but attenuated and more constant over time. The inequality in use of NOAC, however, increased with time for both education, income and cohabiting status.

5.3. STUDY 3

Study 3 is submitted for publication and was authored by Elin Danielsen Lunde, Kirsten Fonager, Albert Marni Joensen, Søren Paaske Johnsen, Søren Lundbye-Christensen, Mogens Lytken Larsen and Sam Riahi (72).

Aim

To investigate the association between AF and work disability and potential effect modification by SEFs.

Methods

This was a register-based cohort study including all Danish residents with hospital diagnosed incident AF or atrial flutter (index date) in the age ≥30 to ≤63 years old in the study period January 1, 2000 to September 30, 2014. To find a reference cohort from the Danish population, patients with AF were matched 1:10 with a random age- and sex matched individual free of AF at baseline from the general population. We excluded all patients who received permanent social security benefit, early retirement or state pension at baseline. In a sub analysis, we calculated work participation score (WPS) in a population who were still alive and not received permanent social security benefit 15 months after index date.

Exposure was AF and outcomes were work disability and work participation. Individuals receiving permanent social security benefit (disability pension or flexi-job) (56,90) were defined as having permanent work disability. Work participation was calculated as WPS from 0% to 100% in a 13-weeks period one year after index date with number of weeks being self-supported in the numerator and total number of weeks in the denominator (74).

For the binary outcome permanent work disability, we used a GLM (79) to calculate absolute risk and RD and 95% confidence intervals (95% CI) over 15 months in different SEF strata. Competing risks of permanent work disability were death, state pension, early retirement and emigration. We adjusted for potential confounder as presented in Table 3.

For the continuous outcome WPS, difference between AF cohort and matched reference cohort was calculated using multivariable linear regression (75). WPS was not normally distributed across all 3 months; hence, we used bootstrap (77) with 1000 replications for calculation of standard errors.

All analyses were stratified on income, education and cohabiting status.

Table 3. Overview of confounders adjusted for in work disability analysis.	
Model 1	Age, sex, residence, income, education, and cohabiting status.
Model 2	Model 1 and CHF, IHD, DM, hypertension, renal disease, alcoholism, liver disease, abuse, peripheral vascular disease, connective tissue disease, backpain and schizophrenia.
Model 3	Model 2 and stroke, dementia and anxiety/mood disorder/depression.

Abbreviations: CHF; congestive heart failure, IHD; Ischemic heart disease, DM; diabetes mellitus.

Results

Overall, 41, 856 patients with AF and 418, 560 matched individuals were included. After excluding those who received permanent social security benefit, early retirement, state pension at baseline or missing SEFs, 28, 059 patients with AF and 312, 667 in the matched reference cohort remained.

Mean age of participants were 54.5 years old (54.4 in AF cohort and 54.5 in matched reference cohort) and 71.1% were men (72.7% in AF cohort and 70.9% in matched reference cohort). All baseline morbidities were more common in AF cohort, for example, 12.5% had hypertension in matched reference cohort versus 30.0% in AF cohort.

Table 4 shows risk of permanent work disability. Absolute risk of work disability after 15 months was higher for individuals in AF cohort compared to individuals in matched reference cohort. Adjusted RD showed the same; however, the strength of the association was attenuated. Risk of work disability was higher in strata with lower income, lower education and living alone compared to risk in strata with high income, high education and living together with someone.

Table 5 shows WPS for AF cohort and matched reference cohort. WPS was higher in matched reference cohort compared to AF cohort. The difference between AF cohort and matched reference cohort was stronger in lower SEF strata compared to higher SEF strata.

Table 4. Absolute risk and risk difference (RD) with 95% confidence interval (95% CI) for work disability stratified on SEFs.			
	Risk for AF cohort	**Risk for reference cohort**	**Adjusted RD (Model 2)**
All	4.5 (4.3 to 4.8)	1.3 (1.3 to 1.4)	2.4 (2.1 to 2.6)
Income			
Low	8.5 (7.9 to 9.2)	3.1 (2.9 to 3.2)	3.8 (3.2 to 4.5)
Medium	4.1 (3.7 to 4.5)	1.1 (1.0 to 1.1)	2.4 (2.0 to 2.8)
High	2.2 (1.9 to 2.5)	0.5 (0.5 to 0.6)	1.3 (1.0 to 1.6)
Education			
Low	6.9 (6.3 to 7.5)	2.1 (2.0 to 2.2)	3.7 (3.1 to 4.3)
Medium	4.4 (4.1 to 4.7)	1.3 (1.2 to 1.3)	2.3 (2.0 to 2.6)
High	2.4 (2.0 to 2.7)	0.8 (0.7 to 0.8)	1.2 (0.8 to 1.5)
Cohabiting status			
Alone	5.7 (5.2 to 6.3)	1.8 (1.7 to 1.9)	2.7 (2.1 to 3.3)
Not alone	4.2 (3.9 to 4.4)	1.2 (1.2 to 1.2)	2.3 (2.0 to 2.5)

This table consists of parts from Table 2 in Study 3: Lunde ED, Fonager K, Joensen AM, Johnsen SP, Lundbye-Christensen S, Larsen ML, et al. The association between newly diagnosed atrial fibrillation and work disability: a nationwide Danish cohort study [Submitted] (72).

Table 5. Work participation score (WPS) for AF cohort and matched reference cohort stratified on SEFs.			
	Mean WPS (AF cohort) %	**Mean WPS (ref. cohort) %**	**Adjusted WPS difference***
All	83.1	89.9	-5.9 (-6.3 to -5.5)
Income			
Low	67.7	78.3	-8.7 (-9.6 to -7.7)
Medium	84.3	91.5	-6.7 (-7.3 to -6.0)
High	91.6	95.4	-3.6 (-4.1 to -3.1)
Education			
Low	74.9	84.5	-7.7 (-8.7 to -6.7)
Medium	83.1	90.2	-6.2 (-6.8 to -5.6)
High	90.5	94.5	-3.7 (-4.3 to -3.0)
Cohabiting status			
Alone	78.4	86.4	-6.7 (-7.6 to -5.7)
Not alone	84.4	90.9	-5.6 (-6.1 to -5.2)

This table consist of parts from Table 3 in Study 3: Lunde ED, Fonager K, Joensen AM, Johnsen SP, Lundbye-Christensen S, Larsen ML, et al. The association between newly diagnosed atrial fibrillation and work disability: a nationwide Danish cohort study [Submitted] (72).

*Adjusted for age, baseline WPS and gender.

Abbreviations: Ref, reference; WPS, work participation score

Conclusion

Patients with AF had a risk of permanent work disability of 4.5% within 15 months. This was about three times higher than the risk of permanent work disability for the general population. The RDs between AF patients and reference cohort were slightly reduced after adjusting for confounders, however, still present. Risk difference between AF cohort and matched reference cohort in work disability and WPS was larger in patients with low income, low education and living alone compared to strata of patients with high income, high education and not living alone.

CHAPTER 6. DISCUSSION

The overall aim of this PhD-thesis was to investigate the association between SEFs and the risk and treatment of AF and social consequences following AF. We found an association between low education, low income and the risk of being diagnosed with AF; however, the direction and strength of the association varied with age, sex, SEF used, and measure of association used (Study 1). Low education, low income and living alone were associated with an increased risk of not being initiated with OAC according to guidelines, however, the crude inequality was reduced from around 2011 for cohabiting status and education. The association was attenuated and more constant over time after adjusting for potential confounders, especially age (Study 2). Patients with AF had higher risk of permanent work disability and lower work participation compared to individuals in the general population, especially if they had low level of education, low level of income or living alone (Study 3).

6.1. STUDY 1. SOCIOECONOMIC INEQUALITY IN THE RISK OF ATRIAL FIBRILLATION

In Study 1, we found an association between low level of education, low level of income and higher risk of being diagnosed with AF, especially for young and middle-aged women (35 and 50 years old), whereas the association was attenuated or even reversed for elderly (65 years old and 80 years old). Overall, prior studies have reported contradicting results between SEP and the risk of AF (10). Low educational status has been linked to a slightly higher risk of AF for men and women combined (48,91) or for women separately (92). However, other studies found no significant association between education and risk of AF (93,94). Similarly, low levels of income have been associated with a higher risk of AF (92), whereas another study reported that individuals with low income had lower HRs of AF (93). Our Study 1 suggests an explanation for the diverging results from prior studies; different impact of SEFs based on sex and various age. To our knowledge, no prior studies have examined the age-specific impact of SEFs on the risk of AF. We observed that the association was most prominent in young individuals. Various factors might explain this. For example, the aetiology of AF differs between young and elderly patients (19,95). For elderly, some typical causes of AF are ischemic heart disease, heart failure and hypertension, whereas these conditions are not common in younger individuals. For young, however, some potential causes include idiopathic, genetic, alcohol, smoking and BMI (95). Hence, SEFs might also play a more important etiological role in younger than elderly. Yet, the risk differences were very small due to the low incidence of AF in this age group indicating a less important public health burden. Even though the HRs between e.g. low education and AF was stronger for 35 years old individuals, the RD were slightly larger for e.g. 50 years old individuals at baseline because the absolute risk is higher in this age group. For elderly (especially 80 years old at baseline), however, the association were attenuated or even reversed for e.g. medium-

educated men and women. The cause of this might be multifactorial. One possible cause is the competing risk of death; lower educated individuals simply die before they have the time to develop AF. Indeed, risk factors for various diseases normally decline with ageing because they died or experienced an event previously (96). Furthermore, an information bias might have influenced the results as the completeness and validity of the educational variables were limited among the eldest (62).

The causal pathway linking SEFs to an increased risk of AF are not entirely obvious. In other words, there is no clear biological explanation linking SEFs to AF in the same way that e.g. smoking is linked to lung cancer (97). However, there might be many different pathways linking SEFs to AF. Low levels of SEFs are associated with unhealthy behaviours such as tobacco use, poor nutrition and physical inactivity (98) which in turn results in lifestyle related conditions such as diabetes, hypertension and obesity (99) which are known risk factor AF (100). Even though life-style related diseases typically occur in middle aged individuals after long exposure to unhealthy behaviour (99), obesity and overweight are also prevalent in young adults (101) and more often in lower educated (102). Obesity could, among other things, be one of the things which caused a higher risk of young, low educated individuals to have a higher risk of AF (103). Education is normally accomplished many years before AF occurs. Hence, the causal path connecting education to AF is probably mainly through other mediators (104). Regarding income, however, there might be other explanations as well. Low income can be associated with stress and economic worries, whereas high income might be associated with e.g. stressful jobs. As a result, stress and anxiety mediated through low or high income might promote AF through various factors, e.g. modulation of the autonomic nervous system (105,106). Young individuals might have more work related stress compared to older colleagues as they are still learning to adapt into working environment (107). Speculatively, the higher risk of AF in young men with high income might mediated through work-related stress, whereas the higher risk in middle-aged women could be stress triggered by economic worries. Supporting this explanation, it is previously suggested that occupational psychosocial stress might increase the risk of AF (108). Also, like education, some of the association observed for income might be mediated through other risk factors such as ischemic heart diseases and heart failure. Notwithstanding, because diseases also can cause low income, we don't know if they are part of the causal pathway linking SEFs to AF, or if they were present before an individual had low income and that they confuse the effect by acting as confounders.

6.2. STUDY 2. SOCIOECONOMIC INEQUALITY IN ORAL ANTICOAGULATION INITIATION

In Study 2, we found that initiation of OAC increased with time for all levels of SEFs. Also, individuals with high risk of stroke and low income, low education or living alone had a higher risk of not being initiated with OAC therapy. The inequality

observed was slightly reduced over time for education and cohabiting status whereas it was more constant over time for income. After adjusting for age, the association was reduced and more constant over the years. Furthermore, after adjusting for other potential confounders, the association was reduced even more, but it was still present.

An increased use of OAC over the years is consistent with prior studies (51,89,109). However, we also described a socioeconomic inequality in OAC initiation, which is only partly consistent with prior literature as previously summarized (10). For example, several studies found no statistically significant association between SEFs and treatment with OAC (47–49,110). A possible explanation for this lack of association could be the study population included in these studies; it was mainly an unselected population of patients with AF and different levels of stroke risk. Hence, as individuals from lower socioeconomic classes tend to have multimorbidity (111), patients with low SEFs might simply have had more stroke risk factors than individuals with moderate and high levels of SEFs. Consequently, the confounding effect of comorbidities might have biased the results towards no difference. This explanation is partly supported by looking at studies which found similar results as our (51,112). Arbel et al. included all patients with incident AF and a CHA_2DS_2-VASc score ≥ 2 and they reported that patients with a high socioeconomic class had a higher likelihood of receiving OAC with an OR of 1.19 (95% CI 1.12 to 1.26) (51). Another study, Sjölander et al., included patients with AF and with prior stroke (and consequently a high risk of stroke) and reported that patients with the highest income and highest education had a higher likelihood of receiving OAC with an OR of 1.16 (95% CI 1.04–1.30) and 1.18 (95% CI 1.04–1.35), respectively (112). Hence, studies examining social inequality in AF populations with high risk of stroke seem to have found similar results as ours.

Our results showed a reduction in educational inequality and inequality for cohabiting status in OAC initiation after adjusting for age (income was already age-adjusted at baseline as it was divided into age-specific tertiles). Paradoxically, older age is often a reason given for not initiating OAC even though age is a very strong risk factors for stroke in patients with AF. However, risk of bleeding is probably often overestimated (113). When looking at the socioeconomic trends in OAC initiation over time, the crude inequality was reduced around 2011. Speculatively, one possible theory of this observation could be that new and explicit clinical guidelines might have contributed to reducing the age-specific undertreatment. However, the age-adjusted inequality was more constant the entire period. Hence, some of the inequality observed for education and cohabiting status was probably explained by the fact that patients with lower socioeconomic levels simply are older than patients with higher socioeconomic levels. Additionally, the associations were slightly attenuated after adjusting for other potential confounders. Overall, some of the association observed between low levels of SEFs and initiation of OAC because patents of lower socioeconomic strata simply are older and sicker, and that clinicians then estimate their bleeding risk to be high and therefore not initiated OAC. However, after all potential confounders were

adjusted for, there was still a consistent socioeconomic inequality in initiation of OAC. The reasons for this are unknown. Possibly, it might be because patients of lower socioeconomic strata choose not to claim the prescription on OAC, that patients with lower levels of SEFs intentionally or unintentionally are discriminated or that the physician choose not to prescribe it for other unknown causes. Another Danish study looked at OAC uptake in depressed AF patients with high risk of stroke, and they found comparable results as ours: Depressed patients with AF and with high risk of stroke had a lower OAC uptake compared to a matched reference cohort. Like our study, they also found that this difference was attenuated over time (2005-2016). They concluded that depressed patients with AF might not have sufficient support to manage the condition (114). The latter point could also be applicable for our population; patients who is older, sicker and with lower levels of SEFs might need more support to handle the burden of AF in their life.

Our study also showed an association between low levels of SEFs and higher likelihood of receiving NOAC. This association was strong in both crude and adjusted models; though, slightly attenuated in adjusted models. This association has also consistently been reported by prior studies (45,46,115–119). The causal pathway linking low levels of SEFs to less NOAC prescribing are more obvious; NOACs are more expensive than VKA and thus probably deselected by patients who cannot afford it.

6.3. STUDY 3. ATRIAL FIBRILLATION AND SOCIAL CONSEQUENSES: RISK OF WORK DISABILITY

In Study 3, we found that patients with AF had approximately three times as high risk of work disability 15 months after index date compared to general population and the results were slightly attenuated after adjusting for potential confounders. Additionally, patients with AF who were alive 15 months after index date and who had not received permanent social security benefit had lower work participation. To our knowledge, no prior studies has examined the association between AF and permanent work disability. Yet, other studies have reported an association between arrythmias and disability, thus, primarily in older adults (120,121). Rohrbacker et al., however, examined the burden of AF and other arrhythmias in an employed population. They found that arrhythmias were present in 1.05% off all employees and 3.38% of male employees aged ≥55 years. They concluded that workers with a cardiac arrythmia, especially AF, was a burden to the workforce due to e.g. many days absent from work, lower productivity and work absence costs (53). Our study supports these findings.

AF was clearly associated with a higher risk of permanent work disability and lower worker participation. The cause of this is probably multifactorial. As seen in baseline characteristics of AF cohort versus matched reference cohort, all comorbidities were more prevalent in AF cohort. Hence, some of the association observed might be confounded by the fact that individuals in AF cohort had more comorbidity which

predisposed to work disability. The association was only slightly reduced after adjusting for potential confounders at baseline. Contrary, we don't know how many patients who experience an AF related consequence (e.g. stroke) *after* follow-up: however, it is probably considerable. Nevertheless, consequences of AF are not confounding variables but rather intermediate variables on the causal path between AF and permanent work disability. Likewise, we don't know how many patients who experienced an event not related to AF after follow-up, but it might be possible that it is more often in the AF cohort than reference cohort because they share many risk factors. For example, back pain, a common cause of disability pension, is not apparently related to AF. However, we would expect that it occurs more often in the AF cohort because it shares risk factors with AF such as increasing age, obesity and alcohol consumption (122). Furthermore, there was major effect modification by SEFs; RDs were significantly higher in lower socioeconomic strata compared to higher socioeconomic strata. However, when looking at the risk differences, we can see that the relative differences seem to be more constant across all SEFs; around three times as high in AF cohort compared to reference cohort in all socioeconomic strata, even though the absolute difference was largest in the lowest income strata. Nevertheless, socioeconomic factors probably play an important role in the risk of work disability for AF patients.

To be entitled permanent social security benefit, workability must be evaluated through a 'resource' scheme. Hereafter, actions will often be made in attempt to improve workability, e.g. treatment, rehabilitation or activation. However, for people with less than six years from retirement age, they might more easily be granted senior disability pension than people who are younger (123). In other words, when looking at number of people being granted permanent social security benefits, 15 months might not be long enough, especially for younger individuals. On the other hand, if more time passes, other diseases not related to AF might occur (e.g. cancer, back pain, etc.) and become the true causes of work disability. Hence, those granted permanent social security benefit within this timeframe are probably older or severely physically disabled. Thus, if younger patients with AF are feeling work disabled due to e.g. symptoms or psychosocial problems, but not granted permanent social security benefit, their WPS might reflect their workability better than permanent work disability.

Worth noticing, a large percentage of patients with incident AF were still in work and with a high work participation, indicating that AF not necessarily is fatal. Thus, improving prevention, treatment and information might possibly improve work ability and prevent work disability in patients with AF.

6.4. METHODOLOGICAL CONSIDERATIONS

Limitations and strengths of the studies included in this PhD-thesis have been discussed in detail in the respective studies (Study 1-3). However, some limitations,

strengths and potential issues of Study 1-3 will be discussed in the following paragraphs.

Traditionally, the validity of epidemiological studies is divided into two parts; the internal validity and the extern validity. Potential violations against the internal validity of a study can be divided into three broad categories: selection bias, information bias and confounding (124).

Selection bias

A selection bias can be described as distortions that occur from the process used to select study subjects and from other factors that can influence the participation in a study (124). Consequently, the association between exposure and disease can differ between the participants and those who theoretically are eligible for the study, including the non-participants (124,125). It is generally assumed that participants with low SEP tend to be underrepresented in epidemiolocal studies (126,127). This can bias the result as SEP can be related to both exposure and outcome. Hypothetically, selection bias in Study 3 could be a problem. In this study, exposure of interest was AF and outcome of interest was work disability. If a selection bias of people with high SEP had occurred in this study, it could potentially incorrectly estimate the results. In this case, an underestimation of the results would probably be most likely. More specifically, we know that low SEP can be associated with a higher risk of AF (exposure) (10,70) and with a higher risk of work disability (outcome) (128). Hence, if patients with low SEP were underrepresented in in our study, and especially in the AF cohort, the association between AF and work disability could potentially have been underestimated (125). In our Study 1 and Study 2, however, exposure of interest were SEFs. It has been less clear if differential loss to follow-up would influence the results when SEFs were exposure. Yet, Howe et al. indicated that loss to follow-up in cohort study where SEFs were exposure could result in biased results for several outcomes (127). The latter examples illustrate the great strength of using Danish, nationwide registers where the entire target population is the sample: selection bias due to non-response not an issue (129) as the study is not dependent on response and compliance of participants. Hence, the registers are very suitable when investigating socioeconomic issues in relation to disease and treatment, both regarding selection issues and generalizability. In Study 1, another selection bias might arise due to the exclusion criteria. A large percentage of the population (~10%) was excluded due to lack of income information at baseline, and especially among the youngest and citizens who was not born in Denmark. Hence, this could have led to a selection bias where the study population was slightly different from the true Danish population. In Study 2, we aimed to include a population with high risk of stroke. However, a selection bias where only those with the most severe diseases (registered at hospital) were included might have occurred (59). In Study 3, we excluded any individuals who was not alive, on permanent social security benefit or emigrated during the period in the analysis of the sub cohort. Hence, the patients included in this analysis had to be

survivors to be included. Consequently, the WPS-score calculated in this study sample is probably higher and not representative for a general AF population or the general population, and this limitation should be kept in mind when interpreting the results of the WPS analysis.

Selection bias is not restricted to the beginning of a study, it can also occur after the study is initiated in terms of differential loss to follow-up (130) as individuals with low SEP also tend to be lost during follow-up (127). However, loss to follow-up due to drop-out from the study is not an issue either as we used nationwide registers (129). Yet, in cohort studies with time-to-event data and long follow-up time, differential loss to follow up due to emigration and deaths might be an issue. Hence, methods to handle death, emigration and other issues during follow-up was considered in the study design. For Study 1, administrative censoring and death during follow-up were handled with calculation of cause-specific hazard rate ratios (131). Furthermore, when calculating RDs, administrative censoring and the competing risk of death were handled by using the pseudo-observation method (82). In Study 2, due to the short follow-up (90 days), time-event-analysis was not used. However, instead of using logistic regression resulting in odds ratio, we chose to use a GLM so we could estimate RD which is a more intuitive and easily understood measure of association. Notice, 12% died during 90 days of follow up. Hence, some of the inequality might be explained by the fact that patients from lower socioeconomic classes simply died before they had the time to fulfil their prescription. Contrary, they might as well e.g. choose not to claim the prescription or died because they were not prescribed OAC. For example, if a person died at day 60, death did not preclude a patient from claiming a prescription of OAC before this. Excluding patients who died during follow-up would not be recommended as this would be to condition on the future and potential result in a sort of immortal time bias where the groups were defined by a future event (132). Nevertheless, the 12% dying must be noticed when interpreting the results. In Study 3, state pension, early voluntary pension and death are events which can occur and consequently preclude the risk of receiving social security benefit. Also, one might say that a person who choose to emigrate have a decreased risk of work disability as those who choose to emigrate are probably not dependent on Danish social benefit transfers due to work disability. Hence, we have complete follow-up on all participants, bearing in mind that the other potential competing events preclude permanent work disability.

Information bias

Several types of information bias can occur during data collection (125,133). One type of information bias is misclassification of exposure, outcome or potential confounders (124). Misclassification bias can be categorized into differential or non-differential. Differential misclassification bias means that the error in information is different for the groups being compared and that the results might be underestimated, overestimated or estimated towards zero. Non-differential misclassification on the

other hand, indicate that the misclassification is the same across the different groups and that it influences the estimates toward zero if variables are binary. Yet, if the variable are polytomous, the direction of the bias might go other ways (125,133). Information issues, e.g. self-reported errors in information due to interviewer bias and recall bias (133) are not an issue when using nationwide registers. Yet, collection of data is not flawless, and misclassification of exposure, outcome and confounding variables might occur. By extension, it can be difficult for researchers to understand how data are collected and generated (129). Information bias is closely related to misclassification in the pre-collected data in the registers but also, to some degree, how researchers use the data and design the studies. Some specific issues will be discussed in relation to Study 1, Study 2 and Study 3 in the following paragraphs.

Misclassification of the study population

In Study 1, the entire population without incident AF of a specific age (35,50, 65 or 80 years old) were included. A misclassification might occur if patients registered without AF had AF, e.g. asymptomatic and undiagnosed or only diagnosed by their general practitioner (and consequently not registered in the DNPR). In Study 2 we aimed to identify a study population of patients with AF and with an indication for OAC (high risk of stroke). We accounted for the fact that guidelines had changed throughout time, but how sure can we be that the stroke risk factors used to define the study population are valid? The positive predictive value (PPV) of the diagnoses in the DNPR are varying (<15% - 100%) (59). However, the conditions used to define stroke risk factors had, in general, a high PPV as demonstrated in supplementary material S3 in Study 2 (71). Most validation studies report the PPV of the disease whereas the negative predictive value (NPV), specificity and sensitivity are rarely reported (59). The consequence of many "false negatives" (which in this case refers to patients which truly have stroke risk factors but that they were not registered in the registers) is that some eligible high risk patients are excluded from the population and/or that the included patients were registered with less comorbidity than they truly had. We can avoid underestimation of some diseases by adding specific pharmacological treatment, for example, we defined hypertension as at least one prescription within a year of two different antihypertensive classes. Olesen et al. reported that this method had a specificity of 94.7% and a sensitivity of 80.0% (134). However, this way of defining hypertension was probably not validated on an AF cohort. It is possible that the validity of a hypertension diagnosis is lower in an AF population where the likelihood of receiving an antihypertensive agent for other causes than hypertension probably is higher (e.g. beta-blocker). Furthermore, some diagnoses remain underreported, for example, Kümler et al. found that heart failure are reported to have a PPV of 81% but a sensitivity of only 29% (135). In Study 3, we aimed to include a population of patients with incident AF and a matched population from the general population. Yet, the same issue as discussed in Study 1, might be present in Study 3 as well, meaning that some patients with AF are undiagnosed. By extension, individuals from the matched reference cohort might have undiagnosed AF

at baseline or develop incident AF before follow-up is over. However, number of people developing AF during follow-up were probably negligible as the follow-up time was short.

Misclassification of exposure

In Study 1 and Study 2, education was one of the SEFs used as exposure. Even though Danish education registers are considered to have high validity for Danes born between 1945-1990, it might be more limited for immigrants and older persons (61). A large percentage of the oldest cohort did not have any formal education registered in the registers. Do they truly don't have any formal education or is it missing in the register? Data for the eldest can be limited (62), but on the other hand, low education is common for the eldest generation (67). However, by excluding them it introduces a selection bias where the remaining population was younger, wealthier and healthier. Overall, some misclassification of educational status might be present, especially for the oldest and immigrants.

In Study 1 and Study 2 we also used income as a proxy for SEP. The simplest way to divide it would be with predefined cut-off values into low, medium and high. However, does a person with low income truly have low income? Technically, yes. In the setting where income serves as a proxy of SEP? Not necessarily. For example, if the person with a yearly income of 600,000 DKK is the sole provider of a family of seven whereas the person with 300,000 DKK is the second provider of a family of two? Or if a person with a yearly income of 300,000 DKK is retired whereas the person with an income of 600,000 DKK is in his prime earning years? Can one compare a salary of 300,000 DKK in the year 2000 with the same salary in the year 2015? As demonstrated in the latter three examples, in the setting of income as a proxy of SEP, it doesn't make sense to just use three single cut-off points for the entire population. We tried to avoid misclassification bias of income by using the equivalized family income and dividing it into age- and year specific terciles.

In Study 2, cohabiting status was also used as proxy of SEP. It was divided into living alone or not alone based on the number of persons living on the same address. There might be cases where persons have another address than the place they are living, however, one must assume that most people live in the address they are registered at.

In Study 3, AF was compared with AF-free matched participants. The PPV of AF has previously been shown to be >90% (73,136). Nevertheless, we don't know the NPV and thus the probability that the matched participants truly are AF-free. Additional, individuals without AF matched with patients with AF at baseline might develop AF during follow up as discussed in the section "misclassification of the study population".

Misclassification of outcome

In Study 1, hospital registered AF was outcome. As discussed above, the PPV of AF in combination with atrial flutter is high (73,136). However, as mentioned, the AF rates might be underestimated as there are probably some undiagnosed cases. One reason of this is that AF can be asymptomatic (1,137) and therefore undiagnosed, and another reason could be that the patients are diagnosed and treated by their general practitioner and therefore not given an ICD-10 code in the DNPR. However, Danish guidelines recommend all incident AF patients to have an echocardiography in relation to their AF medical examination (138). Consequently, all AF patients should be seen by a cardiologist and therefore registered with AF in the register. The number of out-of-hospital cardiologists was relatively small during the study period (139,140); however, there might be some missed cases of AF this way.

In Study 2, a prescription of OAC in the period -30 to 90 days after incident AF was outcome. Few studies have examined the validity of the Danish National Prescription Registry; however, it is generally accepted that it contains complete, high quality data partly due to the barcode-based, reimbursement driven registration of redeemed prescriptions (60).

In Study 3, work disability and work participation score were outcome. It is previously concluded that the DREAM database was feasible to use for follow-up of e.g. exclusion from the workforce (56). Nevertheless, we can not determine the causes of why people receive permanent social security benefit or early retirement. For example, if a person did not have the opportunity to get early retirement, he might have received permanent social security benefit instead. Also, if a person with AF gets uncurable cancer one month after incident AF, uncurable cancer is probably more likely to be the cause of permanent work disability than AF.

Confounding

A confounder can be defined as a variable which confuses the effect between exposure and outcome (124). Specifically, a confounder was defined as a variable which was 1) predictive of study outcome, 2) associated with the exposure of the study, and 3) not an causal link/intermediate variable between the exposure and outcome of the study (141).

In Study 1, Study 2 and Study 3 we reported crude and adjusted results in different models. The interpretation of the different models is complicated. Are we interested in describing the causal relationship between the exposure and outcome, or are we simply interested in describing what the world looks like (142)? We aimed to describe both the crude and the causal association by constructing adjusted models where we tried to include all potential confounders. Potential confounders were carefully selected based on prior literature before any data analyses were performed. For

example, in Study 1 and Study 2, the fully adjusted model for education was very restricted because we believe that most of the inequality would be mediated through intermediate variables such as poor lifestyle, hypertension and ischemic heart disease. The reason for this is that education is normally established before any life-style related diseases occur. Consequently, traditional risk factors for AF (e.g. obesity, hypertension and ischemic heart disease) must be considered intermediate variables on the causal pathway between education and AF (104) (Study 1) and OAC (Study 2), and not confounders. Nevertheless, for income, the association was more complicated. Traditional risk factors for AF (Study 1) and "risk factors"/indicators of OAC (Study 2), can cause low income. For example, heart failure increases the likelihood of being initiated with OAC in patients with AF, however, it can also cause low income due to e.g. work disability. In the latter example, heart failure would be a confounder, and should be adjusted for. However, how do we know, that low income does not cause heart failure? There are several studies indicating that low income can be a predictor of heart failure (42), and if so, then heart failure would be a mediator, and should not be adjusted for. However, we don't know if the factors adjusted for are mediators or confounders in the given situation. Yet, potential overadjustment bias, meaning that intermediate variables are adjusted for (143), should be considered when interpreting the adjusted models. In Study 3, technically, all comorbidities are supposed to have occurred *prior* to AF, and consequently be potential confounders. Nevertheless, we cannot rule out that AF has been present for some time but undiagnosed or not registered in the registers. In this scenario, baseline comorbidities such as stroke might as well have been mediators. Another important factor to consider is residual confounding. Residual confounding might be present both by factors we cannot measure, factors we did not consider as confounders, or factors that were incompletely measured.

Overall, the association is a result of an interplay between multiple factors, and demonstrating a causal association can be very complex (144). Hence, the readers must bear in mind the potential fallacies when interpreting the results from both crude (due to confounding variables) and adjusted models (due to residual confounding and potential overadjustment).

External validity

The external validity, also called the generalizability, refers to the "big picture". More specifically, if the results from the study are determined to be internally valid, are the results likely to be valid in other study samples or settings (145)? An advantage regarding the external validity is that we used nationwide registers on the entire Danish population. Hence, it is not really a sample of the target population (the Danish population), the sample is the target population (129). However, there are some concerns regarding generalizing the results of the studies to the entire Danish population, yet, this is primarily related to the internal validity as previously discussed.

Nevertheless, the results on a Danish population are not necessarily representative for other populations in other countries where the population is more ethnically diverse and the system for education, income and health care is entirely different.

CHAPTER 7. CONCLUSIONS AND PERSPECTIVES

7.1. MAIN CONCLUSIONS

This PhD thesis examined socioeconomic inequality in the risk and treatment of AF and the social consequences following AF.

First, we found that individuals with low education were associated with a higher risk of being diagnosed with AF, especially in young age cohorts. The association, however, was attenuated with age and even reversed for the eldest age cohort. Similar but weaker results were seen when income was used as SEF except for 35-years-old men where the results were opposite. Due to the low incidence of AF in the youngest age cohort, the absolute risk difference was low, indicating that socioeconomic inequality in the risk of AF is not a major public health burden.

Second, we found that patients with AF, with high risk of stroke and with low levels of SEFs were associated with a higher risk of not being initiated with OAC therapy according to guideline recommendations. More specifically, men with low income, men and women with low education and living alone had a higher risk of not being initiated with OAC. The association was, strongly attenuated regarding education and cohabiting status after adjusting for age (income variable was already age adjusted) and the crude inequality observed was reduced over time. For NOACs, men and women with low education, low income and not living alone had a higher risk of not being initiated with NOAC, and this inequality increased over time.

Third, we found that patients with AF had more than three times as high risk of work disability 15 month after incident AF compared to the general population. Furthermore, work participation in the AF cohort was lower than work participation in the general population. Even though AF might be a harmless condition in some situations, our results indicate that there might be social consequences following AF. Also, we found that permanent work disability and low work participation was higher in lower socioeconomic strata which consisted after adjusting for potential confounders, indicating that socioeconomic factors also play an important role.

7.2. PERSPECTIVES

Our findings highlight the complexity of the association between SEP and the risk of AF and that the association significantly varied with age, sex, SEF used, and measure of association used. Overall, an association between SEP and risk of AF seem to be present, however, to a smaller degree compared to other cardiovascular diseases such as ischemic heart diseases. It could be interesting to see if the age-specific inequities

observed is present in other populations and settings. Hence, future studies could examine the age-specific effect of SEFs on the risk of AF.

To our knowledge, no other study has described the inequality over a longer time period and accounted for changing guideline recommendations. However, it could be interesting if future studies looked at the development of socioeconomic inequality in OAC initiation the past five years, especially because two new guidelines have been published the past five years in 2016 (146) and 2020 (7). Also, NOAC is now recommended over VKA as choice of OAC drug (7), and if the inequality in initiation of NOAC still is present, this is unfortunate and should be reduced. New and more unambiguous guidelines might possibly help to reduce inequality in initiation of OAC and fair price of drug might reduce inequality in use of NOAC. Furthermore, patients with low levels of SEFs might be a vulnerable group of patients and need more care, information and support in order to be compliant with recommended treatment. However, the true causes of inequities in OAC initiation are not known and future studies should explore potential causes of socioeconomic inequality in OAC initiation.

It is unknown why patients with AF had a high risk of permanent work disability and poor work participation. It might be related to potential consequences of AF such as stroke, other underlying conditions, severe symptoms and SEFs. A holistic management of AF patients might be advantageous in order to reduce work disability and low work participation in patients with AF, e.g. optimal stroke prevention, more focus on treatment of symptoms, handling of psychosocial side effects, treating underlying factors such as hypertension, obesity and smoking, educating patients about AF and fair prices of recommended drugs. The latter mentioned initiatives are probably also beneficial in other aspects in the public health burden of AF, e.g. to improve the general health, improve symptoms and reduce the risk of severe disability due to other cardiovascular diseases. However, before any specific initiatives targeting work disability in patients with AF can be implemented, potential causes and mechanisms of work disability in patients with AF should be explored.

In summary, this PhD-thesis suggests that socioeconomic inequality in the risk and treatment of AF and social consequences in terms of work disability and low work participation following AF is an issue in Denmark. The presented papers together with other scientific publications on the area may help contribute to public health initiatives to reduce socioeconomic inequality in the public health burden of AF.

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ISSN (online): 2246-1302
ISBN (online): 978-87-7573-999-8

AALBORG UNIVERSITY PRESS