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Obesity, metabolic factors, symptoms of depression and anxiety and risk of atrial fibrillation

The Nord-Trøndelag Health Study
(The HUNT Study)

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Norwegian University of Science and Technology

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Doctoral thesis

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Thesis for the Degree of
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Trondheim, November, 2019

Norwegian University of Science and Technology

Faculty of Medicine

Department of Public Health and Nursing

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Norsk Sammendrag (Norwegian Summary)

Atrieflimmer (AF) er en kronisk hjerterytmeforstyrrelse som har blitt beskrevet som en global epidemi. Så mange som 5 millioner mennesker får AF hvert år og globalt har anslagsvis 33,5 millioner mennesker AF. Antallet voksne med AF er anslått til å mer enn dobles innen 2050. AF er et alvorlig folkehelseproblem fordi det er forbundet med økt risiko for dødelighet og hjerneslag samt økte kostnader i helsevesenet. Derfor er det viktig å ha en bedre forståelse av risikofaktorer for å tidligere kunne påvise og forebygge. I denne avhandlingen undersøkte vi den potensielle sammenhengen mellom fedme, metabolske faktorer, symptomer på depresjon og angst, og risiko for AF.

Studiene er basert på en stor befolkningsundersøkelse, Helseundersøkelsen i Nord-Trøndelag (HUNT). Alle nordtrøndere over 20 år ble invitert (HUNT1, 1984–86; HUNT2, 1995–97; HUNT3, 2007–09), og det ble gjort klinisk undersøkelser inkludert vekt og høyde, blodprøver samt at alle deltakere ble bedt om å fylle ut flere spørreskjema. Her ble deltakerne spurt om siste ukes symptomer på angst og depresjon. De to sykehusene i Nord-Trøndelag (Levanger og Namsos) har registrert opplysninger om diagnostikk og behandling av alle pasienter med AF. Diagnosene har blitt validert av kardiologer, noe som sikrer høy spesifisitet..

Artikkel I undersøkte den prospektive sammenhengen mellom fedme og vektendring, og risiko for AF. Her fant vi at langsiktig overvekt og BMI-endring var assosiert med økt risiko for AF. Fedme tidligere i livet og vektøkning over tid hadde kumulative effekter på risiko for AF selv etter å ha justert siste BMI. Artikkel II undersøkte risikoen for å utvikle AF hos overvektige med og uten metabolsk sykdom. Her fant vi at både metabolsk sunn og usunn fedme var assosiert med økt AF-risiko i like stor grad. Alvorlighetsgrad av fedme var positivt assosiert med økt risiko for AF uavhengig av metabolsk status. Manuskript III undersøkte den prospektive sammenhengen mellom symptomer på depresjon, og angst og risiko for AF. Her fant vi at mild til moderat depresjon var

assosiert med økt risiko for AF. Derimot fant vi ingen sammenheng mellom angstsymptomer eller alvorlige depresjonssymptomer og risiko for AF. Våre resultater bekrefter at det er særlig viktig å forebygge og behandle fedme for å forebygge AF. Den uventede assosiasjonen av mild til moderat depresjon med økt AF-risiko krever bekreftelse i andre studier.

Kandidat: Tingting Feng
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Finansieringskilde: Landsforeningen for hjerte- og lungesyke og Regionalt samarbeidsorgan for utdanning, forskning og innovasjon i region Midt-Norge

Contents

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This work has been performed at the Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology during 2017-2019. Financial support from Norwegian Heart and Lung Association and Liaison Committee for Education, Research and Innovation in Central Norway made this work possible.

I thank the participants of Nord-Trøndelag (now part of the county of Trøndelag) who participated in the Nord-Trøndelag Health Study and thus made data for extensive health research available.

I wish to express my deepest gratitude towards my main supervisor Imre Janszky who introduced me to the field of epidemiology in 2017. He has been a tremendous mentor for me. I would like to thank him for the trust and confidence that he has shown in me. His vast knowledge has been an inspiration, and his encouragement and guidance truly pivotal for the completion of this thesis. I am also sincerely grateful to my co-supervisors Jan Pål Loennechen, Hanne Ellekjær, Linn Beate Strand, Lars Erik Laugsand for their invaluable guidances and support throughout this period. I want to thank my co-authors Kenneth Mukamal, Lise Tuset Gustad, Dagfinn Aune, Malmo Vegard, Bjørn Mørkedal and Lars Vatten for their important contributions to these papers.

I thank my friend, previous colleague and office mate Camilla Nguyen for all discussions, laughter and shared frustrations. To my Chinese friend Xing Mengtan; I highly appreciate our lunch talk every week and your tasty dumplings. And to my kjæreste Bjørnar Bell; thank you for your accompanying, delicious pizzas and chocolate cakes.

Nobody has been more important to me in the pursuit of this degree than the members of my family. I would like to thank my parents, whose love and guidance are with me in whatever I pursue. Most

importantly, I wish to thank my loving grandmother who is a strong, independent and caring woman and the most amazing woman I have ever met. I could not ever put into words how grateful I am for her or how much I love her.

Trondheim, November 2019

Tingting

献给我最最亲爱的姥姥

姥姥，你离开我已经快10年了。这10年里，你眼里那个20出头的不懂事的小姑娘长大了。从你离开后，我经历了很多事，做了很多好的和坏的决定。时间真的是良药，我从开始时动不动就痛哭到现在只是会在不经意间才想到你。比如当我吃到好吃的东西时，比如听到有人叫姥姥时，比如看到你的衣服，比如看到祖孙二人走在街上.

你含辛茹苦把我拉扯大，你陪我走过了我童年和青少年最美好的时光。你的老房子，永远是我感觉最最温暖和安全的地方。有你在那忙碌的身影，那才是个家。你端着我喜欢吃的热呼呼的猪肘子和烙的大饼,跟正在看电视剧的我说："别等姥姥，趁热吃。凉了就不好吃了。" 那时的我因为你的宠爱任性娇蛮,我的童年没有缺少受宠爱这样东西。每次想到你，我都是痛并快乐着。快乐是因为曾经我们有如此珍贵的回忆，痛苦是因为我永远失去了你。我们的家，那个老房子已经被拆了，所有人都住上了楼房。我好希望再回到那个老房子，打开大门，你站在那里，像往常一样给我一个拥抱，笑着说："大宝回来了"。好希望听你说："大宝，帮姥姥穿针纫线，姥姥看不清"。然后我屁颠屁颠地跑去帮你。

这么多年了，即使不看你的照片，我依然清晰记得你的样子。你喜欢将花白的头发染黑；你满脸皱纹，可在我心里你是最美的；你的衣着朴素，却见不到一个褶皱污渍；你矮小瘦弱，却独立承担着所有的家务。你一生经历种种苦难，却依然乐观生活，善对他人。你的温暖，你的关怀，你的坚强，永远是我生命里的光。

每次想到你曾经是那样的爱我，都让我感觉我是幸福的且是幸运的。你为我做的太多太多，而我为你做的太少太少。你走之后，我最最最最大的梦想就是可以再次见到你，再拉一次你的手，再抱你一次，再给你读一次杂志，再搀着你和你逛一次街，再和你学一次烙饼，再听你给我讲你的经历，再叫你一次姥姥，再听你叫我一次大宝.....

我现在懂事儿了。我会做饭了，我多想给你做一次饭啊。我赚钱了，我多想用我的工资给你买好多好吃的和好穿的。你一直想坐飞机，我现在可以用赚的钱买很多机票，我们可以坐飞机去很多地方。当我过年给姥爷红包时，我多希望你也在啊，这样我就可以给你一个非常大的红包了。以前每年过年你都给我一个好大的红包，你对我从不吝啬。我可以想象当你收到我的红包时你开心的笑脸。你说如果你出生在新社会，你一定上学念书，找一份好工作，自由自在的生活。你期盼着我成为一个独立自主，不靠男人的女性，我做到了。我从来没有放弃奋斗。也许你看到我没有选择做医生，会失望吧。如果哈医大没有给你误诊的话，如果你还在的话，我应该会硕士毕业就当ICU医生或者麻醉医生了。我阴差阳错得在挪威读了博士，如果你看到我拿到博士学位，一定会无比自豪的。我们可以像当年我考上哈医大时那样宴请宾客，好好庆祝，唯一不同的是我要对所有宾客说"谢谢你，姥姥"。

我希望有时光穿梭机能把我带回10年前，我一定要一直一直陪在你身边，不让你突然的离开我。我一直在懊悔当初自己相信庸医的诊断，认为你的病不重。在你生病时，我本应该请假陪着你，我本应该恳求我的硕士生导师给你找专家，可是当时的我太自私，把考职业医师证的事情放在了首位，对不起，千千万万个对不起。你是那么那么的好，老天爷为什么要把你带走啊？也许是世上的苦难太多了，所以老天爷把你带到没有痛苦的天堂，在天堂你就能实现你在人世间没有实现的所有梦想了吧。你走之后，我开始愿意相信来生。我好希望有来世，这样我们能够再见面，我一定要好好爱你和照顾你。姥姥，谢谢你那么那么的爱我，你的爱和温暖一直都给我力量和勇气。没有你的爱和鼓励,就没有今天的我。

爱你和想念你的大宝

LIST OF PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Feng, Tingting; Vegard, Malmo; Strand, Linn B; Laugsand, Lars Erik; Mørkedal, Bjørn; Aune, Dagfinn; Vatten, Lars Johan; Ellekjær, Hanne; Loennechen, Jan Pål; Mukamal, Kenneth J; Janszky, Imre. Weight and weight change and risk of atrial fibrillation: the HUNT study. European Heart Journal (2019) 40, 2859–2866

II. Feng, Tingting; Malmo, Vegard; Strand, Linn B; Laugsand, Lars Erik; Mørkedal, Bjørn; Aune, Dagfinn; Vatten, Lars Johan; Ellekjær, Hanne; Loennechen, Jan Pål; Mukamal, Kenneth; Janszky, Imre. Metabolically Healthy Obesity and Risk for Atrial Fibrillation: The HUNT Study. Obesity (Silver Spring). 2019 Feb;27(2):332-338.

III. Feng, Tingting; Vegard, Malmo; Strand, Linn B; Laugsand, Lars Erik; Gustad, Lise; Ellekjær, Hanne; Loennechen, Jan Pål; Mukamal, Kenneth J; Janszky, Imre. Symptoms of anxiety and depression and risk of atrial fibrillation-the HUNT study. Under review.

LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
BMI	Body Mass Index
CI	Confidence Interval
ECG	Electrocardiogram
ESC	European Society of Cardiology
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS Anxiety Subscale
HADS-D	HADS Depression Subscale
HDL	High-Density Lipoprotein
HR	Hazard Ratio
HUNT	Nord-Trøndelag Health Study
HUNT1	The First Wave of the HUNT Study
HUNT2	The Second Wave of the HUNT Study
HUNT3	The Third Wave of the HUNT Study
ICD-10	International Classification of Diseases Tenth Revision
RR	Relative risk
SSRIs	Selective Serotonin Reuptake Inhibitors

1 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia and has been described as a global epidemic.[1] Globally, an estimated 33.5 million people have AF with 5 million new cases each year.[1, 2] The number of adults with AF is projected to more than double by 2050.[1] AF is a serious public health problem because it is associated with an increased risk of mortality and stroke as well as increased health care costs.[3] Therefore, it is important to have a better understanding of its risk factors to allow earlier detection and prevention. In this thesis, we examined the prospective association of some metabolic and psychological factors with risk of AF.

Below, the introduction provides an overview of the definition of AF, its pathophysiology and epidemiology and the previous literature on the prospective association of lifestyle-related and psychological factors with risk of AF.

1.1 DEFINITION

According to European Society of Cardiology (ESC) guidelines for the management of AF, AF is a supraventricular tachyarrhythmia that deteriorates atrial mechanical function with the following electrocardiogram (ECG) features (Figure 1)[1]:[5]

(1) Consistent P waves are replaced by fast oscillations or fibrillatory waves that differ in size, shape, and timing, associated with irregular, often fast ventricular reactions when atrioventricular conduction is intact.

(2) A totally irregular RR interval. That is, there are no patterns to the RR intervals on ECG.

[1] Note: Figure 1 is adapted from 'Diagnosis and treatment of atrial fibrillation[4] Gutierrez C, Blanchard DG. Diagnosis and treatment of atrial fibrillation. Stroke. 2016;100:29-31.' and is permitted for reuse by American Academy of Family Physician.

(3) The QRS complexes are narrow (usually < 120 ms) in absence of a pre-existing bundle branch block, accessory pathway, or rate related aberrant conduction.

(4) Multiple disorganised 'fibrillatory' waves that induce the chaotic atrial activation.

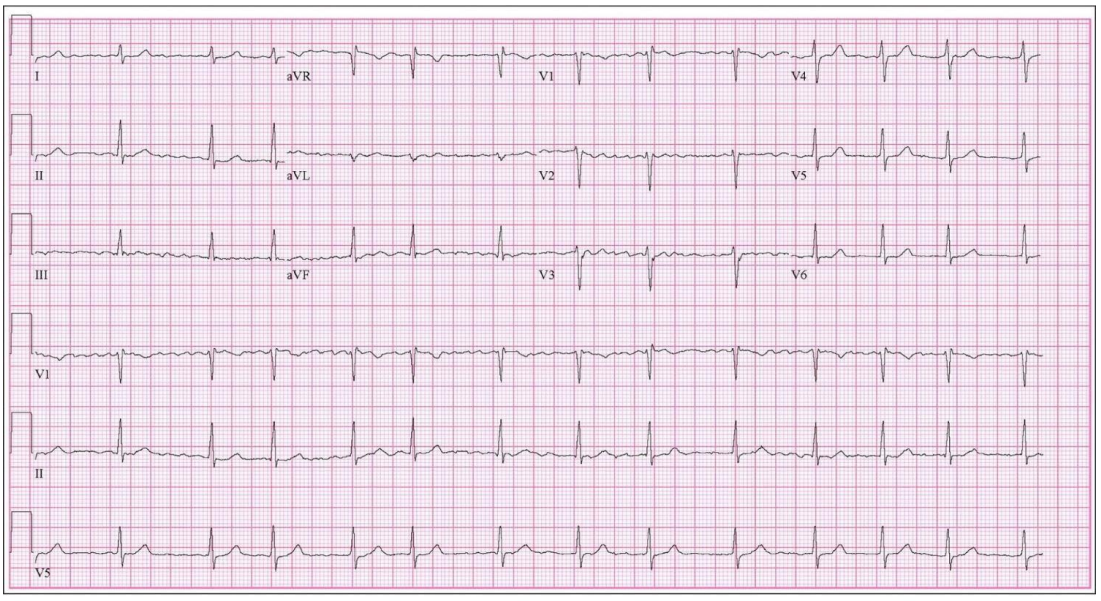


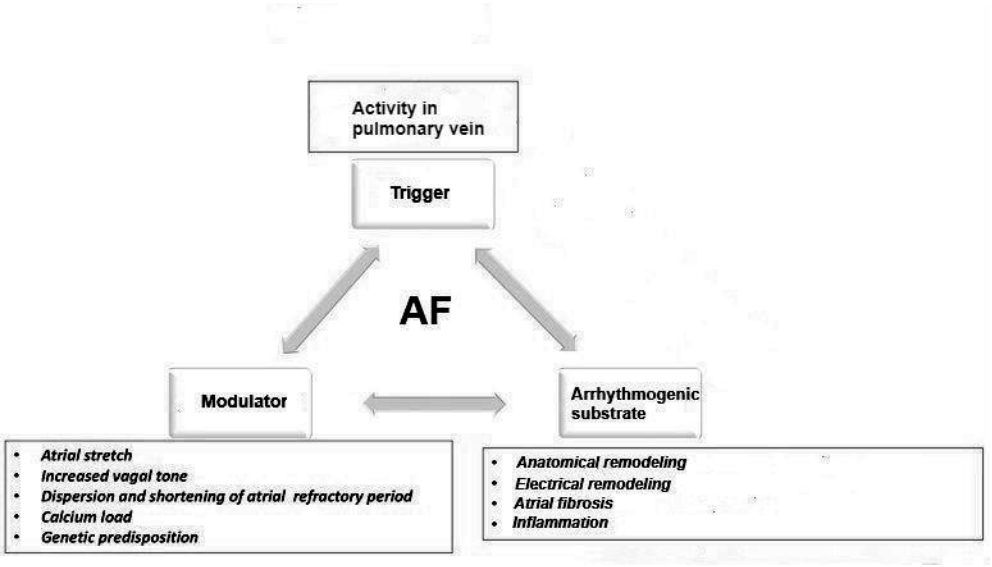
Figure 1. Electrocardiogram showing atrial fibrillation. Note the absence of distinct P wave, chaotic activity of atria, irregular R-R intervals with narrow QRS complex.

1.2 PATHOPHYSIOLOGY

AF is a complex multifactorial disease. Though the overall electrophysiological, genetic and anatomical pathogenesis of AF remains unclear, AF has been regarded as a result of complex interactions between three elements: trigger factors, arrhythmogenic substrates, and modulating factors.[6]

The triggers initiate AF while the arrhythmogenic substrates determine its persistence.[7] The main triggering, modulating and perpetuating factors include: activity in pulmonary vein, atrial stretch, increased vagal tone, calcium load, genetic predisposition, anatomical remodeling, electrical remodeling, fibrosis and inflammation (Figure 2).[8, 9]

Figure 2. The potential mechanisms underlying atrial fibrillation



1.3 EPIDEMIOLOGY

The estimated global incidence rate of AF was 59.5 and 77.5 per 100 000 person-years in women and men, respectively, with higher incidence rates in developed countries compared to developing countries.[1] In Europe and the USA, AF affects about one in four middle-aged adults during their lifetime.[1, 10] In 2014, it was estimated that approximately 10 million people had AF in Europe.[11] By 2030, according to a recent estimation, this number will reach 14–17 million, with 120 000–215 000 new cases every year.[12, 13] Globally, it has been estimated that AF prevalence will increase 2.5-fold by 2050, due to the aging population,[14] better detection of silent AF[15] and increased prevalence of risk factors predisposing to AF.[16]

1.4 BURDEN OF ATRIAL FIBRILLATION

AF is associated with a 1.5- to 1.9-fold increase in mortality risk,[17] 3- to 5-fold increase in stroke risk[18] and 3- to 8-fold increase in heart failure risk.[19] In addition, AF is associated with a higher risk of dementia and cognitive impairment,[20, 21] as well as decreased quality of life.[22] Furthermore, AF leads to a substantial economic burden on the health care systems and health budgets.[23, 24] The burden of AF may actually be underestimated because of the high prevalence of asymptomatic AF which are difficult to diagnose.[1]

1.5 RISK FACTORS

Several risk factors have recently been established for AF including non-modifiable factors like male sex and advancing age but also lifestyle related factors like hypertension, diabetes mellitus, cigarette smoking, alcohol misuse, and obesity (i.e., body mass index (BMI) ≥ 30 kg/m^2).[9, 25] Specifically, obesity and depression, two strongly correlated factors, are increasingly prevalent and associated with various health complications including cardiovascular diseases.[26, 27] The prevalence of obesity among adults with severe mental

illness is as high as 55%[28] and 23% of obese individuals have a comorbid depression.[29] Therefore, it is imperative to have a deeper understanding of the effect of obesity, depression and anxiety on health. As outlined below there are several unresolved issues regarding the association between obesity, depression and anxiety and risk for AF.

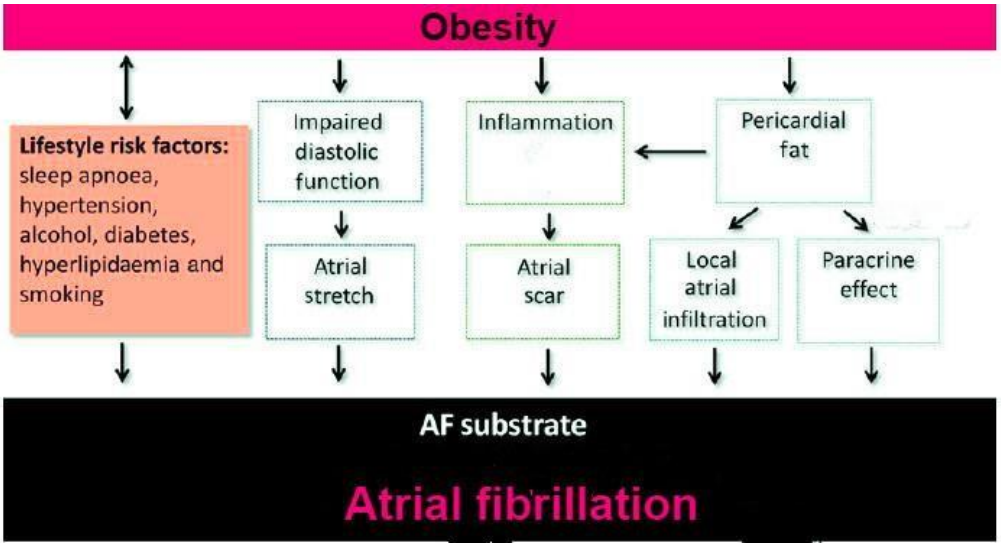
1.5.1 Weight and weight change and risk of atrial fibrillation

Obesity has been regarded as a global pandemic. Since 1980, the global prevalence of overweight and obesity has dramatically increased to the extent that almost one-third of the world's population is now categorized as overweight.[30] In the Nord-Trøndelag Health Study, the prevalence of overweight increased from 42.1% in 1984–1986 to 52.4% in 2006–2008 in men, and from 29.9 to 37.7% in women.[31] During the same period, the prevalence of obesity increased from 7.7% to 22.1% in men, and from 13.3 to 23.1% in women.[31] Overweight and obesity lead to impaired diastolic function, inflammation, pericardial fat and atrial remodeling, which are important mechanisms in the development of AF (Figure 3).[32] Research using measurements of height and weight at a single point in time fails to assess the cumulative effect of obesity over the life course on AF development. Weight variations throughout the life course are common in many people, and this may affect the risk of developing AF. Little attention has been devoted to the impacts of long-term obesity and long-term weight change on AF development. Repeated measurements of height and weight can provide more information than a one-time measurement and can be useful to better understand long-term influences of weight and weight change on AF risk.

Some previous studies have assessed self-reported prior body weight (i.e., individuals recalled their body weight earlier in life) in relation to risk of AF.[33, 34] Self-reported current body weight is generally accurate,[35, 36] but the accuracy of recall of past weight is often imperfect and depends on current and past BMI values, changes in weight, end-digit preferences, and participants' current cognitive ability.[37] With regard to the diagnosis of

AF, most prior studies have relied solely on administrative data without individual validation or verification. [33, 38] This tends to lower the specificity of the AF diagnoses and may introduce a substantial misclassification.[39, 40] Moreover, those few previous investigations with repeated measurements of body weight over time have been limited by small sample sizes,[33, 38] short time intervals between measurements[34, 38, 41-43] and missing information on important covariates like comorbidity.[33, 34, 38, 41]

Figure 3. Obesity and development of atrial fibrillation – potential pathways



1.5.2 Metabolically healthy obesity and risk for atrial fibrillation

Although obesity is a primary determinant of cardiovascular risk factors like dyslipidemia, elevated blood pressure and impaired glucose tolerance that comprise metabolic syndrome, a subset of individuals with obesity do not manifest these adverse factors. The prevalence of what is often termed metabolically healthy obesity amongst individuals with obesity in Europe varies between 7–28% among women and 2–19% among men.[44] Research concerning the metabolically healthy obese phenotype is still in its infancy and the health consequences conferred by metabolically healthy obesity are still under debate. A systematic review and meta-analysis showed that individuals with metabolically healthy obesity are at increased risk for all-cause mortality and cardiovascular events compared to metabolically healthy normal-weight individuals, but the relative risk carried by metabolically healthy obesity (RR: 1.24; 95% CI, 1.02 to 1.55) was substantially lower than the relative risk

carried by metabolically unhealthy obesity (RR, 2.65; CI, 2.18 to 3.12).[45] Current one-size-fits-all approaches to treat obesity, which are mainly based on BMI and measures of body fat distribution and neglect differences between metabolically healthy and unhealthy obese phenotypes, have largely been unsuccessful.[46] Thus, it has been suggested that a further stratification on obesity phenotypes according to metabolic status would provide a promising approach to prioritize and determine more suitable therapeutic interventions.[47] Accordingly, a better understanding of AF risk carried by obesity-associated metabolic health phenotypes is important for early identification of high-risk subgroups who should be prioritized for lifestyle and medical intervention and development of personalized treatment strategies.[46]

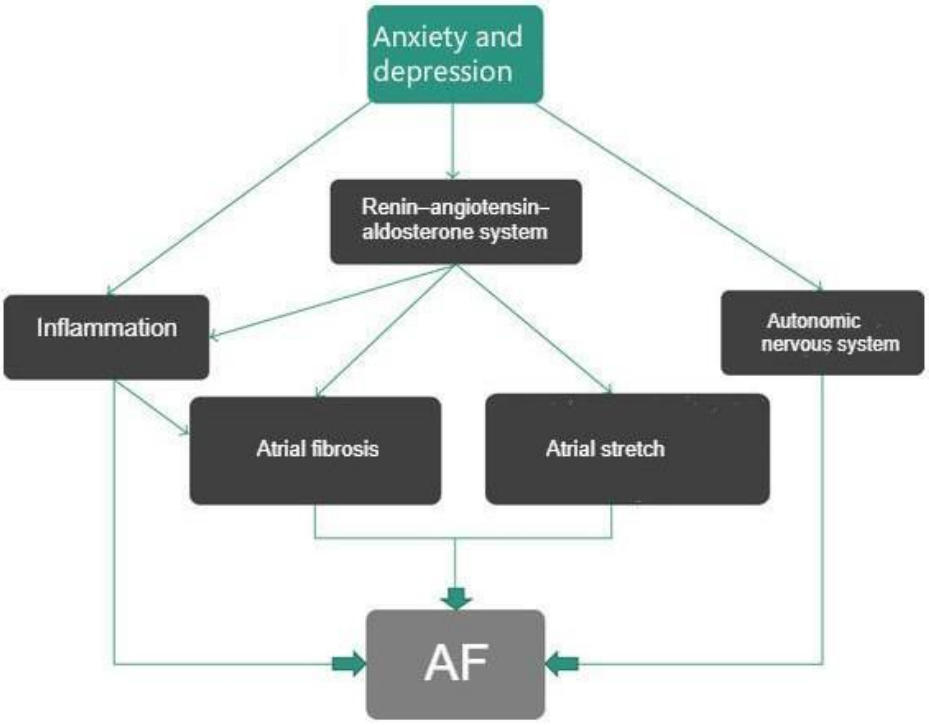
To the best of our knowledge, only two studies have investigated the associations between metabolically healthy obesity and AF risk, and the results were conflicting.[48, 49] A Swedish study suggested essentially similar risk among those with healthy and unhealthy obesity,[48] while the risk for the latter group was much more pronounced in a Korean study.[49] The Swedish study had a sample size of just over 4,000 individuals and in both studies, follow-up was based only on administrative health registers. Furthermore, neither study analyzed the duration or severity of obesity.

1.5.3 Symptoms of anxiety and depression and risk of atrial fibrillation

Anxiety and depressive disorders are the most common mental disorders that frequently co-occur. The worldwide lifetime prevalence of any anxiety disorder has been reported to be 16.6%.[50] The worldwide lifetime prevalence of depression has been reported to be 10.8% .[51] [52] Both conditions occur more frequently among women. Symptoms of depression and anxiety is relatively strongly associated with cardiovascular diseases, including coronary heart disease,[53] acute myocardial infarction[54] and heart failure.[55] However, little is

known about the potential impact of depression and anxiety on AF risk. Depression and anxiety might be associated with increased inflammation[56, 57] and inflammation plays an important role in the etiology of AF.[58] Depression and anxiety might also activate the autonomic nervous and the renin–angiotensin–aldosterone system that might facilitate atrial fibrosis and increase atrial stretch (Figure 4).[59-61] To date, only four previous studies have assessed the prospective association of anxiety or depression with AF risk, and all had potential limitations in their assessments of exposure or outcome, and none had repeated measures of anxiety or depression.[62-65]

Figure 4. Hypothetical mechanisms of atrial fibrillation in depression and anxiety



AIMS OF THE THESIS

The overall aim of this thesis was to investigate whether metabolic and psychological factors are associated the risk of AF in a general population.

The specific aims of the studies were to investigate:

1. The association between weight and weight change and risk of AF (Paper I).

2. The association between metabolically healthy obesity and the risk of AF (Paper II).

3. The association between symptoms of anxiety and depression and risk of AF (Paper III).

2 METHODS

2.1 STUDY POPULATION

This thesis is based on the Nord-Trøndelag Health Study (HUNT), http://www.ntnu.edu/hunt.[66-68] Nord-Trøndelag County is located in the central part of Norway (Figure 5)[2] and has 24 administrative municipalities.[67] Nord-Trøndelag County is a comparatively representative sample of the Norwegian population regarding to age distribution, morbidity and mortality.[67] There are two hospitals in the county, located in Levanger and Namsos which serve the entire population in the county. HUNT is a population based longitudinal health survey and so far four surveys have been completed : HUNT1 in 1984–86,[69] HUNT2 in 1995–97,[70] HUNT3 in 2006–08[68] and HUNT4 in 2017-19 (https://www.ntnu.edu/hunt4). In all surveys, the entire adult population (aged ≥ 20 years) was invited to participate. Data from the last survey were not included in this thesis. The size of the population of the county was relatively stable between HUNT1 (125,835 in 1984) and HUNT3 (128,694 in 2006), and net migration was about 0.3% per year. Most of the participants took part in more than one of the surveys. The detailed numbers of participation in HUNT1-3 is displayed in Table 1. There was a decline in participation rate from 89.4% in HUNT1, with 69.2% in HUNT2 to 54.1% in HUNT3.

[2] Figure 5 is adapted from 'The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation'[67]. It is permitted for reuse by Norsk Epidemiologi.

Figure 5. Norway and Nord-Trøndelag County.

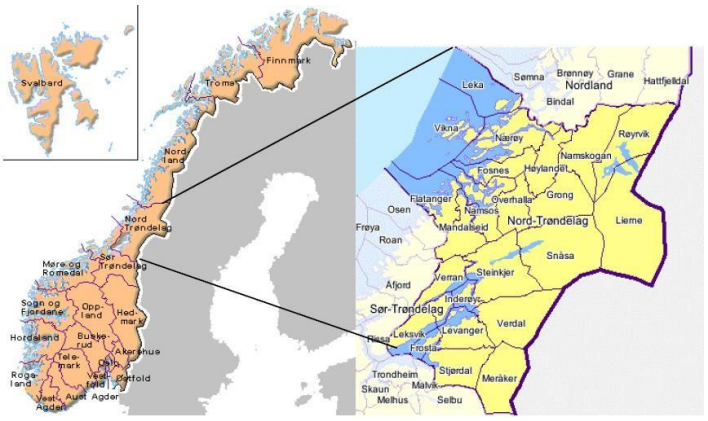


Table 1. Invitation and participation in HUNT1-3

Health survey	HUNT1	HUNT2	HUNT3
Year	1984–86	1995–97	2006–2008
Invited n	86,404	94,187	93,860
Participated n, (%)	77,212 (89.4%)	65,212 (69.2%)	50,807 (54.1%)
Participated in previous HUNT, n	N/A	47,316 (HUNT1)	37,071 (HUNT2)

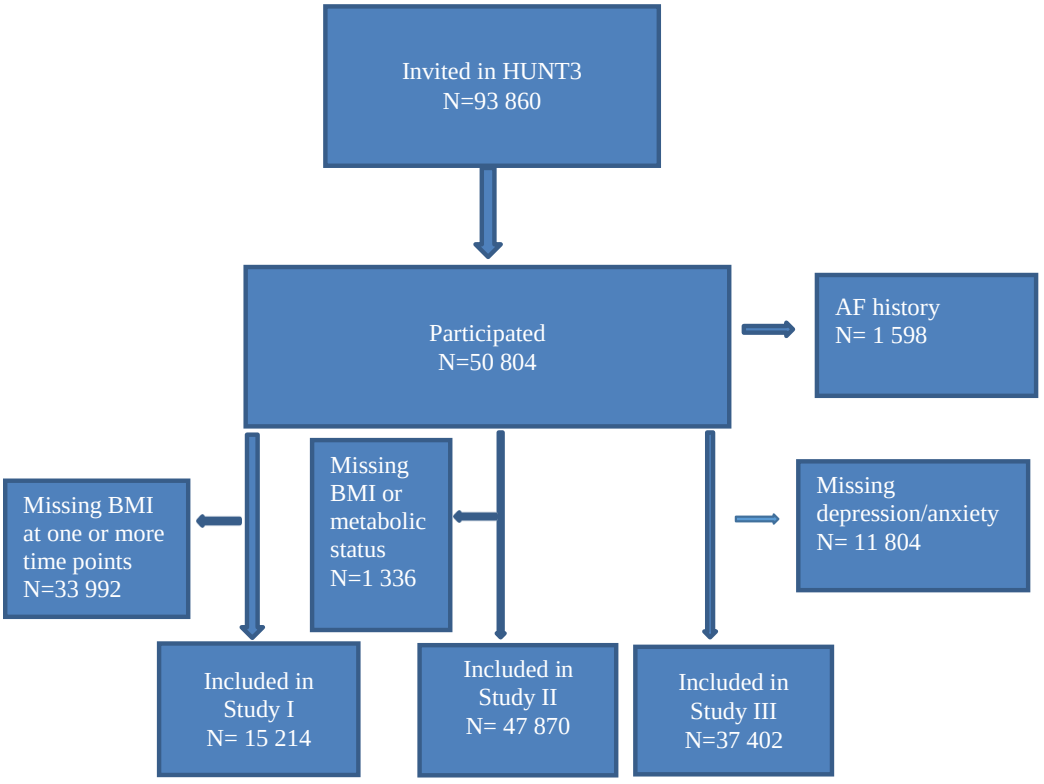
All HUNT surveys were approved by the National Directorate of Health and the Norwegian Data Inspectorate. All participants gave written consent before the baseline examination. Additional approval was given from the regional ethics committee and the HUNT data access committee for all three studies presented in this thesis.

All surveys included standardized clinical examinations (including height, weight, circumferences of the waist and hip, blood pressure) performed by trained nurses and self-report health questionnaires (http://www.ntnu.edu/hunt/data/que). Additionally, blood samples were collected and analyzed, among others, for glucose, triglycerides, high-density lipoprotein (HDL) cholesterol and high-sensitivity C-reactive protein in HUNT2 and HUNT3.[68, 70] The self-report questionnaires were extensive, and were distributed in a

two-step procedure. Questionnaire 1 was delivered by post together with a personal invitation to participate. The participants filled in Questionnaire 1 at home and brought it to the clinical examination. At the examination the attendees received Questionnaire 2, which was taken home, filled in and returned in a prepaid envelope. The response rate was higher on Questionnaire 1 than on Questionnaire 2 in all HUNT waves.[70] Besides measurement of height and weight at HUNT1, 2 and 3, height and weight were also available from a mandatory tuberculosis screening conducted in the county between 1966 and 1969.[71]

For studies included in this thesis, HUNT3 was regarded as the baseline. In total, 93,860 residents were invited and 50,804 (54.1%) of them participated. Participants with history of AF before baseline were excluded (n=1,598). Participants with missing information on BMI, metabolic status, depression/anxiety were excluded from study I-III, respectively. The detailed recruiting process for each study is presented in Figure 6. For study I, we only included individuals who had available information on height and weight from all the four measurements (n= 15,214).

Figure 6. Selection process for the three studies



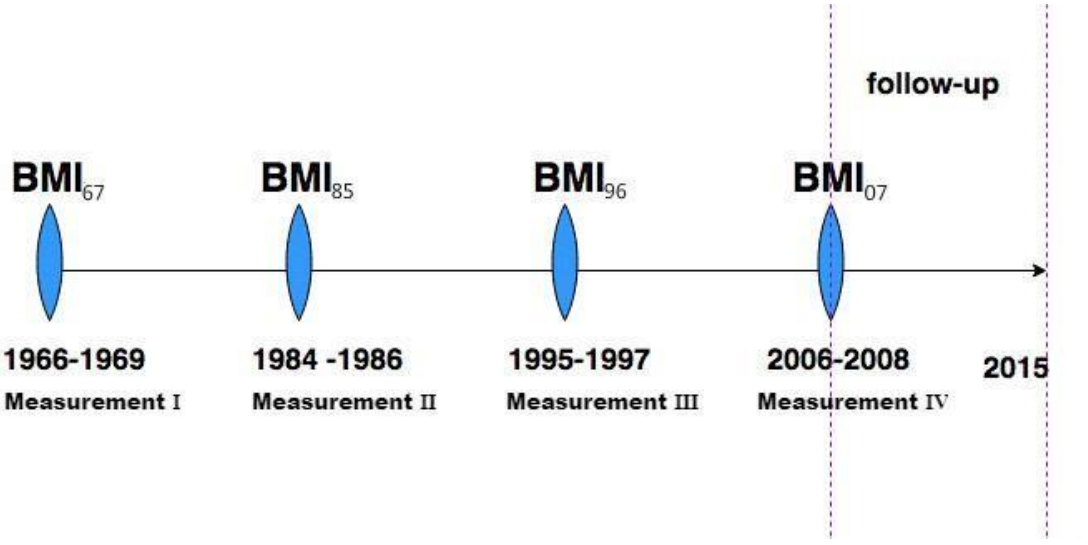
2.2 ASSESSMENT OF EXPOSURE

2.2.1 Weight and weight change

In all surveys, height and weight were measured barefoot and wearing light clothing; height was measured to the nearest cm and weight to the nearest 0.5 kg. BMI was calculated as dividing body weight in kilograms by height in meters squared and divided into 4 categories: <18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).

We denoted BMI at the 4 separate time points by the following terms: at HUNT3 (2006-2008) as BMI_{07}, at HUNT2 (1995-1997) as BMI_{96}, at HUNT1 (1984 -1986) as BMI_{85}, and at the tuberculosis screening (1966-1969) as BMI_{67} (Figure 7)[3].

Figure 7. Flow-chart outlining each body mass index measurement at each time point



Measurement I: BMI measurement at tuberculosis screening (BMI_{67}); Measurement II: BMI measurement at HUNT1 (BMI_{85}); Measurement III: BMI measurement at HUNT2 (BMI_{96}); Measurement Ⅳ: BMI measurement at HUNT3 (BMI_{07}).

[3] Figure 7 is adopted from 'Weight and weight change and risk of atrial fibrillation: the HUNT study' by Feng et al (Paper I)[72] . It is permitted for reuse by Oxford University Press.

We utilized the following equations for further analyses:

1. Average_total_BMI=[(BMI_{67}×$time_{I-II}$)+(BMI_{85}×$time_{II-III}$)+(BMI_{96}×$time_{III-IV}$)+(BMI_{07}×$time_{IV-}$)]/TotalTime.

Where:

$time_{I-II}$=time from measurement I (i.e. in 1966–1969) to measurement II (i.e. in 1984–1986)

$time_{II-III}$=time from measurement II to measurement III (i.e. in 1995–1997)

$time_{III-IV}$=time from measurement III to measurement Ⅳ (i.e. in 2006–2008)

$time_{IV-}$=time from measurement Ⅳ to end of follow-up

TotalTime=total time from measurement I to end of follow-up

2. Average BMI_{67-07}=[(BMI_{67}×$time_{I-II}$)+(BMI_{85}×$time_{II-III}$)+(BMI_{96}×$time_{III-IV}$]/$time_{I-IV}$

Where: $time_{I-IV}$=time from measurement I to measurement Ⅳ.

3. Total BMI change={[(BMI_{85}−BMI_{67})×$time_{I-II}$]+[(BMI_{96}−BMI_{85})×$time_{II-III}$]+[(BMI_{07}−BMI_{96}) ×$time_{III-IV}$]}/$time_{I-IV}$

We then analyzed the effects of BMI change from BMI_{67} to BMI_{07} (total BMI change), from BMI_{67} to BMI_{85} (early BMI change), from BMI_{85} to BMI_{96} (middle BMI change), and from BMI_{96} to BMI_{07} (late BMI change) separately. We classified total, early, middle and late BMI change into 5 categories: <-5 kg/m^2, ≥-5–<-2.5 kg/m^2, ≥-2.5–<2.5 kg/m^2, ≥2.5–<5 kg/m^2, ≥5 kg/m^2.

2.2.2 Metabolically healthy obesity

We used a modified definition of metabolic health based on International Diabetes Federation's description.[73] In our primary analyses, metabolic unhealth was defined as the presence of increased WC (≥102 cm for men, ≥88 cm for women) in addition to 2 or more of the following criteria: increased non-fasting triglycerides (≥1.7mmol/l), decreased HDL (<1.03 mmol/l for men, <1.29 mmol/l for women), increased blood pressure (≥130/85 mm Hg) or use of blood pressure medication, increased non-fasting glucose (≥11.1 mmol/l), or diabetes diagnosis. Stricter criteria for metabolically unhealthy classification was used in secondary analyses, i.e., metabolically healthy individuals had all metabolic parameters within the normal range.

2.2.3 Symptoms of anxiety and depression

The Norwegian version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety (HADS-A) and depression (HADS-D) during the previous week in HUNT2 and 3.[74]

The HADS is a valid and reliable instrument across various patient samples and settings.[75] It comprises 14 self-rated items, with seven items forming the anxiety subscale (HADS-A) and seven items forming the depression subscale (HADS-D). HADS-A reflects symptoms of worry and tension, while HADS-D reflects symptoms of anhedonia and loss of interest. Responses are rated on a 4-point Likert scale ranging from 0 (no symptom) to 3 (highest symptom level). Participants were included in the subsequent analyses only if they answered all of the 14 items. The two subscales were divided into 3 categories: (1) having no symptoms of depression or anxiety (score < 8), (2) having mild to moderate symptoms (score 8–10), and (3) having severe symptoms (score ≥ 11), respectively.[76]

Among the 37,402 eligible participants in HUNT 3, 24,706 individuals had available information on HADS from HUNT2 conducted between 1995 and 1997.[70] A combined burden of anxiety in HUNT2 and 3 was categorized into 3 groups: (1) no anxiety (scoring < 11 on HADS-A in HUNT2 and 3), (2) anxiety at one time (scoring ≥ 11 on HADS-A in one of the HUNT studies), and (3) anxiety at both times (scoring ≥ 11 on HADS-A in both HUNT studies). Accordingly, a combined burden of depression in HUNT2 and 3 was categorized into 3 groups: (1) no depression (scoring < 11 on HADS-D in HUNT 2 and 3), (2) depression at one time (scoring ≥ 11 on HADS-D in one of the HUNT studies), and (3) depression at both times (scoring ≥ 11 on HADS-D in both HUNT studies).

2.3 ASSESSMENT OF OUTCOME

Participants were followed up from October 2006 to June 2008 until the date of diagnosis of AF, death from other causes, emigration from the county or end of follow-up (November 30, 2015), whichever occurred first. AF diagnoses were retrieved from discharge registers at two hospitals that together serve the entire population of Nord-Trøndelag County. We used code I48 from the International Classification of Diseases Tenth Revision (ICD-10) to screen for patients with possible AF. Only physician-diagnosed AF after the date of participation in HUNT3 were included in this study. In addition, persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of hemodynamic instability (e.g., sepsis or non-cardiac surgery) were not regarded as having incident AF.[39] Verified AF was defined as AF or atrial flutter according to ECG recommended by the European Society of Cardiology.[77] If an ECG was unavailable, experts reviewed the medical record for a written interpretation.[39] When the ECG was described by a physician as AF or atrial flutter using standard criteria, the case was defined as verified AF. If the information from medical records was insufficient for exact classification of the diagnosis, two physicians, one specialist in cardiology and one specialist

in internal medicine, evaluated the available information separately, grouping them into two categories: “probable AF” and “not likely AF”. In case of disagreement, the patient was put in the most likely category after a consensus meeting.[39] Information on AF diagnoses before baseline was retrieved from discharge registers and validated in the same way as the AF cases during the follow-up. Only participants free of AF at baseline were included in the study.

2.4 COVARIATES AND OTHER INFORMATION

Self-reported smoking status was assessed using the two questions: “Have you ever tried smoking?” with response options “Yes” and “No”, and “Do you currently smoke?” with response options “Yes” and “No”. Self-reported alcohol consumption was assessed using the question: “How often in the last 12 months did you drink alcohol?”, alcohol consumption was then categorized into (1) abstainers, (2) light drinkers (0 to 1 drinks per day), (3) moderate drinkers (>1 but ≤ 2 drinks per day), (4) heavy drinkers (>2 drinks per day). Self-reported physical activity was assessed by the following question: “How much of your leisure-time have you been physically active in the last year (think of a weekly average for the year)?”. The participants reported number of hours of either light (no sweating or labored breathing) and hard (sweating and labored breathing) activity using the response options: “less than 1 hour”, “1–3 hours”, and “more than 3 hours” for each type of activity. Physical activity was then categorized into (1) inactivity (<3 h of light exercise per week or <1 h hard exercise), (2) moderate activity (≥3 h of light exercise or 1-3 h of hard exercise per week) and (3) high activity (>3 h of hard physical activity per week). Information on common chronic disorders was self-reported and included: angina pectoris, stroke, asthma, osteoarthritis, kidney disease, hyperthyroidism, rheumatoid arthritis, sarcoidosis, ankylosing spondylitis, cancer, epilepsy,

chronic bronchitis, emphysema or chronic obstructive pulmonary disease, psoriasis, diabetes, sleep apnea, acute myocardial infarction, and heart failure. Apart from self-report, information on history of acute myocardial infarction and heart failure was also retrieved from hospital registers.[78]

2.5 STATISTICAL ANALYSIS

In all studies, baseline characteristics were presented as means ± standard deviation for continuous variables and percentages for categorical variables. Cox proportional regression models were used to assess hazard ratios (HRs) and 95% confidence intervals (CI) between exposure groups.[79] We included age, sex, height, smoking, educational level, marital status, physical activity, alcohol consumption, metabolic factors and chronic disorders as potential confounders based on background knowledge. The proportional hazards assumption was tested by comparing -ln-ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption. In additional analyses, multiple imputations (n=5) were used to account for missing data.[80] To assess effect modification, we conducted analyses stratified by age, sex, and chronic diseases. In sensitivity analyses, we regarded possible or single-episode AF during follow-up as events. Furthermore, to address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 2 years of follow-up and repeated the analyses.

For **Paper I**, participants were excluded from the analysis if they had missing values for any of the BMI measurements at any time point (i.e., BMI_{07} at HUNT3, BMI_{96} at HUNT2, BMI_{85} at HUNT1, and BMI_{67} at the tuberculosis screening) (Figure 7). Thus, the main analysis included 15,214 individuals who had available information on BMI at 4 time points. Three distinctive BMI trajectories were identified based on group based trajectory modeling using the Stata Traj Plugin:[81]"normal weight" (51.9% of the population), "overweight" 40.4%, and "obese" 7.7% (Figure 8)[4]. Intraindividual BMI variability was calculated as the square root of the variance or the residual mean square[82] from the 4 residuals from a participant-specific linear regression of the 4 BMI measurements, with participants' age as the independent variable.

HRs for AF were calculated for a given category of (1) average BMI (average BMI 18.5-24.9 kg/m^2 as the reference group), (2) BMI change (change between -2.5 to 2.5 kg/m^2 as the reference group), (3) BMI trajectory (normal weight trajectory as the reference group), (4) BMI variability (the lowest variability between 0 to 1.07 kg/m^2 as the reference group). In the model examining the effect of BMI change and BMI variability, we additionally adjusted for the slope of BMI to disentangle the effects of BMI fluctuations and BMI slope on AF development.[83] To examine whether past or recent BMI was a more important risk factor of AF, we calculated the relative risks according to categories of $BMI_{67\text{-}07}$ (i.e. average BMI from 1967 until baseline), with and without adjustment for the most recent BMI (BMI_{07}), respectively. We did not use the total average BMI (i.e., average BMI from 1967 until the end of follow-up) in these analyses, because the total average BMI included BMI_{07} itself and thus they were highly correlated with each other (Table 2). Similarly, we additionally adjusted for the most recent BMI to calculate HRs among different categories of BMI change.

[4] Figure 8 and Table 2 adopted from 'Weight and weight change and risk of atrial fibrillation: the HUNT study' by Feng et al (Paper I)[72]. They are permitted for reuse by Oxford University Press and Copyright Clearance Center.

Figure 8. Estimated trajectories (solid lines), observed group body mass index (BMI) at each survey year (dot symbols), and estimated group percentages.

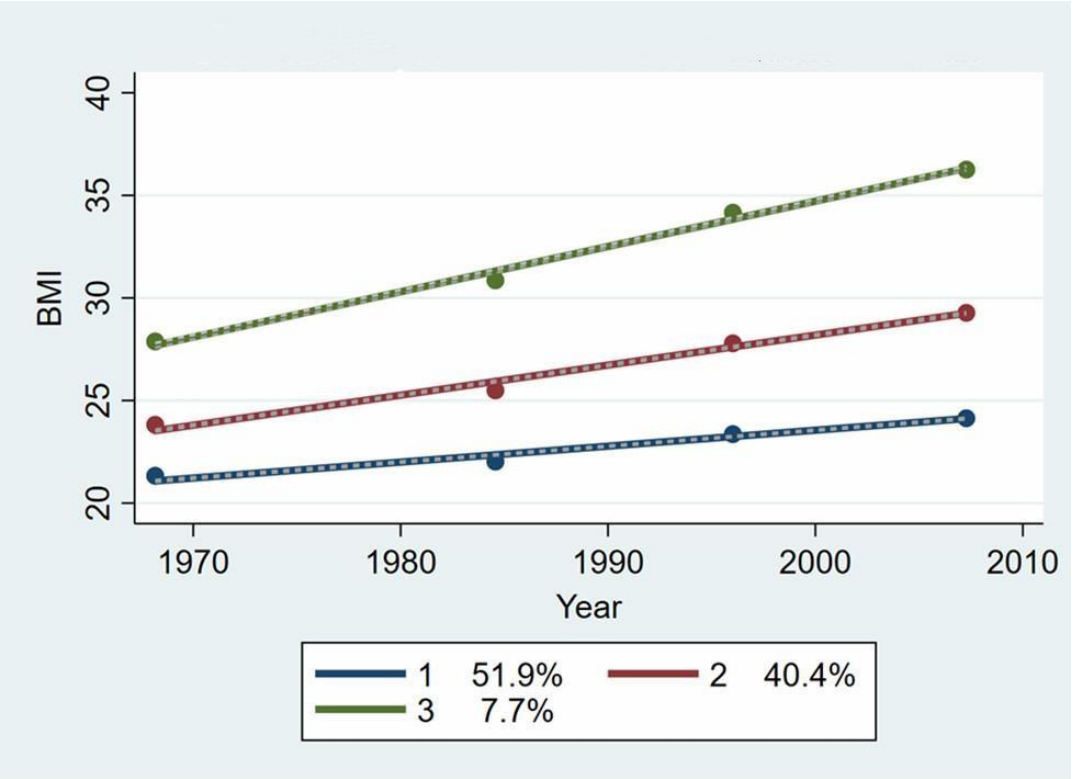


Table 2. Correlations (Spearman's rank correlation coefficients) between measurements of BMI

	Average BMI	$BMI_{67\text{-}07}$	BMI_{07}	BMI_{96}	BMI_{85}	BMI_{67}
Average BMI	1					
$BMI_{67\text{-}07}$	0.9864	1				
BMI_{07}	0.8052	0.7089	1			
BMI_{96}	0.9112	0.8737	0.8735	1		
BMI_{85}	0.9165	0.9213	0.6886	0.8271	1	
BMI_{67}	0.8009	0.8576	0.4188	0.5590	0.6781	1

$BMI_{67\text{-}07}$: average BMI between tuberculosis screening (1966-1969) and HUNT3 (2006-2008), BMI_{07}: BMI at HUNT-3 (2006-2008), BMI_{96}: BMI at HUNT-2 (1995-1997), BMI_{85}: BMI at HUNT-1 (1984 -1986), BMI_{67}: BMI at the tuberculosis screening (1966-1969).

For paper **II**, participants were excluded from the analysis if they had missing values for BMI or metabolic status at the baseline (i.e., at HUNT3). We jointly classified participants into their respective stratum by BMI (<25, 25 to 29.9, and ≥30 kg/m^2) and metabolic status (metabolically healthy and unhealthy). Participants with a BMI <25kg/m^2 and with a healthy metabolic status were regarded as the reference group.

In a separate analysis, we investigated AF risk based on long-term weight stratified by metabolic status. Only participants who had available information on BMI from the tuberculosis screening, HUNT1, HUNT2 and HUNT3 were included in these analysis. Participants were divided into 8 categories: (1) Long-term normal weight (BMI <25 kg/m^2 at all 4 measurements) with metabolically healthy status; (2) Long-term normal weight with metabolically unhealthy status; (3) Long-term overweight/obesity (BMI ≥ 25 kg/m^2 at all 4 measurements) with metabolically healthy status; (4) Long-term overweight/obesity with metabolically unhealthy status; (5) Recently developed overweight/obesity (BMI <25 kg/m^2 in the tuberculosis screening or at HUNT1 or at HUNT2, but ≥25 g/m^2 in HUNT3) with metabolically healthy status; (6) Recently developed overweight/obesity with metabolically unhealthy status; (7) Variable body mass (any other combination of the BMI categories) with metabolically healthy status; (8) Variable body mass with metabolically unhealthy status. We used long-term metabolically healthy normal weight as the reference in these analyses.

For **paper III**, participants were excluded from the analysis if they had missing values for depression or anxiety symptoms at the baseline (i.e., at HUNT3). Participants who reported no symptoms (i.e., scoring < 8 on HADS-A or HADS-D) were regarded as the reference group. We tested linear as well as quadratic trends for the associations of symptoms of anxiety and depression with AF risk. In separate analyses, we assessed the relative risk of AF according to episodes of anxiety and depression in HUNT2 and 3. Participants without

symptoms in any of the HUNT studies were regarded as the reference group.

All statistical analyses were conducted using Stata/MP 15.1 for Windows (College Station, TX: StataCorp LLC).

3 MAIN RESULTS

3.1 WEIGHT AND WEIGHT CHANGE AND RISK OF ATRIAL FIBRILLATION (PAPER I)

During a median follow-up of 8.0 years of 15214 participants (114,511 person-years), 1149 (7.6 %) participants developed AF, 2170 died from other causes and 9 emigrated from the county. Table 3 presents descriptive characteristics of the population (n=15,214) that had available information on BMI at the four time points.[5] Mean BMI increased gradually with time.

[5] Tables and figures in this section are adopted from 'Weight and weight change and risk of atrial fibrillation: the HUNT study' by Feng et al (Paper I)[72]. They are permitted for reuse by Oxford University Press and Copyright Clearance Center.

Table 3. Characteristics of the study population

Age at HUNT-3, y	66.6 (9.5)
Female, n (%)	8743 (57.5)
BMI_{67}, kg /m^2	23.2 (3.1)
BMI_{85}, kg/ m^2	24.7 (3.3)
BMI_{96}, kg /m^2	26.7 (3.8)
BMI_{07}, kg/ m^2	27.6 (4.2)
SBP, mmHg	138.0 (19.6)
DBP, mmHg	75.1 (11.4)
Total cholesterol, mmol/l	5.8 (1.1)
HDL cholesterol, mmol/l	1.4 (0.4)
Triglycerides, mmol/l	1.7 (0.9)
Diabetes mellitus, n (%)	1054 (6.9)
Current smoker, n (%)	2292 (15.7)
Heavy drinkers, n (%)	216 (1.5)
University, n (%)	975 (6.6)
Physically inactive, n (%)	2992 (20.2)
Unmarried, n (%)	839 (5.5)

Values, mean ± standard deviation or number (percent). BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein.

The multivariable-adjusted HRs were 1.2 (95% CI: 1.0-1.4) for average BMI 25.0-29.9 kg/m^2 and 1.6 (95% CI: 1.2-2.0) for average BMI ≥ 30 kg/m^2 when compared to those having a normal weight (Table 4). The risk was lowest among those with an averaged BMI <18.5 kg/m^2.

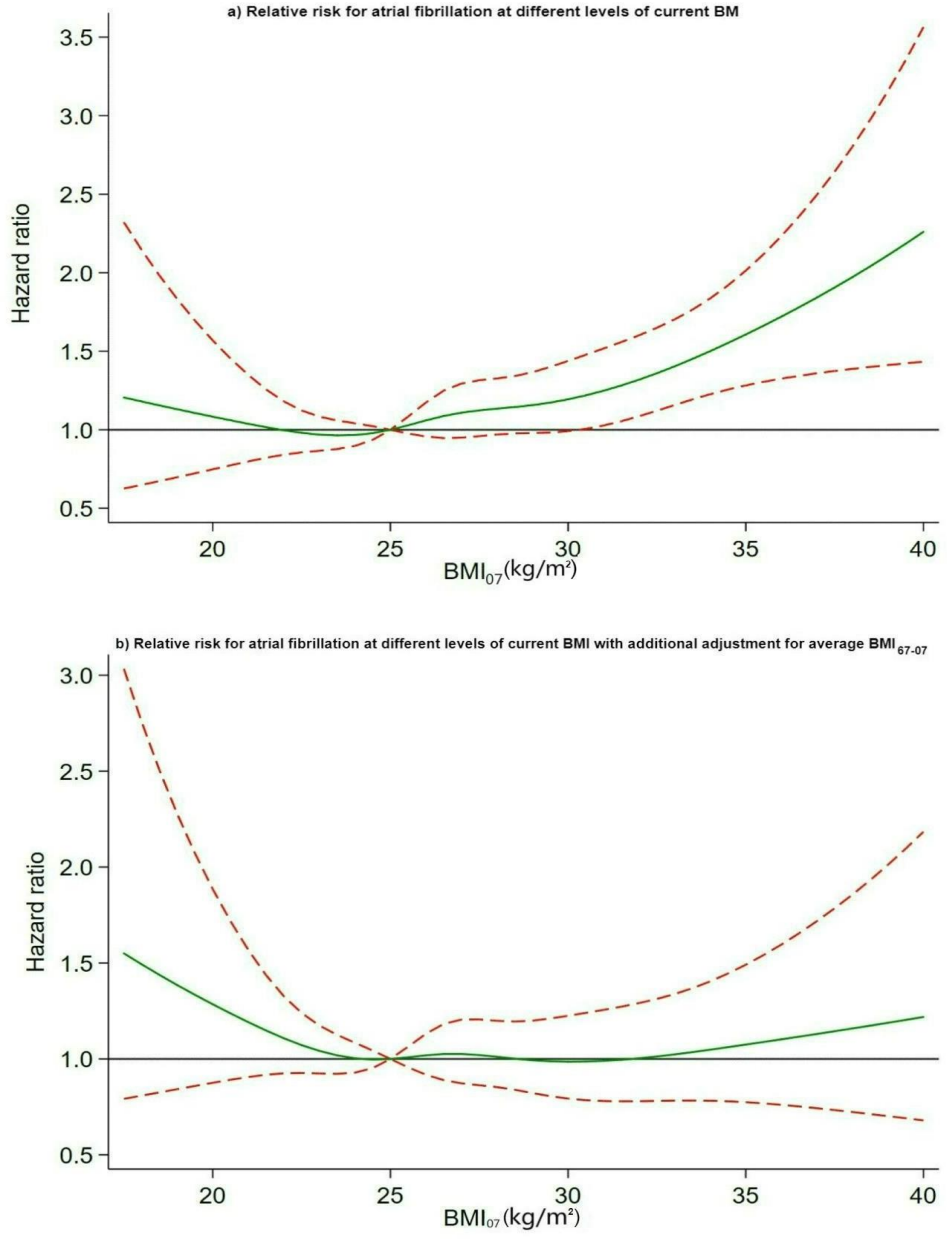
Table 4. Hazard ratios for atrial fibrillation by categories of average body mass index until end of follow-up and by categories of average body mass index until the HUNT-3 measurement

Average BMI from measurement I to end of follow-up							
BMI (kg/m^2)	**Events**	**Person-years**	**Incidence rate[#]**	**HR[a]**	**95% CI**	**HR[b]**	**95% CI**
<18.5	2	386	5.2	0.8	(0.2-3.0)	0.6	(0.1- 4.0)
18.5-24.9	467	61952	7.5	1	(Ref.)	1	(Ref.)
25.0-29.9	555	44725	12.4	1.2	(1.1-1.4)	1.2	(1.0-1.4)
≥30.0	125	7448	16.8	1.6	(1.3-2.0)	1.6	(1.2-2.0)
Average BMI from measurement I to measurement IV							
BMI (kg/m^2)	**Events**	**Person-years**	**Incidence rate[#]**	**HR[b]**	**95% CI**	**HR[c]**	**95% CI**
<18.5	1	586	1.7	-	-	-	-
18.5-24.9	495	69627	7.1	1	(Ref.)	1	(Ref.)
25.0-29.9	537	38540	13.9	1.3	(1.2-1.6)	1.2	(1.0-1.5)
≥30.0	116	5759	20.1	1.9	(1.4-2.4)	1.6	(1.1-2.2)

[#]Incidence rate per 1000 persons-years .
HR[a]: adjusted for age, sex.
HR[b]: adjusted for age, sex, height , smoking status, education, marital status, physical activity, and alcohol consumption,
HR[c]: adjusted for age, sex, height , smoking status, education, marital status, physical activity, alcohol consumption and *the most recent BMI (BMI_{07})*,
BMI= body mass index; CI = confidence interval; HR= Hazard ratio

We examined the relative importance of the most recent BMI and that of the average of the former BMI values. Average BMI earlier in life was associated with AF risk, the risk was higher in both the overweight (HR: 1.2, 95% CI: 1.0-1.5) and obese (HR: 1.6, 95% CI: 1.1-2.2) groups compared to the normal weight group, even after adjustment for BMI at the beginning of follow-up (Table 4). In contrast, current BMI was not strongly associated with the risk of AF after adjustment for average BMI earlier in life (Figure 9).

Figure 9. Hazard ratios of atrial fibrillation and body mass index at baseline.



Hazard ratios of atrial fibrillation and body mass index (BMI) at baseline adjusted for sex, age, height, smoking status, level of education, marital status, physical activity and alcohol consumption (a) and additional adjustment for average BMI up to baseline (b).

Compared to stable BMI, both loss and gain in BMI were associated with increased AF risk (Table 5). For the total BMI change, there was an almost 3-fold increase in AF risk among those with a BMI gain of more than 5.0 kg/m^2 compared to those with a stable BMI (i.e., change between 2.5 to -2.5 kg/m^2). For early, middle and late BMI gain, a BMI gain of more than 5 kg/m^2 also showed a considerably higher AF risk compared to a stable BMI. The relative risks for late-period BMI gain were higher than that for the early- and middle-period BMI gain. The results were similar after additional adjustment for chronic disorders and the most recent BMI, respectively (results not shown). Figure 10 shows the relative risks of AF according to change in BMI (from measurement I to measurement Ⅳ) with and without adjustment for the most recent BMI. After adjustment for the most recent BMI, the association of BMI gain with AF risk was largely unchanged while the association of BMI loss with AF risk was considerably weakened.

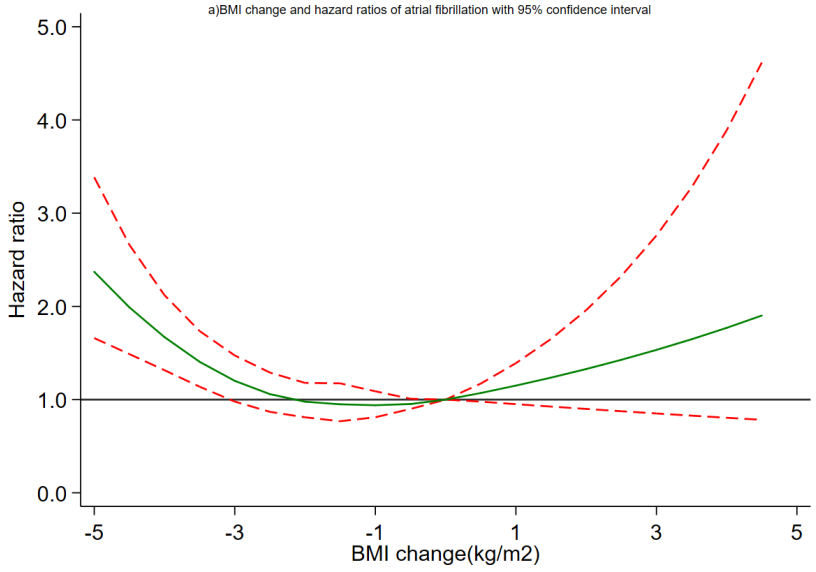
When examining the effect of weight trajectory and weight variability, we found that the relative risk for incident AF was highest in the obese trajectory group (HR: 1.9, 95% CI: 1.5-2.4, when compared to the normal weight trajectory group), followed by the overweight trajectory group (HR: 1.2, 95% CI: 1.0-1.4) (Table 6), and participants with the highest degree of weight variability showed higher AF risk compared to those with the lowest weight variability (HR: 1.5, 95% CI: 1.2-1.8) (Table 6).

Table 5. Hazard ratios for atrial fibrillation by categories of total, early, middle and late body mass index change

BMI change (kg/m^2)	Whole period (1967-2007)	Early period (1967-1985)	Middle period (1985-1996)	Late period (1996-2007)
<-5.0	-	1.5 (0.5-4.6)	-	1.6 (0.8-2.9)
≥-5.0 – <-2.5	1.3 (0.3-5.4)	0.9 (0.6-1.3)	1.7 (1.0-3.1)	1.2 (0.9-1.5)
≥-2.5 – <2.5	(Ref.)	(Ref.)	(Ref.)	(Ref.)
≥2.5 – <5.0	1.1 (0.9-1.5)	1.1 (0.9-1.3)	0.9 (0.8-1.1)	1.0 (0.8-1.2)
≥5.0	2.6 (1.3-5.2)	1.3 (1.0-1.8)	1.1 (0.8-1.4)	1.5 (1.0-2.2)

BMI=body mass index.
Results were presented as hazard ratio (95% confidence interval)
Hazard ratios were adjusted for sex, age, smoking status, education, marital status, physical activity, alcohol consumption, and regression slope of BMI.

Figure 10. Hazard ratios of atrial fibrillation and body mass index change from measurement I to measurement Ⅳ, adjusted for sex, age, height, smoking status, level of education, marital status, physical activity and alcohol consumption (a) and additional adjustment for the most recent body mass index (b). BMI = body mass index.



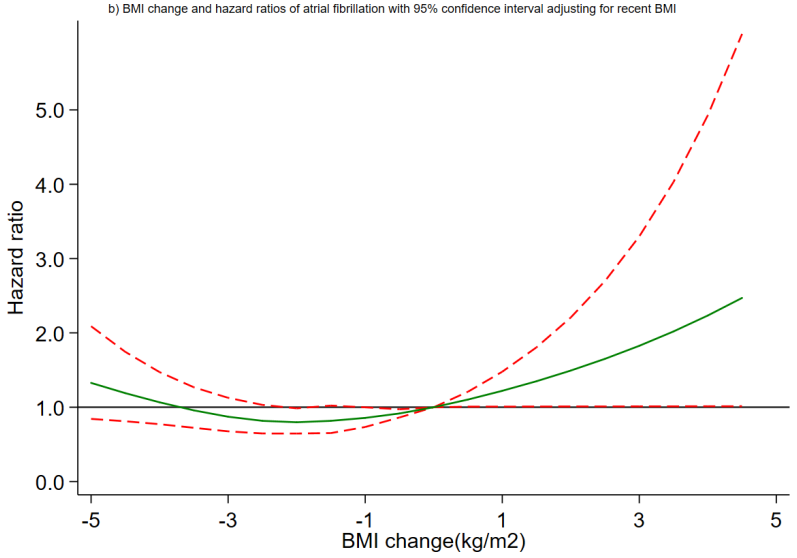


Table 6. Hazard ratios for atrial fibrillation by BMI trajectories and intra-individual BMI variability

	Events	Incidence rate[#]	HR	95% CI
BMI trajectory				
Normal weight	390	7.6	1	(Ref.)
Overweight	587	11.0	1.2	(1.0-1.4)
Obesity	172	17.0	1.9	(1.5-2.4)
Intra-individual BMI variability				
0-1.07	246	8.4	1	(Ref.)
1.08-1.59	287	9.9	1.3	(1.0-1.5)
1.60-2.29	279	9.8	1.1	(0.9-1.4)
≥2.29	337	12.1	1.5	(1.2-1.8)

BMI trajectories were identified based on group-based trajectory modeling by using Stata Traj Plugin.

Intra-individual BMI variability was calculated as the square root of the variance or the residual mean square, from the 4 residuals from the participant-specific regressions.

[#]Incidence rate per 1000 persons-years .

Models were adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, alcohol consumption metabolic status and chronic disorders.

BMI= body mass index; CI = confidence interval; HR= Hazard ratio.

In **stratified analyses**, the relative risks for AF tended to be higher for individuals younger than 65 years than for those who were older by categories of average BMI. For BMI change, the relative risks for AF were lower for individuals younger than 65 years than for those who were older. The relative risks for AF were generally similar between women and men by categories of average BMI and BMI change, respectively.

In **sensitivity analyses**, the results were consistent with the main analyses when possible or single-episode AF events were regarded as AF during follow-up. There were 926 AF cases after the second year of follow-up. There was no decrease in the estimates after exclusion of the first 2 years of follow-up. The results remained generally comparable to that of the main analysis when we used multiple imputation.

3.2 METABOLICALLY HEALTHY OBESITY AND RISK OF ATRIAL FIBRILLATION (PAPER II)

During a median follow-up of 8 years of 47,870 participants (367,515 person-years), 1,758 (3.7 %) participants developed AF, 3,554 participants died from other causes and 133 participants emigrated from the county. There were 10,775 (22.5%) obese and 19,332 (40.4%) metabolically unhealthy participants. Among the obese, 27.4% were metabolically healthy. Participants with metabolically healthy obesity tended to be women, younger, and unmarried compared to those with metabolically unhealthy obesity (Table 7).[6]

[6] Tables in this section are adopted from 'Metabolically Healthy Obesity and Risk for Atrial Fibrillation: The HUNT Study' by Feng et al (Paper II)[84]. They are permitted for reuse by John Wiley and Sons and Copyright Clearance Center.

Table 7. Baseline characteristics by categories of body mass index and metabolic status

Metabolic Status **BMI**	**Healthy** **BMI <25.0** (n = 14,325)	**Unhealthy** **BMI <25.0** (n = 2,049)	**Healthy** **BMI 25-29.9** (n = 11,257)	**Unhealthy** **BMI 25-29.9** (n = 9,464)	**Healthy** **BMI ≥30** (n = 2,956)	**Unhealthy** **BMI ≥30** (n = 7,819)
Incident AF, n (%)	322(2.3)	92(4.5)	295(2.6)	514(5.4)	112(3.8)	423(5.4)
Age, y	47.7 ± 16.6	59.9 ± 15.4	50.7 ± 14.7	58.4 ± 14.1	50.6 ± 15.0	56.2 ± 14.3
Female, n (%)	9035(63.1)	1586 (77.4)	5334(47.4)	4284(45.3)	2018 (68.3)	4006 (51.2)
BMI, kg/m^2	22.6 ± 1.7	23.6 ± 1.2	27.0 ± 1.3	27.7 ± 1.4	32.9 ± 3.0	33.5 ± 3.3
SBP, mm Hg	123.3 ± 17.3	136.4 ± 19.9	127.2 ± 16.6	138.0 ± 17.9	128.6 ± 16.9	138.7 ± 17.6
DBP, mm Hg	69.5 ±10.5	74.0 ± 11.5	72.4 ± 10.6	77.2 ± 11.1	72.9 ± 10.4	77.2 ± 10.9
Total cholesterol, mmol/l	5.3 ± 1.1	5.7 ± 1.2	5.5 ± 1.0	5.7 ± 1.1	5.5 ± 1.0	5.6 ± 1.1
HDL cholesterol, mmol/l	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	1.1 ± 0.3
Triglycerides, mmol/l	1.1 ± 0.6	1.8 ± 0.9	1.3 ± 0.7	2.1 ± 1.1	1.3 ± 0.5	2.4 ± 1.2
Diabetes mellitus, n (%)	185 (1.3)	135 (6.6)	128 (1.1)	674 (7.1)	20 (0.7)	878 (11.2)
Abdominal obesity, n (%)	1071 (7.5)	626 (30.6)	4117(36.6)	5348 (56.5)	2699 (91.3)	7331 (93.8)
CRP, mg/l	1.9 ± 5.4	3.0 ± 6.5	2.2 ± 4.7	2.8 ± 5.7	3.6± 5.2	3.9 ± 6.1
Time since last meal, h	2.8 ± 2.1	2.5 ± 1.8	2.9 ± 2.2	2.6 ± 1.9	3.1 ± 2.3	2.9 ± 2.2
Blood pressure medication, n (%)	1253 (8.8)	557 (27.2)	1357 (12.1)	3125 (33.0)	472 (15.9)	3276 (41.9)
Current smoker, n (%)	2837(20.3)	545 (27.7)	1594 (14.5)	1651 (17.9)	399 (13.9)	1185 (15.6)
Heavy drinkers, n (%)	209 (1.5)	39 (1.9)	157 (1.4)	150 (1.6)	29 (1.0)	93 (1.2)
Graduate school, n (%)	1044 (11.6)	149 (9.1)	790 (9.9)	590 (7.8)	138 (6.8)	317 (5.4)
Physically inactive, n (%)	3437 (30.9)	707 (43.5)	2938 (33.3)	3357(44.4)	966 (42.3)	3086 (50.5)
Unmarried, n (%)	4518(31.6)	272 (13.3)	2707 (24.1)	1431 (15.1)	760 (25.7)	1543 (19.7)

Values mean ± SD or n (%). BMI = body mass index; CRP = C-reactive protein; DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure.

The results showed that metabolically healthy and unhealthy obesity were associated with similarly increased AF risk. Age- and sex-adjusted HRs for metabolically healthy and unhealthy obesity were 1.7 (95% CI: 1.4 to 2.2) and 1.6 (95% CI: 1.4 to 1.9), respectively, compared with metabolically healthy normal weight (Table 8). Multivariable-adjusted HRs for metabolically healthy and unhealthy obesity were 1.6 (95% CI, 1.2–2.1) and 1.6 (95% CI, 1.3–1.9), respectively (Table 8).

Table 8. Hazard ratios of atrial fibrillation, by categories of body mass index and metabolic status

BMI (kg/m^2)	Metabolic Status	N	Events	Person-years	Incidence rate[#]	Crude HR	95% CI	HR[*]	95% CI	HR[†]	95% CI
<25.0	Healthy	14,325	322	109068	2.6	1.0	(Ref.)	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	2,049	92	15232	6.0	2.0	(1.6-2.6)	1.0	(0.8-1.3)	1.0	(0.8-1.4)
25.0-29.9	Healthy	11,257	295	87421	3.4	1.1	(1.0-1.3)	1.0	(0.9-1.2)	1.1	(0.9-1.4)
	Unhealthy	9,464	514	71876	7.2	2.4	(2.1-2.8)	1.3	(1.2-1.5)	1.3	(1.1-1.6)
≥30.0	Healthy	2,956	112	22854	5.0	1.7	(1.3-2.1)	1.7	(1.4-2.2)	1.6	(1.2-2.1)
	Unhealthy	7,819	423	59945	7.1	2.4	(2.1-2.8)	1.6	(1.4-1.9)	1.6	(1.3-1.9)

N: total numbers within each category. [#]Incidence rate per 1000 persons-years .[*]Hazard ratio adjusted for age at baseline (continuous) and sex. [†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

When we subdivided BMI into four categories, AF risk was not consistently higher among metabolically unhealthy than among metabolically healthy participants within each BMI category. AF risk increased according to the severity of obesity (Table 9).

Table 9. Hazard ratios of atrial fibrillation, by 4 categories of body mass index and metabolic status

BMI (kg/m^2)	Metabolic Status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
<25	Healthy	13,989	307	106693	2.9	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	1,935	92	14424	6.4	1.1	(0.9-1.4)	1.1	(0.8-1.5)
25-29.9	Healthy	11,593	310	90169	3.4	1.1	(0.9-1.2)	1.1	(0.9-1.4)
	Unhealthy	9,578	514	73140	7.0	1.3	(1.2-1.5)	1.3	(1.1-1.6)
30-34.9	Healthy	2,423	91	18820	4.8	1.7	(1.3-2.1)	1.6	(1.1-2.1)
	Unhealthy	5,912	300	45535	6.6	1.4	(1.2-1.7)	1.4	(1.2-1.7)
≥35	Healthy	533	21	4082	5.1	2.4	(1.5-3.7)	1.7	(0.8-3.4)
	Unhealthy	1,907	123	14651	8.4	2.5	(2.0-3.0)	2.5	(1.9-3.3)

Ns: total numbers within each category. [#]Incidence rate per 1000 persons-years. [*]Hazard ratio adjusted for age at baseline (continuous) and sex. [†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

The multivariable-adjusted HRs for long-term metabolically healthy and unhealthy overweight/obesity were 1.6 (95% CI: 1.1-2.4) and 1.4 (95% CI: 1.1-1.9), respectively, compared to long-term metabolically healthy normal weight (Table 10). Among those who recently developed overweight/obesity, AF risk was not substantially altered especially among those who were metabolically healthy, but slightly higher risk was observed among those who were metabolically unhealthy.

Table 10. Hazard ratios of atrial fibrillation, by trajectories of body mass index and metabolic status

BMI	Metabolic Status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
Long-term normal weight	Healthy	2,676	147	20330	7.2	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	699	38	5098	7.5	1.0	(0.7-1.4)	1.1	(0.7-1.6)
Long-term overweight/ obesity	Healthy	364	54	2580	20.9	1.6	(1.2-2.2)	1.6	(1.1-2.4)
	Unhealthy	776	112	5449	20.6	1.5	(1.2-1.9)	1.4	(1.1-1.9)
Recently developed overweight /obesity	Healthy	946	43	7354	5.9	0.9	(0.7-1.3)	0.9	(0.6-1.4)
	Unhealthy	906	54	6922	7.8	1.2	(0.9-1.6)	1.3	(0.9-1.8)
Varying body mass	Healthy	3,139	218	23841	9.1	1.2	(0.9-1.5)	1.3	(0.9-1.6)
	Unhealthy	5,494	460	41016	11.2	1.4	(1.2-1.7)	1.4	(1.1-1.7)

Ns: total numbers within each category. [#]Incidence rate per 1000 persons-years. [*]Hazard ratio adjusted for age at baseline (continuous) and sex. [†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

In the **sensitivity analysis**, the multivariable-adjusted HRs were slightly higher after excluding participants with a chronic disease at baseline. The associations were similar as the main analysis when we regarded possible or single-episode AF as events during follow-up. When we used stricter criteria to define metabolic health (i.e., metabolically healthy individuals had all metabolic parameters within the normal range), the HRs were markedly higher among obese participants regardless of metabolic status. The HRs did not differ much among those with and without each metabolic component, except that participants with a hypertension showed a considerably higher AF risk than those without hypertension. There were 1,431 AF cases after the second year of follow-up. The estimates remained essentially unchanged after exclusion of the first 2 years of follow-up. The estimates remained largely comparable to those in main analyses when we used multiple imputation.

3.3 SYMPTOMS OF ANXIETY AND DEPRESSION AND RISK OF ATRIAL FIBRILLATION (PAPER III)

Characteristics of 37,402 participants with and without subsequent AF are presented in Table 11. During a median follow-up of 8 years (288,460 person-years), 1,433 (3.8 %) participants developed AF, 2,457 participants died from other causes and 82 participants emigrated from the county. Using a cutoff score of 11 and above for severe symptoms, 2.2% of the participants reported depression and 4.9% reported anxiety. The participants that developed AF were older and more likely to be men, inactive, heavy drinkers, and scored higher on the HADS-D subscale.

Table 11. Baseline characteristics of participants in the total population according to atrial fibrillation vs. no atrial fibrillation during follow-up

Variable	No. of subjects	Total population	AF during follow-up	No AF during follow-up
Total % (n)	37,402	%	3.8 (1,433)	96.2 (35,969)
Variables, % (n)				
Female	21,122	56.5	41.5 (595)	57.1 (20,527)
Diabetes mellitus	1,636	4.4	10.3 (148)	4.1 (1,488)
Current smoker	6,081	16.7	12.5 (173)	16.8 (5,908)
Heavy drinkers	523	1.4	2.5 (35)	1.4 (488)
Technicians	7,234	20.2	12.3 (164)	20.5 (7,070)
Physically inactive	7,470	20.3	24.1 (336)	20.1 (7,134)
Cohabitation	22,798	61.0	64.7 (927)	60.9 (21,871)
Mean (SD)				
Age, years	37,402	53.4 (15.2)	70.1 (10.9)	52.8 (15.0)
Body mass index, kg/m^2	37,289	27.2 (4.4)	28.2 (4.6)	27.1 (4.4)
HADS—depression score (HUNT 3)	37,402	3.3 (2.9)	4.0 (2.9)	3.3 (2.9)
HADS—anxiety score (HUNT 3)	37,402	4.0 (3.3)	3.7 (3.0)	4.0 (3.3)

AF: atrial fibrillation; HADS: Hospital Anxiety and Depression Scale

The results showed that only mild to moderate depression was associated with an increased AF risk while there was no evidence for an association between severe depression or anxiety and AF risk (Table 12). In comparisons with no depression, the multivariable-adjusted HRs were 1.5 (95% CI: 1.2-1.8) for mild to moderate depression and 0.9 (95% CI: 0.6-1.3) for severe depression, respectively (P = 0.002 for quadratic trend). Additional adjustment for chronic disorders or metabolic status did not materially change the estimates.

Participants with recurrent anxiety or depression did not have higher relative risks of incident AF compared to those without anxiety or depression at any of the HUNT studies (Table 13). In comparisons with no anxiety, the multivariable-adjusted HRs were 1.0 (95% CI: 0.5-1.9) for recurrent anxiety. In comparisons with no depression, the multivariable-adjusted HRs were 0.9 (95% CI: 0.4-2.0) for recurrent depression. Additional adjustment for chronic disorders or metabolic status did not materially change the estimates.

Table 12. Hazard ratios (95% confidence intervals) for atrial fibrillation during follow up according to symptoms of anxiety (HADS-A) and depression (HADS-D) in HUNT 3

	Model 1	**Model 2**	**Model 3**	**Model 4**
Events/person-years	1,433/ 288,460	1,235/ 266,671	1,186/ 256,765	1,205/ 260,753
HADS-A				
0–7	Reference	Reference	Reference	Reference
8–10	1.0 (0.8-1.3)	1.1 (0.9-1.5)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
≥11	1.1 (0.8-1.4)	1.0 (0.8-1.4)	1.0 (0.7-1.4)	1.1 (0.8-1.5)
***P* for linear trend**	0.5092	0.7865	0.9603	0.6695
***P* for quadratic trend**	0.8193	0.5454	0.5736	0.7501
HADS-D				
0–7	Reference	Reference	Reference	Reference
8–10	1.3 (1.0-1.6)	1.5 (1.2-1.8)	1.4 (1.1-1.7)	1.5 (1.2-1.8)
≥11	0.9 (0.7-1.3)	0.9 (0.6-1.3)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
***P* for linear trend**	0.6503	0.4552	0.3942	0.3648
***P* for quadratic trend**	0.0371	0.0021	0.0070	0.0014

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.
Model 1: adjusted for age and sex.
Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.
Model 3: Mode 2 + chronic disorders.
Model 4: Mode 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein.).

Table 13. Episodes of anxiety and depression in HUNT 2 and 3, and risk for atrial fibrillation

	Model 1	**Model 2**	**Model 3**	**Model 4**
Episodes of anxiety Events/person-years	1,064/ 197,659	941/185,194	905/178,283	919/181,398
No anxiety	Reference	Reference	Reference	Reference
Anxiety at one time	1.2 (0.9-1.6)	1.1 (0.9-1.5)	1.1 (0.8-1.4)	1.2 (0.9-1.6)
Anxiety at two times	0.9 (0.5-1.6)	1.0 (0.5-1.9)	0.9 (0.5-1.8)	1.0 (0.5-2.0)
***P* for linear trend**	0.6947	0.8987	0.8585	0.9624
***P* for quadratic trend**	0.2050	0.5131	0.7950	0.5304
Episodes of depression Events/person-years	1,189/209,075	1,039/194,757	998/187,170	1,015/190,694
No depression	Reference	Reference	Reference	Reference
Depression at one time	1.2 (0.9-1.6)	1.2 (0.9-1.6)	1.1 (0.8-1.6)	1.2 (0.9-1.6)
Depression at two times	0.9 (0.4-1.9)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.8 (0.3-1.9)
***P* for linear trend**	0.8137	0.7818	0.8480	0.5888
***P* for quadratic trend**	0.3748	0.3898	0.4934	0.2843

Model 1: adjusted for age and sex.
Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.
Model 3: Mode 2 + chronic disorders.
Model 4: Mode 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein.).

We found no major effect modification by age, sex, or chronic disease. In general, the HRs tended to be higher among younger individuals, men, and participants without chronic disease.

A total of 1,165 AF cases occurred after the second year of follow-up. Exclusion of the first 2 years of follow-up had little effect on the results. The results were also consistent with the main analyses when possible or single-episode AF events (n=99) were regarded as AF during follow-up. Finally, when we performed multiple imputation, the results were similar to those in the primary analysis.

4 DISCUSSION

4.1 MAIN FINDINGS

We investigated the associations of weight and weight change (Paper I), of metabolically healthy obesity (Paper II) and of symptoms of anxiety and depression (Paper III) with risk of AF. Our main findings are briefly summarized as follows:

(1) Long-term obesity and BMI change were associated with AF risk. Obesity earlier in life and weight gain over time exerted cumulative effects on AF development even after accounting for the most recent BMI.

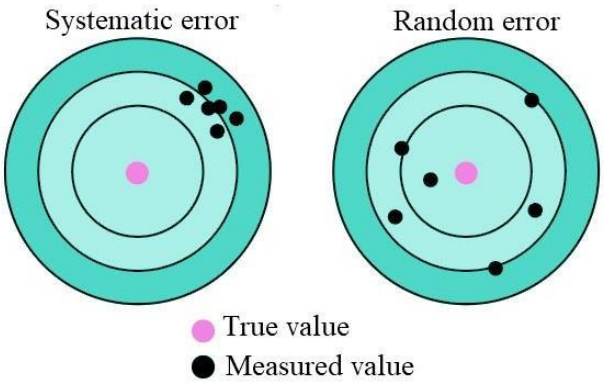
(2) Metabolically healthy and unhealthy obesity increased AF risk to a similar extent. Severity of obesity was positively associated with AF risk regardless of metabolic status.

(3) Anxiety or severe depression was not associated with AF risk, not even for recurrent anxiety or depression. An unexpected association of mild to moderate depression with increased AF risk requires confirmation in subsequent studies.

4.2 METHODOLOGICAL CONSIDERATIONS

This thesis is based on prospective epidemiological studies. The overall general goal in epidemiological studies is to ensure that the estimates of effects are as valid and precise as possible.[40] Error in these estimates is defined as the difference between the observed and the true, i.e., causal value and is classified either as random error (i.e. the degree of precision) or systematic error (i.e. the degree of validity). Figure 11 demonstrates the essential difference between these two types of error in epidemiology.

Figure 11. Random error versus systematic error.

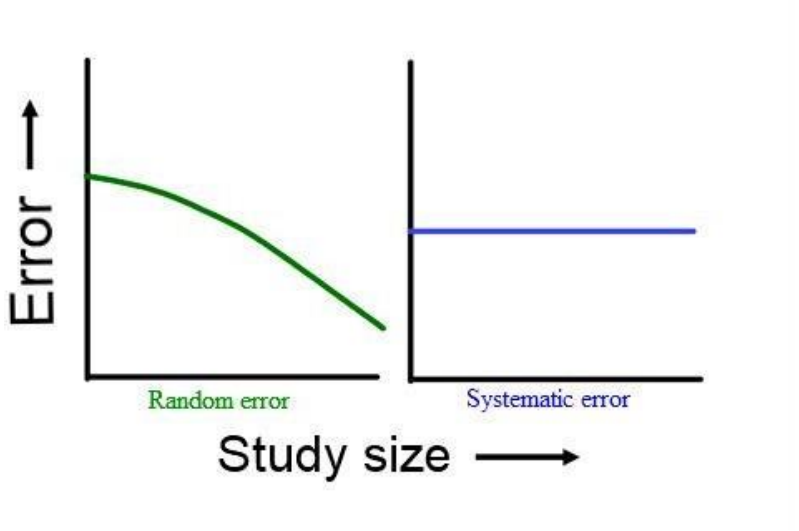


4.2.1 Random error

Kenneth Rothman defines random error as "that part of our experience that we cannot predict".[40] A principal assumption in epidemiology is that we can draw an inference about the experience of the entire population based on the evaluation of a sample of the population. However, a problem with drawing such an inference is that the play of chance may affect the results because of the effects of random variation from sample to sample. Random error can be reduced by increasing the sample size (Figure 12). In study II and III, we used a large sample size of 47,870 and 37,402 subjects, respectively. Although Study I had a relatively smaller sample size compared to Study II and III, the sample size was still larger than most prior studies in this field. The large sample size in these studies also allowed us to perform several sub-group analyses.

The most common way to express random error in epidemiology is by presenting confidence intervals. In our studies, the width of the confidence intervals was generally narrow when comparing to previous studies.

Figure 12. The relationship between random error, systematic error, and study size.



4.2.2 Systematic error

Systematic error is not determined by chance and cannot be reduced by increasing the sample size.[40] (Figure 12). Systematic error can originate from selection bias, information bias or confounding.[40]

Selection bias is due to an erroneous selection of study participants.

Factors affecting enrollment of participants into a population based cohort study such as HUNT generally do not introduce a major selection bias.[85] However, retention of subjects may be related to the exposure and outcome and thus can lead to a considerable over- or underestimation of an association. This type of selection bias is also referred to as biased loss to follow up.[40] Administrative loss to follow-up in our studies was minimal due to: 1) use of health registries and tracking the individuals by their unique Norwegian 11-digit personal identification number; 2) the high residential stability of the Nord-Trøndelag county (with less than 0.3% net migration/year).[67]

Our studies were probably somewhat more susceptible to biased follow up due to competing risks.[86] Competing risks are events during follow-up that can preclude the observation of the event of interest, and thereby prevent us from knowing whether the event of interest would happen had the competing event not have happened.[86] For example, hypertension is an important risk factor for both AF and mortality,[87, 88] thus the competing risk event (i.e., death due to hypertension) might have precluded us from observing AF during follow-up. However, given the relatively low number of deaths, competing risks was most probably not a major threat for validity in this thesis.

Information bias is a distortion in the estimate of an association due to incorrect measurement of study variables. The measurement error can be differential or non-differential.[40]

Differential misclassification occurs when the misclassification of the exposure or the outcome is affected by the outcome or the exposure, respectively. That is, the misclassification of exposure is dependent on disease status, or the misclassification of disease status is dependent on exposure status. Differential misclassification can lead to either over- or underestimation of the true association.[40]

Non-differential misclassification occurs when there is an equal likelihood of misclassification across diseased/nondiseased or exposed/unexposed groups, respectively.[40] That is, misclassification of exposure is non-differential if the misclassification is independent of a person's outcome status. And misclassification of outcome is non-differential if the misclassification is independent of a person's exposure status. Non-differential misclassification usually leads to an underestimation of the strength of association, i.e., to a bias “towards the null", rarely leads to an overestimation, and in some situations it does not cause any bias just increases the amount of random error.[40]

There was a possibility for both differential and non-differential misclassification of the identification and ascertainment of AF in our study. However, in contrast to several previous studies, AF diagnoses were retrieved from hospital discharge registers and were then verified by experts, which ensured the minimization of false positive cases. However, AF can be occult and we only identified AF cases that came to clinical attention. Therefore, under-detection of AF is likely to exist in our findings. Weight, metabolic status or anxiety/depression of the participants might have affected their motivation to seek for clinical examinations. For example, metabolically unhealthy people may tend to have a higher detection rate of AF due to comorbidity demanding check-ups or hospitalizations,[89]

compared to metabolically healthy counterparts. Thus, there may exist a higher degree of underestimation of incident AF among metabolically healthy than among unhealthy participants.

In most previous studies, anthropometric indices derived from self-reported information has been suggested to contribute to an exposure misclassification.[89-91] Most previous research used self-reported prior weight status,[33, 34] and thus can suffer from substantial misclassifications.[92] In contrast, we relied on actual measurements of weight and height, hence minimizing such misclassifications. However, we had a lot of self-reported information in our studies. Self-report is particularly prone to exposure misclassification as during self-reporting, participants have a tendency to present themselves in a more positive light that is socially acceptable, e.g., respondents are inclined to underreport undesirable behaviors, such as smoking and drinking, and overreport their exercise levels in terms of frequency, duration, and intensity.[93]

Confounding arises when the exposure and outcome share a common cause, which can lead to a biased estimate of the effect of exposure on disease. The bias can be negative—resulting in an underestimation of the exposure effect—or positive and can even reverse the true direction of effect. We attempted to control or minimize confounding by adjusting for potential confounding factors. In the three studies, expert knowledge, prior evidence and careful reasoning were used to identify confounders.[43, 48, 62] A wide range of variables were available for us including demographic factors, education level, marital status, occupation, established cardiovascular risk factors and presence of several comorbid conditions among others. Meanwhile, unmeasured confounding or residual confounding cannot be excluded and may have contributed to the observed results. However, in order to considerably influence our results, a residual confounder has to fulfill the following 3 criteria.[94] It has to (1) be strongly associated with the exposure without being its consequence; (2) be strongly associated with the outcome without being its consequence; (3) be largely independent of all the covariates already in the model. If one of these 3 criteria does not hold, the variable is unlikely to be a strong residual confounder.

4.2.3 External validity

External validity is the extent to which the findings in a study can be generalized to other populations.[40] Demographic, ethnic, or socioeconomic characteristics should be taken into account when generalizing findings from studies conducted in one population to other populations.[95, 96] Thus, our findings may not readily be generalizable to populations outside of Scandinavia.

4.3 INTERPRETATION OF MAIN FINDINGS AND COMPARISON WITH PREVIOUS STUDIES

4.3.1 Weight and weight change and risk of atrial fibrillation

Our findings showed that both current and long-term obesity were associated with increased AF risk compared to normal weight, respectively. Findings from study I also showed that BMI change was associated with increased AF risk. The cumulative effects of long-term obesity and weight change on AF have salient clinical and public health implications. According to the 2016 ESC Guidelines for the management of AF,[97] identification and prevention of modifiable risk factors bring significant returns on investment in terms of AF management, number of lives saved and healthcare resources freed. Because obesity leads to AF over an extended period of time, our results highlight the particular importance of obesity prevention and treatment at younger ages to tackle the AF epidemic. Our findings also highlight the importance of considering weight history when assessing AF risk, rather than considering current weight status only.

The findings regarding the effects of current and long-term obesity on AF development are consistent with previous results.[34, 43, 98] Among these previous studies, only one study had direct weight and height measurements when investigating cumulative effects of sustained weight on incident AF.[43] However, the study had a relatively short time window for repeated BMI measurements and chronic disorders were not ascertained.

Several potential mechanisms link sustained obesity and AF, see Figure 3. Sustained obesity increases the risk and severity of left atrial enlargement,[99] atrial fibrosis,[99] electrical derangements of the atria,[99] impaired diastolic function,[100] inflammation,[101] and accumulation of pericardial fat,[99] which are all key mechanisms in the pathogenesis of AF.[32, 98] Sustained obesity is also associated with AF risk factors such as hypertension,[102] diabetes mellitus,[103] metabolic syndrome,[104] coronary artery disease[105] and obstructive sleep apnea,[98] which may contribute to atrial remodeling and

the onset of AF.[98]

Our findings are in line with previous studies on the effect of weight gain on AF development,[33, 34, 38, 41, 106] which suggest that weight gain is associated with a 10%-60% higher AF risk compared to stable body weight. Regarding weight loss, results from previous research are somewhat conflicting. In one prior study that included 14,219 participants with direct weight and height measurements,[41] a 10-year weight loss was associated with a 50% higher AF risk compared to stable weight. However, this study only adjusted for prior cardiovascular disease as a chronic condition. It should be noted that several previous studies have failed to document a higher AF risk in association with weight loss.[33, 38, 42]

The effects of weight loss might be due to unmeasured confounding variables. Briefly, unintentional weight loss is part of the natural history of many diseases and a consequence of pre-existing chronic disorders,[107] which can distort the true association between body weight and AF risk. Since we could not distinguish the reasons for weight loss, we adjusted for a range of chronic conditions that are associated with unintentional weight loss. However, we cannot exclude the possibility that an occult disease might be associated with both unintentional weight loss and incident AF, which might have caused a spurious association between weight loss and AF risk in our study.

The effects of BMI variability on AF risk in our study tend to match previous research that found weight variability to be associated with risks of coronary heart disease and mortality.[83] However, no previous research has examined its effect on the onset of AF. A previous study found that weight variability >5% was associated with a 2-fold greater likelihood of arrhythmia recurrence in obese individuals with preexisting AF.[108] One possible explanation for the adverse effects of weight variability may be its association with increased risks of hypertension [109] which is a strong risk factor for AF.[102, 104]

4.3.2 Metabolically healthy obesity and risk for atrial fibrillation

We found that AF risk was associated with the severity of obesity regardless of metabolic status. That is, overweight/obesity was associated with similarly increased AF risk among metabolically healthy and unhealthy participants. However, among those who only recently developed overweight or obesity, only metabolically unhealthy participants had higher AF risk. This may suggest that metabolically healthy overweight/obesity represents an initially benign condition but exacts a greater toll with continued duration.

To the best of our knowledge, only two studies have investigated the associations between metabolically healthy obesity and AF risk, and the results were conflicting.[48, 49] A Swedish study suggested essentially similar risk among those with healthy and unhealthy obesity,[48] while the risk for the latter group was much more pronounced in a Korean study.[49] However, the Swedish study was rather small and in both studies, AF ascertainment was based only on administrative health registers without validated AF diagnoses. The specificity of an AF diagnosis can be compromised in such settings,[39, 110, 111] which is usually a greater threat to validity than imperfect sensitivity.[112]

Our results showed that metabolic syndrome did not play an important role in the association between obesity and risk of AF, though metabolic syndrome has been reported as a risk factor of AF which appears to occur largely through increased blood pressure.[104] Our findings also suggested that hypertension plays a more important role in the pathogenesis of AF than other components of metabolic syndrome.

A possible explanation regarding our findings might be that obesity is associated with left atrial structural changes regardless of metabolic factors and may be the strongest risk factor for left atrial enlargement besides aging.[113, 114] Given that left atrial enlargement is a key risk factor for AF, it may play a central role in the association between obesity and AF

beyond metabolic status.

4.3.3 Symptoms of anxiety and depression and risk of atrial fibrillation

We found no evidence of an association between severe depression and AF risk, not even when depression was recurrent. Likewise, we also found no association of anxiety with AF risk. Unexpectedly, only mild to moderate depression was associated with an increased AF risk.

The potential pathway between depression and AF risk is unclear. It has been suggested that depression may lead to increased inflammation,[115] oxidative stress[116] and sympathetic activation which in turn could increase the risk for AF. However, depression has also been associated with parasympathetic suppression,[117] which might actually reduce AF risk, thus, potentially explaining the null effects of severe depression. It is also possible that the null effect for anxiety and for severe depression may be related to cardiac effects of different antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs) seem to have a cardio-protective profile.[118] SSRIs have been documented to improve glucose metabolism, dyslipidemia, and reduce inflammatory markers, which may contribute to reduced AF risk.[119]

Only four previous studies have assessed the prospective association of anxiety or depression with AF risk, and all had important potential limitations in their assessments of exposure and/or outcome, and none had repeated measures of anxiety or depression. In the Framingham Offspring study which had a relatively small sample size (n=3,682) and a 10-year follow-up,[62] anxiety in men (HR:1.1; 95% CI, 1.0 –1.3) had a weak association with AF risk while there was no such an association in women (HR:1.0; 95% CI, 0.8–1.3). In the Multi-Ethnic Study of Atherosclerosis (n=6,644),[63] depression was moderately associated with a higher AF risk (HR:1.3; 95% CI, 1.0-1.7). However, few details of these results are available, since these were published only as an abstract. Furthermore, both the Framingham

Offspring study and the Multi-Ethnic Study of Atherosclerosis used instruments (i.e., the Tension and Symptoms of Anxiety Scales[62] and Depression Scale of Epidemiologic Studies[64], respectively) that include somatic symptoms. Consequently, the potential overlap of somatic symptoms caused by a physical illness with that of psychological distress might have limited the ability of these studies to examine the genuine effects of core psychological and cognitive symptoms of anxiety and depression on AF risk. On the other hand, our study used the HADS scale, which replaces somatic symptoms with non-somatic alternatives.[74] Thus, in our study, we were able to examine the association of core psychological and cognitive symptoms of anxiety and depression with AF risk. In the Women's Health Study,[65] depression was unrelated to AF risk (HR:1.0; 95% CI, 0.8-1.3). The Mental Health Inventory-5, which has similar features as HADS in terms of exclusion of somatic symptoms, was used to assess depression.[65] However, AF events were self-reported in that study, which would tend to lower the specificity of the AF diagnoses. A Danish matched cohort study compared AF risk in all Danes initiating antidepressant medication (n= 785,254) with that in a 1:5-matched sample from the general population.[120] The study defined depression as the condition within the month before initiation of antidepressant medication. Substantially increased AF risk was observed even before antidepressant medication (HR = 3.18; 95% CI: 2.98–3.39) and within the first month (4.29; 95% CI: 3.94–4.67) after antidepressant initiation, but AF risk decreased 6–12 months after antidepressant initiation (HR = 1.11; 95% CI: 1.06–1.16). However, antidepressant medication is only a proxy for depression and these medications have common indications beyond depression as well,[121] such as pain or insomnia. Furthermore, the study retrieved AF diagnosis from registers without further manual verification, which could have caused a substantial misclassification.

5 CLINICAL SIGNIFICANCE

Understanding the relation of long-term obesity, metabolically healthy obesity, and anxiety/depression with incident AF is imperative for early identification of high-risk subgroups who should be prioritized for lifestyle and medical intervention and development of personalized anti-AF strategies. Our findings implied that obese patients, irrespective of their metabolic status, should consider seeking for a treatment focusing on reducing their excess adiposity. If successful, this could reap long-term benefits regarding AF outcomes and improve cost-effectiveness of healthcare. Moreover, we found that obesity earlier in life exerted cumulative effects on AF risk even after accounting for the most recent weight status, suggesting that maintaining a healthy weight across the lifespan is important for minimizing the risk of AF.

Additionally, our work might also help improving current screening strategies. For secondary prevention (i.e., trying to detect a disease early and prevent it from getting worse), success in getting appropriate high-risk individuals to take screening is essential. Although a large-scale screening for AF has not been applied, it has been a hot debate regarding its feasibility and applicability.[122, 123] It has been suggested that screening based on risk stratification is of vital importance for accurate allocation of resources and to improve the efficacy of screening.[124]

6 CONCLUSION

The studies described in this thesis provide knowledge regarding risk factors for AF with focus on weight, weight change, metabolic syndrome, anxiety and depression. In detail, long-term obesity and BMI change were associated with AF risk. Obesity earlier in life and weight gain over time exerted cumulative effects on AF development even after accounting for the most recent BMI. Metabolically healthy and unhealthy obesity increased AF risk to a similar extent. Severity of obesity was positively associated with AF risk regardless of metabolic status. All of these findings indicate that obesity is an important target for public health strategies aiming to prevent and reduce AF risk and it is important to prevent and treat obesity already at young ages. Regarding the effect of anxiety and depression, there was no evidence of an association between anxiety or severe depression and AF risk, not even for recurrent anxiety or depression. An unexpected association of mild to moderate depression with increased AF risk requires confirmation in subsequent studies.

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CLINICAL RESEARCH
Prevention and epidemiology

Weight and weight change and risk of atrial fibrillation: the HUNT study

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Aims Although obesity has been associated with risk of atrial fibrillation (AF), the associations of long-term obesity, recent obesity, and weight change with AF risk throughout adulthood are uncertain.

Methods and results An ambispective cohort study was conducted which included 15 214 individuals. The cohort was created from 2006 to 2008 (the baseline) and was followed for incident AF until 2015. Weight and height were directly measured at baseline. Data on previous weight and height were retrieved retrospectively from measurements conducted 10, 20, and 40 years prior to baseline. Average body mass index (BMI) over time and weight change was calculated. During follow-up, 1149 participants developed AF. The multivariable-adjusted hazard ratios were 1.2 (95% confidence interval 1.0–1.4) for average BMI 25.0–29.9 kg/m^2 and 1.6 (1.2–2.0) for average BMI ≥30 kg/m^2 when compared with normal weight. The association of average BMI with AF risk was only slightly attenuated after adjustment for most recent BMI. In contrast, current BMI was not strongly associated with the risk of AF after adjustment for average BMI earlier in life. Compared with stable BMI, both loss and gain in BMI were associated with increased AF risk. After adjustment for most recent BMI, the association of BMI gain with AF risk was largely unchanged, while the association of BMI loss with AF risk was weakened.

Conclusion Long-term obesity and BMI change are associated with AF risk. Obesity earlier in life and weight gain over time exert cumulative effects on AF development even after accounting for most recent BMI.

Keywords Atrial fibrillation • BMI • Weight • Weight change

Introduction

Obesity has reached epidemic proportions globally, with an estimated 38% of the world's adult population expected to be obese by 2030.[1] The last few decades have also witnessed a global rise in the incidence and prevalence of atrial fibrillation (AF), with an estimated 33.5 million people globally suffering from AF in 2010 and 5 million new cases expected to arise annually.[2] Atrial fibrillation increases mortality, morbidity, and reduces quality of life. Considering that prevention and treatment of AF are enormous medical and socioeconomic tasks, a deeper understanding of risk factors for AF is imperative.

Obesity has well-known associations with AF risk.[3,4] However, research using measurements of height and weight at a single point in time fails to assess the cumulative effect of obesity over the life course on AF development. Accordingly, little attention has been devoted to the impacts of long-term obesity and long-term weight change on AF development. Some previous studies have used

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self-reported prior body weight, in which individuals recalled their body weight earlier in life.[5,6] Self-reported current body weight is generally accurate,[7,8] but the accuracy of recall is imperfect and depends on current and past body mass index (BMI) values, changes in weight, end-digit preferences, and participants' current cognitive ability.[9] With regard to the diagnosis of AF, most prior studies have relied solely on administrative data without individual validation or verification.[5,10] This tends to lower the specificity of the AF diagnoses and introduce substantial misclassification.[11,12] Moreover, those few previous investigations with repeated measurements of body weight over time have been limited by small sample sizes,[5,10] short-time intervals between measurements,[6,10,13,14] and missing information on important covariates like comorbidity.[5,6,10,13]

In this large, population-based study, we investigated the cumulative effects of obesity and weight change on AF risk over four decades. We used repeated measurements of weight and height, relied on verified AF diagnoses and included information on a wide range of cardiovascular risk factors.

Methods

Study population

All 93 860 residents ≥20 years of age in Nord-Trøndelag County in Norway were invited to participate in the third HUNT study (HUNT-3) from October 2006 to June 2008. Of these, 50 804 participants (54%) answered questionnaires and underwent clinical examinations (baseline examinations). Holmen *et al.*[15] have described the HUNT study in more detail.

We excluded 1598 participants from the analysis who had a history of AF at baseline and 360 participants with missing values for baseline BMI.

Clinical examination

A clinical examination was conducted by trained nurses. Height and weight were measured barefoot and wearing light clothing; height was measured to the nearest centimetre and weight to the nearest 0.5 kg. Waist and hip circumferences were measured to the nearest centimetre with the participants standing erect and arms hanging relaxed.[15] Waist circumference (WC) was measured at the level of the umbilicus, and hip circumference was measured at the widest part of the hip/buttocks. Non-fasting blood samples were analysed for glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein.[15] Blood pressure was measured three times using a Dinamap 845XT (Critikon) based on oscillometry, with the arm resting on a table, and the average of the second and third measurement was used for analysis.[15]

Body mass index

Body mass index was calculated as body weight in kilograms divided by the squared value of height in metres, and divided into four categories: <18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).

Height and weight measurements were also available from a mandatory tuberculosis screening that was conducted between 1966 and 1969,[16] as well as the two previous rounds of the HUNT study; the HUNT-1 (1984–1986)[17] and HUNT-2 (1995–1997).[15] In all these studies, BMI was measured with similar methods to the HUNT-3 study. Among the 48 846 eligible participants in HUNT-3, 15 214 individuals had available information on previous height and weight from all the three previous measurements and were therefore eligible for the main analyses. Details about inclusions are provided in the Supplementary material online, *Figure S1*.

We denoted BMI at the four separate time points by the following terms: at HUNT-3 (2006–2008) as BMI_{07}, at HUNT-2 (1995–1997) as BMI_{96}, at HUNT-1 (1984–1986) as BMI_{85}, and at the tuberculosis screening (1966–1969) as BMI_{67} (Supplementary material online, *Figure S2*).

We utilized the following equations for further analyses:

1. Average BMI = $[(BMI_{67} \times time_{I-II}) + (BMI_{85} \times time_{II-III}) + (BMI_{96} \times time_{III-IV}) + (BMI_{07} \times time_{IV-})]/TotalTime$.
   where:
   $time_{I-II}$ = time from measurement I (i.e. in 1966–1969) to measurement II (i.e. in 1984–1986);
   $time_{II-III}$ = time from measurement II to measurement III (i.e. in 1995–1997);
   $time_{III-IV}$ = time from measurement III to measurement IV (i.e. in 2006–2008);
   $time_{IV-}$ = time from measurement IV to end of follow-up;
   Total Time = total time from measurement I to end of follow-up.
2. Average $BMI_{67-07} = [(BMI_{67} \times time_{I-II}) + (BMI_{85} \times time_{II-III}) + (BMI_{96} \times time_{III-IV}]/time_{I-IV}$
   where: $time_{I-IV}$ = time from measurement I to measurement IV.
3. Total BMI change = $\{[(BMI_{85} - BMI_{67}) \times time_{I-II}] + [(BMI_{96} - BMI_{85}) \times time_{II-III}] + [(BMI_{07} - BMI_{96}) \times time_{III-IV}]\}/time_{I-IV}$

We then analysed the effects of BMI change from BMI_{67} to BMI_{07} (total BMI change), from BMI_{67} to BMI_{85} (early BMI change), from BMI_{85} to BMI_{96} (middle BMI change), and from BMI_{96} to BMI_{07} (late BMI change) separately. We classified total, early, middle, and late BMI change into five categories: <-5 kg/m^2, ≥-5 to <-2.5 kg/m^2, ≥-2.5 to <2.5 kg/m^2, ≥2.5 to <5 kg/m^2, and ≥5 kg/m^2.

In addition, three distinctive BMI trajectories were identified based on group based trajectory modelling using the Stata Traj Plugin[18]: 'normal weight' (51.9% of the population), 'overweight' 40.4%, and 'obese' 7.7% (Supplementary material online, *Figure S3*). Detailed information on the process of trajectory modelling is provided in the Supplementary material online. Intra-individual BMI variability was calculated as the square root of the variance or the residual mean square,[19] from the four residuals from a participant-specific linear regression of the four BMI measurements, with participants' age as the independent variable.

Waist circumference and waist–hip ratio

Waist circumference and waist–hip ratio (WHR) measurements were available at HUNT-2 (1995–1997) and HUNT-3 (2006–2008).

We denote WC and WHR at the two time points by the following terms: at HUNT-3 (2006–2008): WC_{07} and WHR_{07}; at HUNT-2 (1995–1997): WC_{96} and WHR_{96}.

We utilized the following equations for the further analysis:

$$\text{Average waist circumference} = [(WC_{96} \times time_{III-IV}) + (WC_{07} \times time_{IV-})]/time_{II-end}.$$

$$\text{Average waist} - \text{hip ratio} = [(WHR_{96} \times time_{III-IV}) + (WHR_{07} \times time_{IV-})]/time_{III-end}.$$

where: $time_{III\text{-}end}$ = time from measurement III to end of follow-up.

Average WC was categorized according to the definition of abdominal obesity recommended by the Adult Treatment Panel[20]: ≤88 cm and >88 cm for women; ≤102 cm and >102 cm for men. Average WHR was also categorized according to the definition of abdominal obesity recommended by World Health Organization[21]: <0.85 and ≥0.85 for women; <0.90 and ≥0.90 for men. Waist circumference change was classified into five categories: <0 cm, ≥0 to <4 cm, ≥4 to <9 cm, ≥9 to <14 cm, and ≥14 cm. Waist–hip ratio change was classified into four categories: <0.03, ≥0.03 to <0.07, ≥0.07 to <0.11, and ≥0.11.

Atrial fibrillation

Atrial fibrillation diagnoses were retrieved from discharge registers at the two hospitals in Nord-Trøndelag County from the baseline examination until 30 November 2015. We used code I48 from the International Classification of Diseases Tenth Revision to screen for patients with possible AF. Medical records of these patients were then reviewed by a cardiologist (J.P.L.) and two specialists in internal medicine (M.V. and H.E.), and AF was adjudicated according to the electrocardiographic criteria recommended by the European Society of Cardiology (ESC).[22] Persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of haemodynamic instability (e.g. sepsis or non-cardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of the diagnosis, two physicians evaluated the available information separately. Only cases where both physicians concurred were regarded as AF. The rest were classified as possible AF and were not regarded as AF cases in the main analyses. The validation process is described in detail elsewhere.[11]

Covariates

Covariates were collected at HUNT-3. Smoking status was assessed as never, former, or current. We used self-reported alcohol consumption to classify individuals as abstainers, light drinkers (0 to 1 drinks per day), moderate drinkers (>1 but ≤2 drinks per day), or heavy drinkers (>2 drinks per day). Level of physical activity was self-reported; activity that did not make individuals sweat or cause laboured breathing was regarded as light (such as simple walking) and was otherwise considered hard (such as skiing, swimming, and working out). Physical activity was categorized into (i) inactivity (<3 h of light exercise per week or <1 h hard exercise), (ii) moderate activity (≥3 h of light exercise or 1–2 h of hard exercise per week), and (iii) high activity (≥3 h of hard physical activity per week). In addition, we used an alternative assessment of physical activity that incorporated the frequency, intensity, and duration of exercise.[23] Educational level was categorized as (i) primary and secondary school, (ii) vocational school and high school, (iii) junior college, (iv) undergraduate school, and (v) graduate school. Marital status was categorized as (i) unmarried, (ii) married, (iii) widow[er], (iv) divorced, (v) separated, (vi) live-in partner. Metabolic syndrome based on the International Diabetes Federation[24] was defined as the presence of elevated WC (≥102 cm for men, ≥88 cm for women) in addition to two or more of the following criteria: (i) increased non-fasting triglycerides (≥1.7 mmol/L), (ii) decreased HDL (<1.03 mmol/L for men, <1.29 mmol/L for women), (iii) increased blood pressure (≥130/85 mmHg) or use of blood pressure medication, (iv) increased non-fasting glucose (≥11.1 mmol/L) or diabetes diagnosis. Information on other chronic conditions was self-reported and included: (i) angina pectoris, (ii) stroke, (iii) asthma, (iv) osteoarthritis, (v) kidney disease, (vi) hyperthyroidism, (vii) fibromyalgia, (viii) rheumatoid arthritis, (ix) sarcoidosis, (x) ankylosing spondylitis, (xi) cancer, (xii) epilepsy, (xiii) osteoporosis, (xiv) chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, (xv) psoriasis, and (xvi) hypothyroidism. Information on history of acute myocardial infarction and heart failure was retrieved from hospital registers and diagnoses were reviewed by cardiologists.[25]

Statistical analyses

The main analysis included 15 214 individuals who had available information on BMI at four time points. Baseline characteristics were presented as means ± standard deviation for continuous variables and percentages for categorical variables. We also calculated the interquartile ranges of BMI values over time stratified by subsequent AF development.

Cox proportional regression models were used to assess the hazard ratio (HR) for AF for a given category of (i) average BMI (average BMI 18.5–24.9 kg/m^2 as the reference group), (ii) BMI change (change between -2.5 and 2.5 kg/m^2 as the reference group), (iii) BMI trajectory (normal weight trajectory as the reference group), (iv) BMI variability (the lowest variability between 0 and 1.07 kg/m^2 as the reference group), (v) average WC (average WC ≤88/102 cm women/men as the reference group), (vi) WC change (change between 0 and 4 cm as the reference group), (vii) average WHR (average WHR ≤0.85/0.90 women/men as the reference group), and (viii) WHR change (change between 0.03 and 0.07 as the reference group), respectively. Time was defined as days from inclusion to either incident AF or censoring due to death from other causes ($N = 2170$), emigration from the county ($N = 8$), or end of follow-up. We calculated HRs with their 95% confidence intervals (CIs). We included age, sex, height, smoking, educational level, marital status, physical activity, and alcohol consumption as potential confounders. In additional analyses, we also adjusted for metabolic status and chronic disorders. In the Cox model examining the effect of BMI change and BMI variability, we also adjusted for the slope of BMI to disentangle the effects of BMI fluctuations and BMI slope on AF development.[26] The correlation coefficients between BMI change and BMI slope are presented in Supplementary material online, *Figure S4*.

To examine whether past or recent BMI was a more important risk factor of AF, we calculated the relative risks according to categories of $BMI_{67\text{-}07}$ (i.e. average BMI from 1967 until baseline), with and without adjustment for the most recent BMI (BMI_{07}), respectively. We did not use the total average BMI (i.e. average BMI from 1967 until the end of follow-up), because the total average BMI included BMI_{07} itself and thus they were highly correlated with each other (Supplementary material online, *Figure S5*). We also calculated the relative risks for the four time points separately (Supplementary material online, *Table S1*). Similarly, we additionally adjusted for the most recent BMI to calculate HRs among different categories of BMI change.

The proportional hazards assumption was tested by comparing -ln-ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption.

To assess effect modification, we conducted analyses stratified by age, sex, and central obesity (WC ≥102/88 cm for men/women), respectively.

In sensitivity analyses, we regarded possible or single-episode AF during follow-up as events. To address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 2 years of follow-up and repeated the analyses. In addition, we repeated our analyses by adjusting for alternative assessment of physical activity (i.e. the product of the frequency, intensity, and duration of exercises) instead of aforementioned categories of physical activity. Considering that hypertension is a potential consequence of obesity and is strongly associated with AF, we compared models with and without adjustment for hypertension. Lastly, to examine the possibility of survival bias, we used multivariable-adjusted logistic regression models to assess the cross-sectional associations of BMI at baseline, average BMI, and BMI change with risk of prevalent AF at baseline.

All statistical analyses were conducted using Stata 14.2 for Windows (StataCorp LP, College Station, TX, USA) and R 3.5.2 for Windows.

Results

Table 1 presents descriptive characteristics of the population ($n = 15\ 214$) that had available information on BMI at the four time points. Mean BMI increased gradually with time. During a median

Table 1 Characteristics of the study population

Age at HUNT-3 (years)	66.6 (9.5)
Female, *n* (%)	8743 (57.5)
BMI_{67} (kg/m^2)	23.2 (3.1)
BMI_{85} (kg/m^2)	24.7 (3.3)
BMI_{96} (kg/m^2)	26.7 (3.8)
BMI_{07} (kg/m^2)	27.6 (4.2)
SBP (mmHg)	138.0 (19.6)
DBP (mmHg)	75.1 (11.4)
Total cholesterol (mmol/L)	5.8 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.4)
Triglycerides (mmol/L)	1.7 (0.9)
Diabetes mellitus, *n* (%)	1054 (6.9)
Current smoker, *n* (%)	2292 (15.7)
Heavy drinkers, *n* (%)	216 (1.5)
University, *n* (%)	975 (6.6)
Physically inactive, *n* (%)	2992 (20.2)
Unmarried, *n* (%)	839 (5.5)

Values are presented as mean ± standard deviation or number (percentages). BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

follow-up of 8.0 years (114 511 person-years), 1149 (7.6%) participants developed AF.

Average body mass index and atrial fibrillation risk

The multivariable-adjusted HRs were 1.2 (95% CI 1.0–1.4) for average BMI 25.0–29.9 kg/m^2 and 1.6 (95% CI 1.2–2.0) for average BMI ≥30 kg/m^2 when compared with those having a normal weight (*Table 2*). The risk was lowest among those with an averaged BMI <18.5 kg/m^2. The relative risks were similar after additional adjustment for metabolic status and chronic disorders (*Table 2*).

We examined the relative importance of the most recent BMI and that of the average of the former BMI values. Average BMI earlier in life was associated with AF risk in the overweight (HR 1.2, 95% CI 1.0–1.5) and obese (HR 1.6, 95% CI 1.1–2.2) group compared with the normal weight group, even after adjustment for BMI at the beginning of follow-up (*Table 2*). In contrast, current BMI was not strongly associated with the risk of AF after adjustment for average BMI earlier in life (*Take home figure*).

When we calculated the relative risks for the four time points separately, the overweight and obesity groups had higher HRs compared with the normal weight group at each time point, respectively (Supplementary material online, *Table S1*).

Body mass index change and risk of atrial fibrillation

The box plots showed BMI increased over the follow-up, regardless of the subsequent AF status (Supplementary material online, *Figure S6*). However, the interquartile range of BMI in the AF development group was higher than that in the AF-free group over time.

Compared with stable BMI, both loss and gain in BMI were associated with increased AF risk (*Table 3*). For the total BMI change, there was an almost three-fold increase in AF risk among those with a BMI gain of more than 5.0 kg/m^2 compared with those with a stable BMI (i.e. change between 2.5 and -2.5 kg/m^2). For early, middle, and late BMI gain, a BMI gain of more than 5 kg/m^2 also showed a considerably higher AF risk compared with a stable BMI. The relative risks for late-period BMI gain were higher than that for the early- and middle-period BMI gain. The results were similar after additional adjustment for chronic disorders and the most recent BMI, respectively (results not shown). *Figure 1* shows relative risks of AF and BMI change (from measurement I to measurement IV) with and without adjustment for the most recent BMI. After adjustment for the most recent BMI, the association of BMI gain with AF risk was largely unchanged, while the association of BMI loss with AF risk was considerably weakened.

Body mass index trajectory, body mass index variability, waist circumference, waist–hip ratio, and risk of atrial fibrillation

Incident AF risk was highest in the obese trajectory group (HR 1.9, 95% CI 1.5–2.4), when compared with the normal weight trajectory group, followed by the overweight trajectory group (HR 1.2, 95% CI 1.0–1.4) (Supplementary material online, *Table S2*).

Participants with the highest degree of weight variability showed higher AF risk compared with those with the lowest weight variability (HR 1.5, 95% CI 1.2–1.8) (Supplementary material online, *Table S2*).

Averaged WC >88/102 cm for women/men was associated with higher AF risk (HR 1.2, 95% CI 1.1–1.4) compared with averaged WC ≤88/102 cm for women/men. The effects disappeared after additional adjustment for BMI (Supplementary material online, *Table S3*). Average WHR was not strongly associated with AF risk (Supplementary material online, *Table S3*). Neither WC change nor WHR change was strongly associated with AF risk (Supplementary material online, *Tables S4* and *S5*).

The role of hypertension

Among hypertensive participants, 44.1% took antihypertensive medication. Compared with participants with long-term lower BMI, those with long-term BMI ≥30 kg/m^2 were more likely to have hypertension and to take antihypertensive medication (Supplementary material online, *Figure S7*). Similarly, with comparison with participants who did not develop AF, those who developed AF were more likely to have hypertension and use antihypertensive medication. However, when we examined the effect of adjustment for hypertension, our results were little changed (results not shown).

Stratified analyses and sensitivity analyses

In stratified analyses, the relative risks for AF tended to be higher for individuals younger than 65 years than for those who were older by categories of average BMI (Supplementary material online, *Table S6*). For BMI change, the relative risks for AF were lower for individuals younger than 65 years than for those who were older (Supplementary material online, *Table S6*). The relative risks for AF were generally similar between women and men by categories of

Table 2 Hazard ratios for atrial fibrillation by categories of average body mass index until end of follow-up and by categories of average body mass index until the HUNT-3 measurement

BMI (kg/m^2)	Events	Person-years	Incidence rate[a]	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI
Average BMI from measurement I to end of follow-up									
<18.5	2	386	5.2	0.8	(0.2–3.0)	0.6	(0.1–4.0)	0.6	(0.1–4.1)
18.5–24.9	467	61 952	7.5	1	(Ref.)	1	(Ref.)	1	(Ref.)
25.0–29.9	555	44 725	12.4	1.2	(1.1–1.4)	1.2	(1.0–1.4)	1.1	(1.0–1.3)
≥30.0	125	7448	16.8	1.6	(1.3–2.0)	1.6	(1.2–2.0)	1.4	(1.0–1.8)
BMI (kg/m^2)	**Events**	**Person-years**	**Incidence rate[a]**	**HR[b]**	**95% CI**	**HR[c]**	**95% CI**	**HR[e]**	**95% CI**
Average BMI from measurement I to measurement IV									
<18.5	1	586	1.7	0.3	(0–2.3)	—	—	—	—
18.5–24.9	495	69 627	7.1	1	(Ref.)	1	(Ref.)	1	(Ref.)
25.0–29.9	537	38 540	13.9	1.3	(1.2–1.5)	1.3	(1.2–1.6)	1.2	(1.0–1.5)
≥30.0	116	5759	20.1	1.9	(1.6–2.4)	1.9	(1.4–2.4)	1.6	(1.1–2.2)

BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a]Incidence rate per 1000 persons-years.
[b]Adjusted for age, sex.
[c]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, and alcohol consumption.
[d]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, alcohol consumption, metabolic status, and chronic disorders.
[e]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, alcohol consumption, and the most recent BMI (BMI_{07}).

average BMI and BMI change, respectively (Supplementary material online, *Table S7*). Neither was there statistical evidence for an interaction with central obesity (results not shown).

In sensitivity analyses, the results were consistent with the main analyses when possible or single-episode AF events were regarded as AF during follow-up (Supplementary material online, *Table S8*). There were 926 AF cases after the second year of follow-up. There was no decrease in the estimates after exclusion of the first 2 years of follow-up (Supplementary material online, *Table S8*). The cross-sectional associations of BMI with prevalent AF at baseline generally echoed the corresponding prospective associations (Supplementary material online, *Table S9*). The models where we adjusted for the frequency, intensity and duration of exercises instead of the categories of physical activity did not materially change the estimates (results not shown).

Discussion

In this large population-based study, long-term obesity and BMI change were associated with increased AF risk. Importantly, obesity earlier in life and BMI change exerted cumulative effects on AF development even after accounting for the most recent BMI. AF risk was increased not only among the obese but also among overweight individuals. A BMI gain of more than 5 kg/m^2 over 40 years was associated with an almost three-fold greater likelihood of AF development. A BMI gain in later life posed higher AF risk than that during an earlier period in life. Increased BMI variability was also associated with increased AF risk.

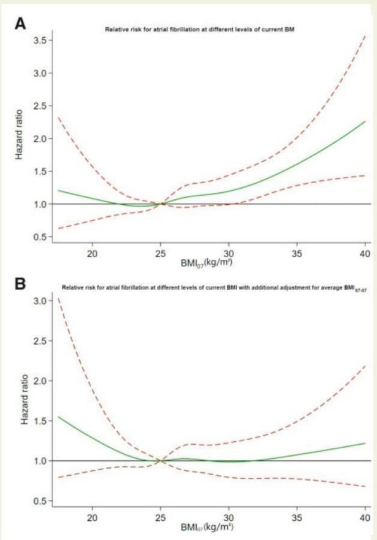
The cumulative effects of long-term obesity and weight change on AF have salient clinical and public health implications. According to 2016 ESC Guidelines for the management of AF,[27] identification and prevention of modifiable risk factors bring significant returns on investment in terms of AF management, number of lives saved and healthcare resources freed. Because obesity leads to AF over an extended period of time, our results highlight the particular importance of obesity prevention and treatment at younger ages to tackle the AF epidemic. Our findings also highlight the importance of considering weight history when assessing AF risk, rather than considering current weight status only.

The findings regarding the effects of long-term obesity are consistent with previous results on the effects of high BMI at a single point[28] and high long-term BMI[6,14] on AF development. To date, only one previous study with direct weight and height measurements has investigated cumulative effects of sustained weight on incident AF.[14] The study included 10 559 individuals with height and weight measurements at four time points (between 1987 and 1998) with a 15-year follow-up, and showed a 39% (95% CI 14–70%) increased AF risk in the long-term obese group compared with the non-obese group after controlling for the most recent BMI. However, the study had a relatively short-time window for repeated BMI measurements and chronic disorders were not ascertained.

Several potential mechanisms link sustained obesity and AF. Sustained obesity increases the risk and severity of left atrial enlargement,[29] atrial fibrosis,[29] electrical derangements of the atria,[29] impaired diastolic function,[30] inflammation,[31] and accumulation of pericardial fat, which are all key mechanisms in the pathogenesis of AF.[28,32] Sustained obesity is also associated with AF risk factors such as hypertension,[33] diabetes mellitus,[34] metabolic syndrome,[35] coronary artery disease,[36] and obstructive sleep apnoea,[28] which may contribute to atrial remodelling and the onset of AF.[28] Specifically, hypertension is a major risk factor for AF and is also strongly associated with obesity.[33] Our study showed that the proportion of hypertensive participants was highest among those with long-term obesity, and participants who developed AF were also more likely to have hypertension. Thus, hypertension might play a role in the pathway between obesity and AF, although our analyses did not support a major mediating effect for hypertension.

Our findings are in line with previous studies on the effect of weight gain on AF development,[5,6,10,13,37] which suggests that weight gain is associated with a 10–60% higher AF risk compared with stable body weight. Regarding weight loss, results from previous research are conflicting. In one prior study that included 14 219 participants with direct weight and height measurements,[13] 10-year weight loss was associated with a 50% higher AF risk compared with stable weight. However, this study only adjusted for prior cardiovascular disease as a chronic condition. Several other previous studies have failed to document a higher AF risk in association with weight loss.[5,6,10]

The effects of weight loss might be due to unmeasured confounding variables. Briefly, unintentional weight loss is part of the natural history of many diseases and a consequence of pre-existing chronic



Take home figure Hazard ratios of atrial fibrillation and body mass index at baseline adjusted for sex, age, height, smoking status, level of education, marital status, physical activity, and alcohol consumption (*A*) and additional adjustment for average body mass index up to baseline (*B*).

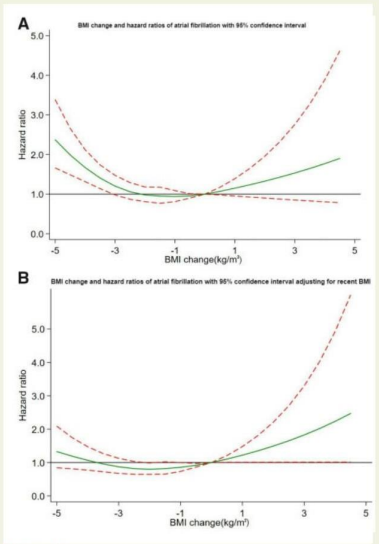


Figure 1 Hazard ratios of atrial fibrillation and body mass index change from measurement I to measurement IV, adjusted for sex, age, height, smoking status, level of education, marital status, physical activity, and alcohol consumption (*A*) and additional adjustment for the most recent body mass index (*B*).

Table 3 Hazard ratios for atrial fibrillation by categories of total, early, middle, and late body mass index change

BMI change (kg/m^2)	Whole period (1967–2007)	Early period (1967–1985)	Middle period (1985–1996)	Late period (1996–2007)
<-5	—	1.5 (0.5–4.6)	—	1.6 (0.8–2.9)
≥-5 to <-2.5	1.3 (0.3–5.4)	0.9 (0.6–1.3)	1.7 (1.0–3.1)	1.2 (0.9–1.5)
≥-2.5 to <2.5	(Ref.)	(Ref.)	(Ref.)	(Ref.)
≥2.5 to <5	1.1 (0.9–1.5)	1.1 (0.9–1.3)	0.9 (0.8–1.1)	1.0 (0.8–1.2)
≥5	2.6 (1.3–5.2)	1.3 (1.0–1.8)	1.1 (0.8–1.4)	1.5 (1.0–2.2)

Results were presented as hazard ratio (95% confidence interval).
Hazard ratios were adjusted for sex, age, smoking status, education, marital status, physical activity, alcohol consumption, and regression slope of BMI.
BMI, body mass index.

disorders,[38] which can distort the true association between body weight and AF risk. Since we could not distinguish the reasons for weight loss, we adjusted for a range of chronic conditions that are associated with unintentional weight loss. However, we cannot exclude the possibility that an occult disease might be associated with both unintentional weight loss and incident AF, which might cause a spurious association between weight loss and AF risk. Another issue is that the CIs of HRs were quite wide among individuals having experienced weight loss due to their relatively small numbers.

The effects of BMI variability on AF risk in our study tend to match previous research that found weight variability to be associated with risks of coronary heart disease and mortality.[26] However, no previous research has examined its effect on the onset of AF, although one previous study found that weight variability >5% was associated with a two-fold greater likelihood of recurrent AF.[39] One possible explanation for the adverse effects of weight variability may be its association with increased risks of hypertension[40] and metabolic syndrome,[41] which are reported to be risk factors for AF.[33,35] Furthermore, weight regain during weight cycling is associated with rapid adipose tissue growth and hyperplasia due to metabolic shifts favouring lipid storage,[42] and adipose tissue growth and hyperplasia is considered to be associated with AF risk.[28]

Additionally, we found that underweight was associated with reduced risk of AF. It has been suggested that underweight is associated with lower risk of hypertension, dyslipidaemia, and insulin resistance,[28] which may in turn reduce AF risk. The association between underweight and cardiovascular disease has been investigated extensively with conflicting results.[43,44] Research on the association of underweight with AF risk is still sparse, since most of studies investigating the association of obesity and AF have included underweight individuals with normal-weight due to the small sample size of the underweight individuals. One recent Korean nationwide population-based study showed that underweight was associated with increased risk of AF (HR 1.2, 95% CI 1.0–1.5).[45] However, this association could be due to unadjusted chronic diseases that confer higher risk of both underweight and AF. In our study, we were able to adjust for a broader spectrum of common chronic disorders than in this earlier study and we found no indication for an increased risk among the underweight participants after extensive adjustment for these disorders. In addition, a meta-analysis of 25 prospective studies on BMI and AF found no evidence of an increased risk with underweight.[3]

Study strengths and limitations

Our study population was stable (the net migration out of the county was 0.3% per year)[15] and homogeneous (less than 3% of the participants was non-Caucasian),[15] reducing the possibility of confounding by factors related to these characteristics. The exceptionally long-time window with repeated measurements of weight and height provided a unique opportunity to capture lifetime overweight and obesity, as opposed to most previous studies restricted to single measurements of BMI. The repeated measurements of weight and height allowed for the detection of weight change and weight variability over life course and quantifying their effects on AF development. The carefully supervised hospital information, register data, and validated AF as well as other cardiovascular events ensured virtually complete follow-up and minimized misclassification of incident AF. In addition, we included a wide range of covariates, including chronic disorders that may distort the associations between body weight and AF risk.

Apart from its strengths, our study also had several limitations. First, BMI does not differentiate between fat tissue and muscle mass, although we also had information on WC. Second, longitudinal data with exceptionally long-time windows are naturally subject to missing data at different time points,[46] which was also the case in the current study. The tuberculosis screening was conducted approximately 40 years before the baseline and was mandatory only for those who were at least 15 years old at that time.[16] Thus, a great proportion of the participants at baseline were simply too young to participate at the tuberculosis survey 40 years earlier. Since AF mainly occurs among the elderly,[47] the loss in statistical power was limited. Third, individuals with obesity may tend to have a higher detection rate of AF due to comorbidity demanding check-ups or hospitalizations, compared with non-obese counterparts. Thus, there may exist a higher detection rate for incident AF among obese than non-obese participants. Fourth, we had no information on intentional and unintentional weight loss. Fifth, the type of AF (paroxysmal vs. persistent) was not available to us. Sixth, we were not able to model BMI as a time-varying covariate because the follow-up for AF started at the last weight measurement (HUNT-3). We excluded participants with AF prior to the last measurement among those who attended HUNT-3, but the previous AF records from those who did not attend HUNT-3 were not available. However, we observed generally similar cross-sectional associations as had been observed for incident AF, providing assurance that substantial survival bias due to exclusion of those who had developed AF in the period up to HUNT-3 was unlikely. In addition, due to the strong age-dependency of AF, relatively few cases occurred prior to HUNT-3. Lastly, we were unable to use the echocardiographic data when investigating the association of BMI and AF risk, since in HUNT, echocardiographic data was available only in a small subset of healthy individuals ($n = 1296$), none of whom had hypertension or cardiovascular disease.[48] As reported previously, these echocardiographic examinations showed that higher BMI was associated with lower left ventricular (LV) function that LV strain was reduced by approximately 5% per 5 kg/m^2 increase in BMI, and that indexed LV mass was higher among those with higher BMI.[48]

Conclusions

In this population-based study with directly measured weight and height, long-term obesity, and weight change were associated with increased AF risk, even after accounting for current BMI. Our findings highlight the potential for population-wide weight control strategies to mitigate the emerging epidemic of AF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Supplementary material-BMI trajectory modelling

Group based trajectory modelling (GBTM)

Group based trajectory modelling (GBTM)[1] is a specialised application for analyzing developmental trajectories over time [2, 3]. This method has shown to be suitable for identifying underlying longitudinal trajectories [4].

The Traj Stata Plugin was used for estimating group-based trajectory models[5]. The Traj Plugin allows the calculation of a) the probability of group membership; b) the predicted trajectory for each group; and c) the posterior probabilities of group membership. BMI trajectories in the current study were modelled using the censored normal distribution. That is, designed for the analysis of repeatedly measured continuous variables [5].

Bayesian information criterion was used as the criterion for model selection[6]. Besides that, model selection involved the iterative estimation [3] of (a) the parsimony of the model which fitted the data well; (b) adequate correspondence between the proportion of sample numbers and estimated probability in each group based on the maximum posterior probability assignment rule; (c) the odds of correct classification based on the posterior probabilities of group membership >5 for each group; (d) the shape/order of each trajectory group ; (e) an average posterior probability value >0.7 for each group; (f) biological plausibility which current scientific evidence supports the identified trajectories. Trajectories were compared to WHO BMI cut-offs [7] for overweight and obesity, see Figure S3.

Identification of BMI trajectories by using group-based trajectory modelling (GBTM)

Group-based trajectory modelling (GBTM) started with the selection of the number of trajectory groups in the model (GBTM-Table 1). The modelling process started with 2-group models, testing

different orders (i.e., zero-order, linear and quadratic) for the trajectory shapes. Extra groups were added (3-, 4- and 5-groups) until the best fitting model was established.

The 3-group model with three linear trajectories (1 1 1) was chosen based on the model selection criterion. The model had an adequate proportion and sample number in each group: “normal weight” 51.9%, “overweight” 40.4%, and “obese” 7.7% (Figure S3). The average posterior probability (AvePP) value was 0.89 or more for each group; larger than the recommended minimum AvePP value of 0.70 (GBTM-Table 2). The odds of correct classification were over 5.0 for all three groups, indicating the model had good assignment accuracy (GBTM-Table 2). And there was close correspondence between estimated probability and the proportion of study members assigned to it in each group (GBTM-Table 3).

GBTM-Table 1. Bayesian information criterion for body mass index (BMI) group-based trajectory modelling (GBTM) groups according to number of groups and trajectory shapes.

Number of groups	Trajectory shapes[1]	BIC[2](N=48846)	BIC[3](N=130293)
2	0 0	-357209.20	-357211.16
2	0 1	-347682.81	-347685.26
2	0 2	-347657.69	-347657.69
2	1 1	-340409.49	-340412.43
2	1 2	-340384.36	-340387.80
2	2 2	-340387.80	-340387.80
3	0 0 0	-352678.52	-352681.46
3	0 1 1	-333621.68	-333625.60
3	0 1 2	-333617.68	-333622.10
3	0 2 2	-333541.92	-333546.82
3	**1 1 1**	**-329958.71**	**-329963.12**
3	1 1 2	-329962.23	-329967.13
3	1 2 1	-329867.92	-329872.83
3	1 2 2	-329872.83	-329876.46
3	2 1 0	-334299.41	-334303.83
3	2 1 1	-329867.92	-329872.83
3	2 1 2	-329871.07	-329876.46
3	2 2 1	-329821.38	-329826.78
3	2 2 2	-329823.56	-329829.45
4	0 0 0 0*	-351121.28	-351125.20
4	1 1 1 1	-325380.55	-325386.43
4	2 2 2 2	-325204.49	-325212.34
4	1 2 1 1	-325353.23	-325359.60
4	1 1 1 2	-325386.01	-325392.39
4	1 1 2 1	-325256.52	-325262.90
5	0 0 0 0 0*	-350621.40	-350626.31

[1]Trajectory shapes; 0 = zero-order; 1 = linear; 2 = quadratic.

[2]BIC = Bayesian information criterion (for the total number of participants)

[3]BIC = Bayesian information criterion (for the total number of observations)

*One or more of the groups had a very small proportion of the observations, i.e., less than 5%.

GBTM-Table 2. Average posterior probability (AvePP) value and odds of correct classification for BMI GBTM groups

	BMI GBTM groups		
	Normal weight	Overweight	Obese
Average posterior probability value	0.92	0.89	0.93
Odds of correct classification	9.72	11.61	153.71

GBTM-Table 3. Body mass index trajectory groups' estimated probability and the proportion of study members classified to each group according to the maximum posterior probability assignment rule

	BMI GBTM groups		
	Normal weight	Overweight	Obese
Estimated group probability	51.9	40.4	7.7
Proportion assigned to group according to the maximum posterior probability assignment rule	52.6	39.9	7.4

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Supplementary material

Figure S1. Flow-chart outlining the selection of the study participants

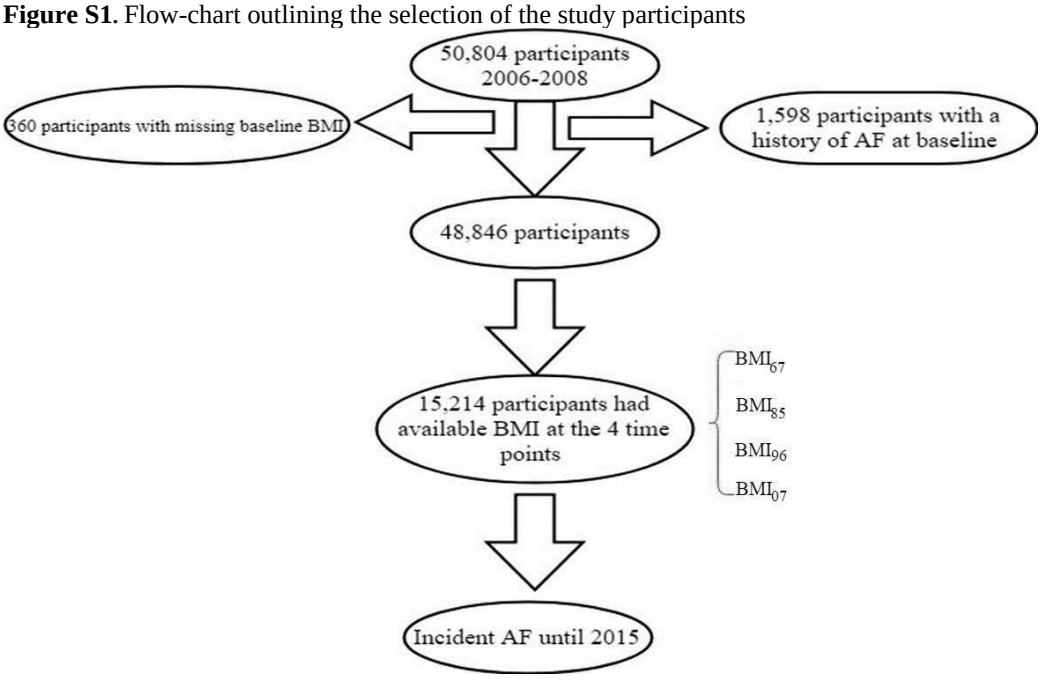


Figure S2. Flow-chart outlining each body mass index measurement at each time point

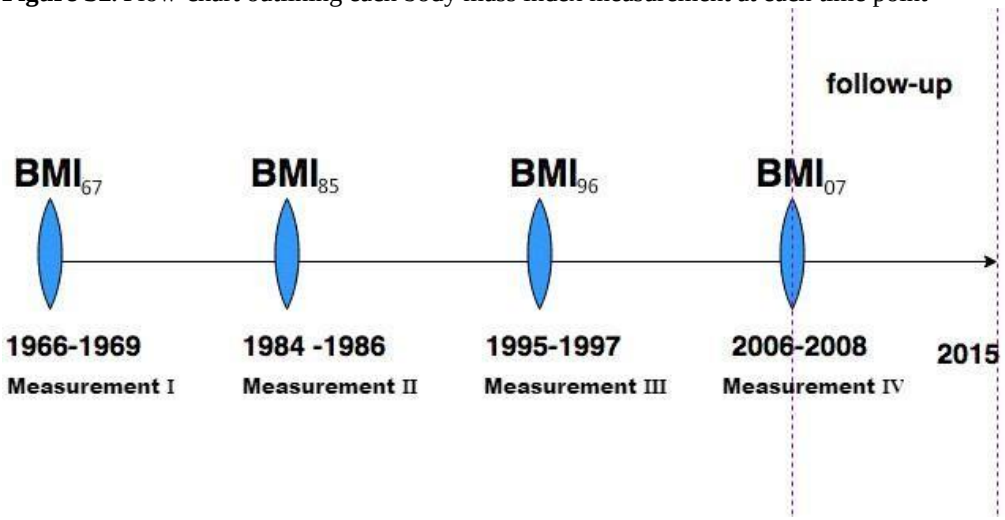


Figure S3. Estimated trajectories (solid lines), observed group BMI at each survey year (dot symbols), and estimated group percentages. Dashed lines are 95% confidence intervals on the estimated trajectories.

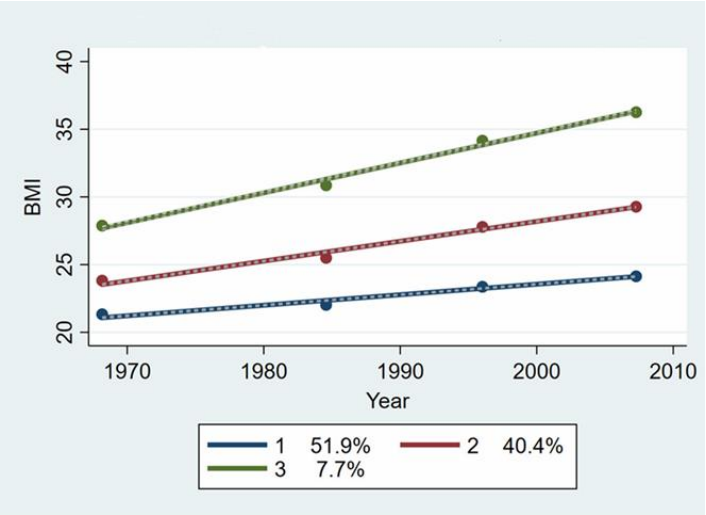
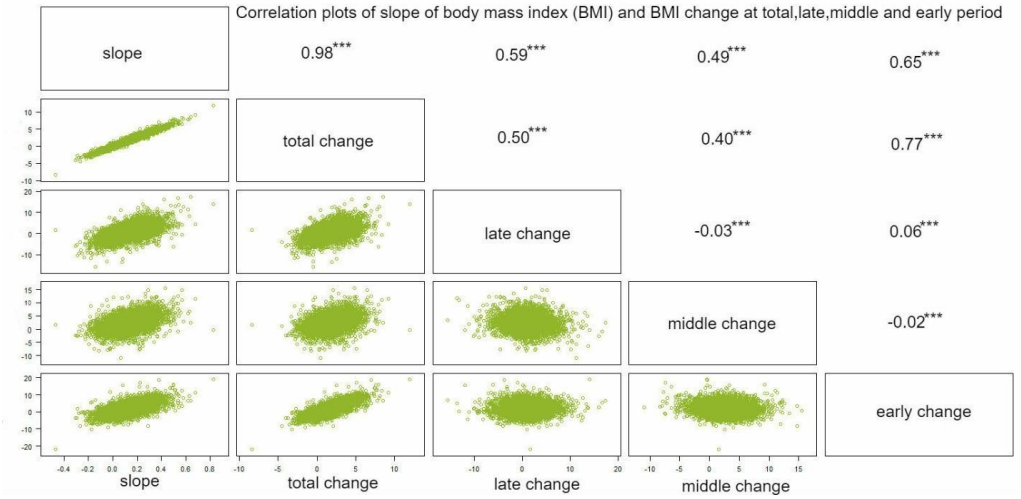
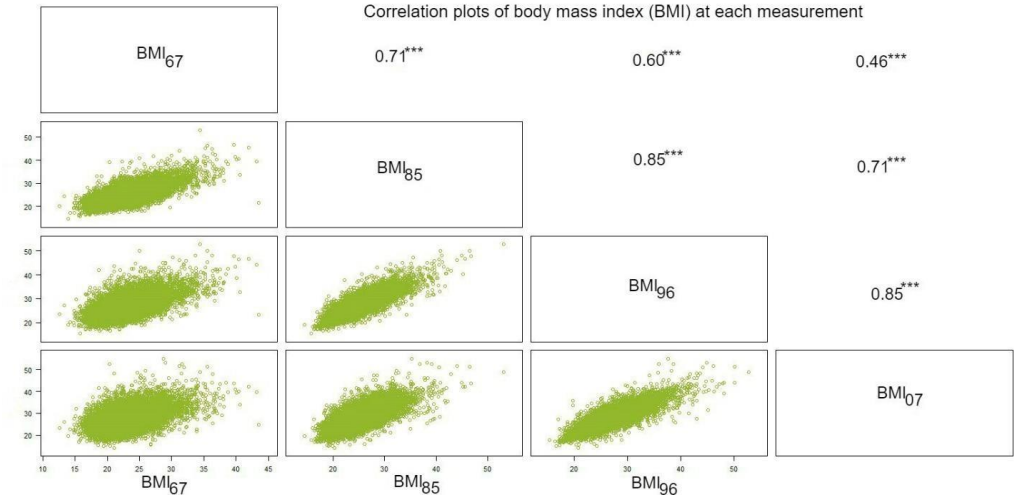


Figure S4.



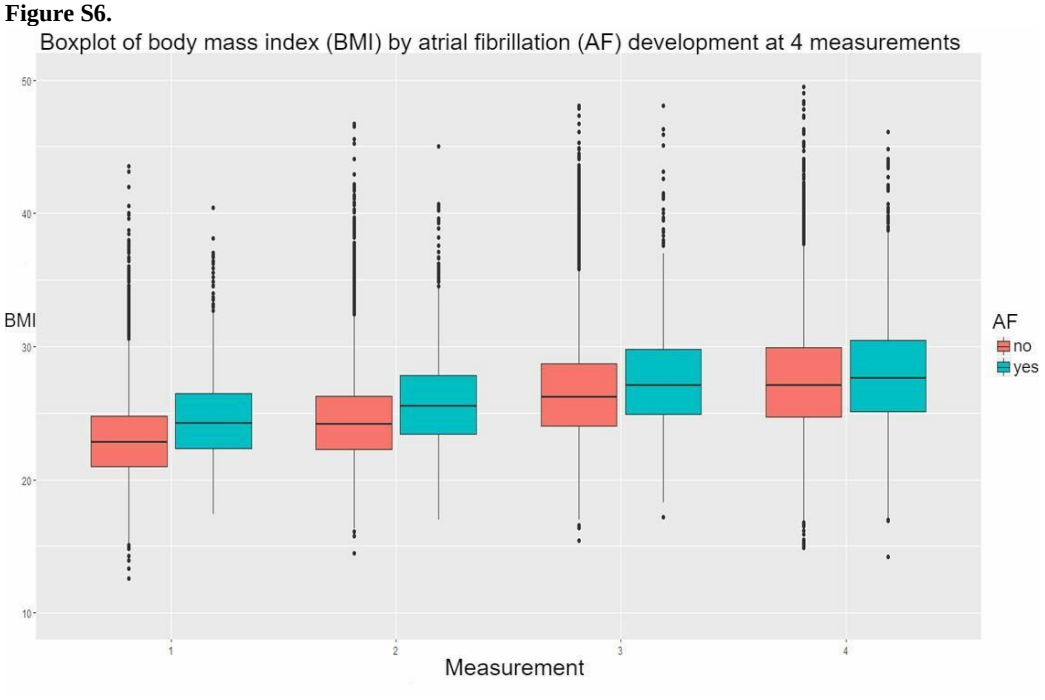
The plot is split in two: the lower left triangle shows the scatter plots of pairs of variables.
The upper right triangle shows Pearson correlation coefficient between pairs of variables and the associated degree of significativity.
The degree of significativity is as follows: $p \leq 0.001$: '***'; $p \leq 0.01$: '**'; $p \leq 0.05$: '*'; $p \leq 0.1$: '-'.

Figure S5.



The plot is split in two: the lower left triangle shows the scatter plots of pairs of variables.
The upper right triangle shows Pearson correlation coefficient between pairs of variables and the associated degree of significativity.
The degree of significativity is as follows: $p \leq 0.001$: '***'; $p \leq 0.01$: '**'; $p \leq 0.05$: '*'; $p \leq 0.1$: '-'.

Figure S6.



Measurement 1:1966–1969; Measurement 2: 1984–1986; Measurement 3: 1995–1997; Measurement 4: 2006–2008.
The box represents the lower and upper quartiles; the medians are indicated by a line inside each box; the whiskers represent the 10th and 90th percentiles.

Figure S7. Percentage of hypertension and antihypertensive medication by weight and atrial fibrillation status

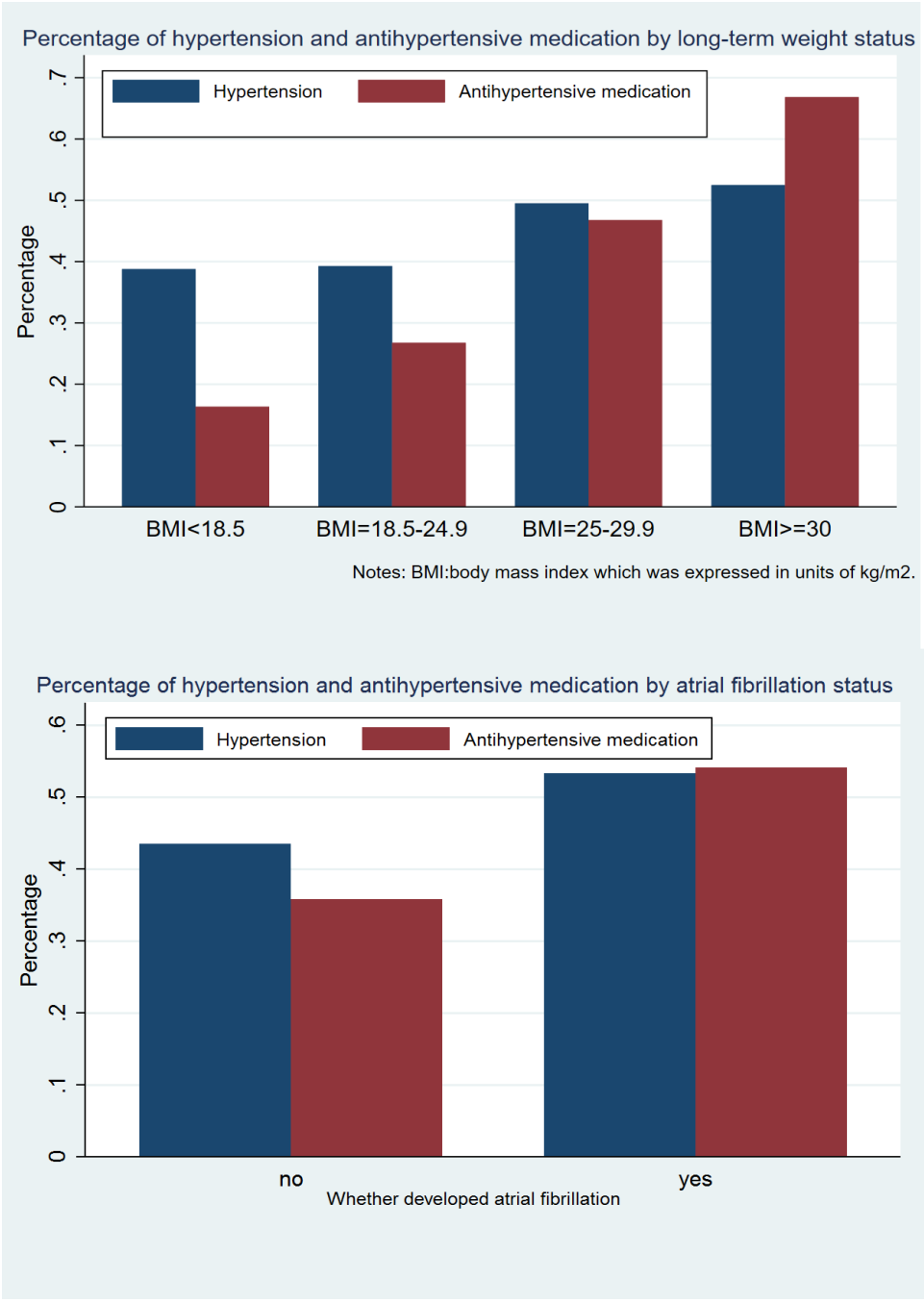


Table S1. Hazard ratios for atrial fibrillation according to categories of body mass index at each time point

	BMI_{67}			BMI_{85}			BMI_{96}			BMI_{07}		
BMI (kg/m^2)	Events	HR	95% CI	Events	HR	95% CI	Events	HR	95% CI	Events	HR	95% CI
<18.5	6	0.4	(0.1- 0.9)	4	0.9	(0.3-2.8)	2	0.6	(0.1-4.4)	10	1.1	(0 .4-3.0)
18.5-24.9	679	1	(Ref.)	483	1	(Ref.)	289	1	(Ref.)	257	1	(Ref.)
25.0-29.9	396	1.3	(1.1-1.5)	523	1.3	(1.1-1.5)	582	1.2	(1.0-1.4)	548	1.1	(0.9- 1.3)
≥30.0	68	1.4	(1.0-2.0)	139	2.0	(1.6-2.6)	276	1.8	(1.4-2.1)	334	1.4	(1.2 -1.8)

Hazard ratio adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, and alcohol consumption.
BMI= body mass index; CI = confidence interval; HR= Hazard ratio.

Table S2. Hazard ratios for atrial fibrillation by body mass index trajectories and intra-individual body mass index variability

	Events	Incidence rate[#]	HR	95% CI
BMI trajectory				
Normal weight	390	7.6	1	(Ref.)
Overweight	587	11.0	1.2	(1.0-1.4)
Obesity	172	17.0	1.9	(1.5-2.4)
Intra-individual BMI variability				
0-1.07	246	8.4	1	(Ref.)
1.08-1.59	287	9.9	1.3	(1.0-1.5)
1.60-2.29	279	9.8	1.1	(0.9-1.4)
≥2.29	337	12.1	1.5	(1.2-1.8)

BMI trajectories were identified based on group-based trajectory modeling by using Stata Traj Plugin.
Intra-individual BMI variability was calculated as the square root of the variance or the residual mean square, from the 4 residuals from the participant-specific regressions.
[#]Incidence rate per 1000 persons-years .
Models was adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, alcohol consumption metabolic status and chronic disorders.
BMI= body mass index; CI = confidence interval; HR= Hazard ratio.

Table S3. Hazard ratios for atrial fibrillation by average waist circumference and average waist-hip ratio from HUNT-2 until the end of follow-up

	Events	Incidence rate[#]	HR[a]	95% CI	HR[b]	95%CI
Waist circumference (cm)						
≤88 /102 women/men	738	9.3	1	(Ref.)	1	(Ref.)
>88 /102 women/men	409	11.8	1.2	(1.1-1.4)	0.8	(0.7-1.0)
Waist-hip ratio						
<0.85 /0.90 women/men	500	8.6	1	(Ref.)	1	(Ref.)
≥0.85 /0.90 women/men	647	11.6	1.0	(0.9-1.1)	0.8	(0.7-0.9)

Average waist circumference(WC) (waist circumference averaged over time from HUNT-2 until end of follow-up)=$[(WC_{96}\times time_{III\text{-}IV})+(WC_{07}\times time_{IV\text{-}})]/time_{III\text{-}end}$.
Average waist-hip ratio (WHR) (waist-hip ratio averaged over time from HUNT-2 until end of follow-up)=$[(WHR_{96}\times time_{III\text{-}IV})+(WHR_{07}\times time_{IV\text{-}})]/time_{III\text{-}end}$.
[#]Incidence rate per 1000 persons-years .
HR[a]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, and alcohol consumption.
HR[b]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, alcohol consumption, average BMI from HUNT-2 to the end of follow-up.
CI = confidence interval; HR= Hazard ratio.

Table S4. Hazard ratios for atrial fibrillation by categories of waist circumference change from HUNT-2 to HUNT-3

WCD(cm)	HR[a]	95% CI	HR[b]	95% CI
<0	1.1	(0.9-1.3)	1.1	(0.9-1.3)
≥0–<4	1	(Ref.)	1	(Ref.)
≥4–<9	1.0	(0.8-1.2)	1.0	(0.8-1.2)
≥9–<14	0.9	(0.8-1.1)	0.9	(0.8-1.1)
≥14	1.1	(0.9-1.3)	1.0	(0.8-1.2)

Waist circumference(WC) change from HUNT-2 to HUNT-3=WC_{07}-WC_{96}.

HR[a]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, and alcohol consumption.

HR[b]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, alcohol consumption, average BMI from HUNT-2 to the end of follow-up.

WCD= waist circumference change from HUNT-2 to HUNT-3; CI = confidence interval; HR= Hazard ratio.

Table S5. Hazard ratios for atrial fibrillation by categories of waist-hip ratio change from HUNT-2 to HUNT-3

WHD	HR[a]	95% CI	HR[b]	95% CI
<0.03	0.9	(0.8- 1.1)	0.9	(0.8-1.1)
≥0.03–<0.07	1	(Ref.)	1	1
≥0.07–<0.11	1.0	(0.9-1.2)	1.0	(0.8-1.1)
≥0.11	1.0	(1.8-1.1)	0.9	(0.8-1.1)

Waist-hip ratio change (WHD) from HUNT-2 to HUNT-3=WHR_{07}–WHR_{96}.
HR[a]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, and alcohol consumption.
HR[b]: adjusted for age, sex, height , smoking status, level of education, marital status, physical activity, alcohol consumption and average BMI from HUNT-2 to the end of follow-up.
WHD= Waist-hip ratio change from HUNT-2 to HUNT-3; CI = confidence interval; HR= Hazard ratio.

Table S6. Hazard ratios for atrial fibrillation by average body mass index and total body mass index change stratified by age at 65 years

	< 65 years	**≥ 65 years**
Average BMI (kg/m^2)		
<18.5	1.9 (0.3-13.6)	-
18.5-24.9	(Ref.)	(Ref.)
25.0-29.9	1.3 (0.9-1.8)	1.2 (1.0-1.4)
≥30	2.3 (1.4-4.0)	1.4 (1.1-1.9)
BMI change (kg/m^2)		
<-5.0	-	-
≥-5.0 – <-2.5	-	1.8 (0.7-5.2)
≥-2.5 – <2.5	(Ref.)	(Ref.)
≥2.5 – <5.0	0.9 (0.6-1.5)	1.5 (1.1-2.0)
≥5.0	1.8 (0.6-5.3)	2.7 (0.8-9.0)

Results were presented as hazard ratio (95% confidence interval). BMI: body mass index.
Models were adjusted for age, sex, height, smoking status, level of education, marital status, physical activity, alcohol consumption, regression slope of BMI (this term was only for the models of BMI change).

Table S7. Hazard ratios for atrial fibrillation by average body mass index and total body mass index change stratified by sex

	Women	**Men**
Average BMI (kg/m^2)		
<18.5	0.7 (0.1-5.3)	-
18.5-24.9	(Ref.)	(Ref.)
25.0-29.9	1.2 (0.9-1.5)	1.2 (1.0-1.4)
≥30	1.6 (1.2-2.2)	1.4 (0.9-2.1)
BMI change (kg/m^2)		
<-5.0	-	-
≥-5.0 – <-2.5	2.0 (0.6-6.5)	1.8 (0.2-13.5)
≥-2.5 – <2.5	(Ref.)	(Ref.)
≥2.5 – <5.0	1.5 (1.0-2.2)	1.1 (0.8-1.6)
≥5.0	3.2 (1.3-7.8)	3.5 (1.1-10.5)

Results were presented as hazard ratio (95% confidence interval). BMI: body mass index.
Models were adjusted for age, sex, height, smoking status, level of education, marital status, physical activity, alcohol consumption, regression slope of BMI (this term was only for the models of BMI change).

Table S8. Hazard ratios for atrial fibrillation by average body mass index and total body mass index change in sensitivity analyses

	Inclusion of possible or single-episode AF as events	**Exclusion of first 2 years of follow-up**
Average BMI (kg/m^2)		
<18.5	0.5 (0.7- 3.8)	0.7 (0.1- 4.9)
18.5-24.9	(Ref.)	(Ref.)
25.0-29.9	1.2 (1.1-1.4)	1.2 (1.0-1.4)
≥30	1.4 (1.1-1.7)	1.6 (1.2-2.1)
BMI change (kg/m^2)		
<-5.0	-	-
≥-5.0 – <-2.5	1.5 (0.6-4.2)	2.1 (0.6-6.8)
≥-2.5 – <2.5	(Ref.)	(Ref.)
≥2.5 – <5.0	1.3 (1.0-1.6)	1.2 (0.9-1.6)
≥5.0	2.7 (1.4-5.3)	2.7 (1.2-5.8)

Results were presented as hazard ratio (95% confidence interval). BMI: body mass index.
Models were adjusted for age, sex, height, smoking status, level of education, marital status, physical activity, alcohol consumption, regression slope of BMI (this term was only for the models of BMI change).

Table S9. Odds ratios (OR) and 95% confidence intervals (CI) for prevalent atrial fibrillation at baseline (2006-2008), by categories of body mass index (BMI) at baseline, average BMI and BMI change

	OR[a]	95% CI	OR[b]	95% CI
BMI at baseline (kg/m^2)				
<25.0	1.0	(Ref.)	1.0	(Ref.)
25.0-29.9	1.3	1.0-1.7	1.2	0.9-1.6
≥30	2.0	1.6-2.6	2.0	1.5-2.8
Average BMI (kg/m^2)				
<25.0	1.0	(Ref.)	1.0	(Ref.)
25.0-29.9	1.4	1.1-1.8	1.5	1.1-2.0
≥30	2.4	1.7-3.4	2.4	1.3-3.7
BMI change (kg/m^2)				
<-2.5	3.0	1.0-9.0	-	-
≥-2.5 – <2.5	1.0	(Ref.)	1.0	(Ref.)
≥2.5 – <5.0	1.8	1.3-2.4	1.8	1.3-2.6
≥5.0	3.3	1.2-9.1	4.3	1.5-12.1

OR[a]: adjusted for age and sex at baseline.
OR[b]: adjusted for age, sex, height, smoking status, level of education, marital status, physical activity, alcohol consumption, metabolic status and chronic disorders.

Paper II

Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Metabolically Healthy Obesity and Risk for Atrial Fibrillation: The HUNT Study

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Objective: Atrial fibrillation (AF) is the most common arrhythmia and has been described as a global epidemic. Although AF is associated with both obesity and its metabolic consequences, little is known about the association between metabolically healthy obesity and AF.
Methods: In a population-based study, 47,870 adults were followed for incident AF from 2006 to 2008 until 2015. Participants were classified according to BMI and metabolic status (using waist circumference, triglycerides, high-density lipoprotein cholesterol, blood pressure, and glucose) at baseline.
Results: During a median follow-up of 8.1 years, 1,758 participants developed AF. Compared with metabolically healthy individuals with BMI < 25 kg/m^2, the multivariable-adjusted hazard ratios for metabolically healthy and unhealthy obesity were 1.6 (95% CI: 1.2 to 2.1) and 1.6 (95% CI: 1.3 to 1.9), respectively. AF risk increased according to the severity of obesity.
Conclusions: Metabolically healthy and unhealthy obesity increased AF risk to a similar extent. Severity of obesity was positively associated with AF risk regardless of metabolic status.

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Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia and has been described as a global epidemic (1). An estimated 33.5 million people globally have AF, with 5 million incident AF events annually (1,2).

Metabolic syndrome (3), elevated blood glucose (4), and obesity (5) are thought to increase AF risk. Although obesity is a primary determinant of cardiovascular risk factors like dyslipidemia, elevated blood pressure, and impaired glucose tolerance that make up metabolic syndrome, a subset of individuals with obesity do not manifest these adverse factors. The prevalence of what is often termed metabolically healthy obesity among individuals with obesity (BMI ≥ 30 kg/m^2) in Europe varies between 7% and 28% among women and 2% and 19% among men (6). Research concerning the metabolically healthy obesity phenotype is still in its infancy, and the health consequences conferred by metabolically healthy obesity are still under debate. One systematic review and meta-analysis showed that individuals with metabolically healthy obesity were at increased risk for all-cause mortality and cardiovascular events compared with metabolically healthy normal-weight individuals (7), but several studies have suggested that individuals with metabolically healthy obesity are not at increased risk compared with normal-weight individuals (8,9). Current one-size-fits-all approaches to treat obesity, which neglect differences between metabolically healthy and unhealthy obesity phenotypes, have largely been unsuccessful (10). Given that prevention and treatment of both obesity and AF are enormous medical and socioeconomic priorities, a better understanding of AF risk carried by obesity-associated metabolic health phenotypes is important for early identification of high-risk subgroups who should be prioritized for lifestyle and medical intervention and development of personalized antiobesity strategies (10).

To the best of our knowledge, only two studies have investigated the associations between metabolically healthy obesity and AF risk, and the results were conflicting (11,12). A Swedish study suggested essentially similar risk among those with healthy and unhealthy obesity (11), whereas the risk for the latter group was much more pronounced in a Korean study (12).

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The Swedish study had a sample size of just over 4,000 individuals, and in both studies, follow-up was based only on administrative health registers. Furthermore, neither study analyzed the duration or severity of obesity. Therefore, this large population-based study aimed to assess AF risk in relation to metabolically healthy obesity using validated AF diagnoses.

Methods

Study population

All 93,860 residents ≥ 20 years of age in Nord-Trøndelag County in Norway were invited to participate in the third Nord-Trøndelag Health study (HUNT-3) from October 2006 to June 2008. Of these, 50,804 participants (54%) answered questionnaires and underwent clinical examinations. Holmen et al. have described the HUNT study in more detail (13).

Participants were excluded from this analysis if they had a history of AF at baseline (n = 1,598) or missing values for BMI or metabolic status (n = 1,336). Thus, 47,870 participants (26,263 women and 21,607 men) remained eligible for the main analyses.

Clinical examination

A clinical examination was conducted by trained nurses. Height and weight were measured while the participants were barefoot and in light clothing; height was measured to the nearest centimeter, and weight was measured to the nearest 0.5 kg. Circumferences of the waist and hip were measured to the nearest centimeter with the participants standing erect with their arms hanging relaxed (13). The waist circumference (WC) was measured at the level of the umbilicus, and the hip circumference was measured at the widest part of the hip/buttocks. Nonfasting blood samples were analyzed for glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein (13). Time since last meal (in hours) was recorded. Blood pressure was measured three times using a Dinamap 845XT (Critikon) based on oscillometry, with the arm resting on a table, and the average of the second and third measurement was used for analysis (13).

BMI

BMI was calculated by dividing body weight in kilograms by height in meters squared and was divided into three categories: < 25 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥ 30 kg/m^2 (obesity). We further subcategorized obesity into two categories: 30 to 34.9 kg/m^2 and ≥ 35 kg/m^2.

Height and weight were also available from a mandatory tuberculosis screening conducted in the county between 1966 and 1969 (14), the HUNT-1 study (1984-1986) (15), and the HUNT-2 study (1995-1997) (13). Both were measured similarly as in the HUNT-3 study. Among the 47,870 participants in HUNT-3, 14,970 individuals had available information on previous BMI from all three earlier evaluations.

Metabolic status

We used a modified definition of metabolic health based on the International Diabetes Federation's descriptions (16). In our primary analyses, metabolically unhealthy was defined as the presence of increased WC (≥ 102 cm for men, ≥ 88 cm for women) in addition to two or more of the following criteria: increased nonfasting triglycerides (≥ 1.7 mmol/L), decreased HDL (< 1.03 mmol/L for men, < 1.29 mmol/L for women), increased blood pressure (≥ 130/85 mm Hg) or use of blood pressure medication, increased nonfasting glucose (≥ 11.1 mmol/L), or diabetes diagnosis. Stricter criteria for metabolically unhealthy classification was used in secondary analyses (i.e., metabolically healthy individuals had all metabolic parameters within the normal range).

AF

AF diagnoses were retrieved from discharge registers at the two hospitals in Nord-Trøndelag County from the baseline examination to November 30, 2015. We used code I48 from the *International Classification of Diseases, Tenth Revision* to identify patients with AF. Medical records of these patients were then reviewed by a cardiologist (JPL) and two specialists in internal medicine (MV and HE) and classified as AF or not according to the electrocardiographic criteria recommended by the European Society of Cardiology (17). Persons who had an episode of AF only within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction, or during episodes of hemodynamic instability (e.g., sepsis, noncardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of AF diagnosis, two physicians evaluated the available information separately. Only cases in which both physicians concurred were regarded as AF. The rest were classified as possible AF. The validation process is described in detail elsewhere (18).

Self-reported data

Smoking status was assessed as never, former, or current. We used self-reported alcohol consumption to classify individuals as abstainers, light drinkers (0 to 1 drinks per day), moderate drinkers (> 1 but ≤ 2 drinks per day), or heavy drinkers (> 2 drinks per day). Level of physical activity was self-reported; activity that did not make individuals sweat or cause labored breathing was regarded as light and was otherwise considered hard. Physical activity was categorized into inactivity (< 3 hours of light exercise per week or < 1 hour hard exercise), moderate activity (> 3 hours of light exercise or 1-3 hours of hard exercise per week), and high activity (> 3 hours of hard physical activity per week). Type of work was categorized as desk work, light industry work, construction work, or heavy physical work. Marital status was categorized as unmarried, married, widow[er], divorced, separated, or live-in partner. Information on the following other chronic conditions was self-reported: angina pectoris, stroke, asthma, diabetes mellitus, goiter, hypo- and hyperthyroidism, fibromyalgia, arthrosis, rheumatism, ankylosing spondylitis, cancer, epilepsy, osteoporosis, or use of blood pressure medication. Information on history of acute myocardial infarction and heart failure was retrieved from the hospital registers, and the diagnoses were reviewed by cardiologists (19).

Statistical analyses

Baseline characteristics are presented as means ± standard deviations (SD) for continuous variables and as percentages for categorical variables. We jointly classified participants into their respective stratum by BMI (< 25, 25 to 29.9, and ≥ 30 kg/m^2) and metabolic status (metabolically healthy and unhealthy). We used Cox proportional regression models to assess AF risk for a given stratum of BMI and metabolic status. Time was defined as days from inclusion to either incident AF or censoring due to death from other causes (N = 3,554), emigration from the county (N = 133), or end of follow-up.

We calculated hazard ratios (HRs) and 95% CIs, using BMI < 25 with healthy metabolic status as reference. We included age, sex, height, smoking, time since last meal, type of work, marital status, physical activity, alcohol consumption, and high-sensitivity C-reactive protein as potential confounders. The proportional hazards assumption was tested by comparing –ln–ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption.

In addition, we calculated HRs for four strata of BMI (BMI < 25, BMI 25-29.9, BMI 30-34.9, BMI ≥ 35) with metabolically healthy or unhealthy status.

In a separate analysis, we investigated AF risk based on BMI trajectories stratified by metabolic status. Only participants who had available information on BMI from the tuberculosis screening, HUNT-1, HUNT-2, and HUNT-3 were included in the primary analysis. Participants were divided into four categories: (1) long-term normal weight (BMI < 25 at all four measurements); (2) long-term overweight/obesity (BMI ≥ 25 at all four measurements); (3) recently developed overweight/obesity (BMI < 25 in the tuberculosis screening or at HUNT-1 or at HUNT-2, but ≥ 25 in HUNT-3); or (4) varying body mass (any other combination of the BMI categories; details are provided in the online Supporting Information).We used long-term metabolically healthy normal weight as the reference in the analyses.

In sensitivity analyses, we (1) excluded participants with chronic disease, (2) regarded cases of possible or single-episode AF during follow-up as events, and (3) treated BMI as a continuous variable. In other sensitivity analyses, we (4) regarded only those who had all metabolic parameters within the normal range to be metabolically healthy. We also (5) conducted analyses in which we jointly classified participants into their respective stratum by BMI and each metabolic component separately. To address the possibility of reverse causation as an explanation for the observed associations, we (6) excluded the first 2 years of follow-up and repeated the analyses. Furthermore, we (7) included increased WC in the definition of obesity. Given missing BMI information among some individuals at the earlier evaluations, we (8) also used group-based trajectory modeling (GBTM) to capture BMI trajectories of all available individuals. GBTM is suitable for analyzing developmental trajectories over time and handles missing data by fitting the model using maximum likelihood estimation (20). Three BMI trajectories were identified: "normal weight" (51.9%), "overweight" (40.4%), and "obesity" (7.7%). We then analyzed the associations between AF risk and these BMI trajectories with and without metabolic disorders. To further address the issue of incomplete BMI information at previous time points, we (9) used multiple imputation (21,22) (mi command in Stata) to examine whether the complete-case approach yielded biased estimates. All statistical analyses were conducted using Stata 14.2 for Windows (StataCorp LP, College Station, Texas).

Ethical clearance

The study was approved by the regional committee for ethics in medical research, by the National Directorate of Health, and by the Norwegian Data Inspectorate.

Results

During a median follow-up of 8.1 years (367,515 person-years), 1,758 (3.7 %) participants developed AF. Among 47,870 participants, 10,775 (22.5%) had obesity and 19,332 (40.4%) were metabolically unhealthy. Among participants with obesity, 27.4% were metabolically healthy. Participants with metabolically healthy obesity tended to be women, younger, and unmarried compared with those with metabolically unhealthy obesity (Table 1).

Age- and sex-adjusted HRs for metabolically healthy and unhealthy obesity were 1.7 (95% CI: 1.4-2.2) and 1.6 (95% CI: 1.4-1.9), respectively, compared with metabolically healthy normal weight (Table 2). Multivariable-adjusted HRs for metabolically healthy and unhealthy obesity were 1.6 (95% CI: 1.2-2.1) and 1.6 (95% CI: 1.3-1.9), respectively (Table 2).

When we subdivided BMI into four categories, AF risk was not consistently higher among metabolically unhealthy participants than among metabolically healthy participants within each BMI category (Table 3). AF risk increased according to the severity of obesity.

The multivariable-adjusted HRs for long-term metabolically healthy and unhealthy overweight/obesity were 1.6 (95% CI: 1.1-2.4) and 1.4 (95% CI: 1.1-1.9), respectively, compared with long-term metabolically healthy normal weight (Table 4). Among those who had recently developed overweight/obesity, AF risk was not substantially altered, especially among those who were metabolically healthy, but slightly higher risk was observed among those who were metabolically unhealthy.

In the sensitivity analyses, the multivariable-adjusted HRs were slightly higher after excluding participants with chronic disease at baseline (Supporting Information Table S1). The associations were similar to those of the main analysis when regarding possible or single-episode AF as events during follow-up (Supporting Information Table S2). When we treated BMI as a continuous variable, the multivariable-adjusted HRs of AF per 5-unit increase in baseline BMI were 1.3 (95% CI: 1.2-1.4) and 1.3 (95% CI: 1.2-1.4) with and without additional adjustment for metabolic status, respectively (Supporting Information Table S3). When we used stricter criteria to define metabolic health, the HRs were higher among participants with obesity, regardless of metabolic status, and among metabolically unhealthy participants with BMI < 30.0 (Supporting Information Table S4). However, the CIs were wider compared with the main analysis, leading to less precision of the estimates. There were small differences in HRs between obesity with and without each metabolic component, except that obesity with hypertension showed higher AF risk than obesity without hypertension (Supporting Information Table S5). There were 1,431 AF cases after the second year of follow-up. The estimates remained essentially unchanged after exclusion of the first 2 years of follow-up (Supporting Information Table S6). The HRs attenuated slightly after increased WC was included in the definition of obesity (Supporting Information Tables S7-S8). When we used GBTM to capture trajectories of BMI, the multivariable-adjusted HR in the obesity trajectory was 1.9 (95% CI: 1.2-3.1) for metabolically healthy individuals and 1.8 (95% CI: 1.4-2.3) for metabolically unhealthy individuals (Supporting Information Table S9). We found that the main analysis generally remained unbiased and achieved precision comparable to that using multiple imputation (Supporting Information Table S10).

Discussion

In this large longitudinal study, metabolically healthy obesity and unhealthy obesity were associated with similarly increased AF risk compared with metabolically healthy normal weight.

TABLE 1 Baseline characteristics by categories of BMI and metabolic status

Metabolic status BMI	Healthy, BMI < 25 (*n* = 14,327)	Unhealthy, BMI < 25 (*n* = 2,043)	Healthy, BMI 25-29.9 (*n* = 11,247)	Unhealthy, BMI 25-29.9 (*n* = 9,434)	Healthy, BMI ≥ 30 (*n* = 2,955)	Unhealthy, BMI ≥ 30 (*n* = 7,798)
Incident AF, *n* (%)	322 (2.3)	92 (4.5)	295 (2.6)	514 (5.4)	112 (3.8)	423 (5.4)
Age, y	47.7 ± 16.6	59.9 ± 15.4	50.7 ± 14.7	58.4 ± 14.1	50.6 ± 15.0	56.2 ± 14.3
Female, *n* (%)	9,035 (63.1)	1,586 (77.4)	5,334 (47.4)	4,284 (45.3)	2018 (68.3)	4,006 (51.2)
BMI, kg/m^2	22.6 ± 1.7	23.6 ± 1.2	27.0 ± 1.3	27.7 ± 1.4	32.9 ± 3.0	33.5 ± 3.3
SBP, mm Hg	123.3 ± 17.3	136.4 ± 19.9	127.2 ± 16.6	138.0 ± 17.9	128.6 ± 16.9	138.7 ± 17.6
DBP, mm Hg	69.5 ± 10.5	74.0 ± 11.5	72.4 ± 10.6	77.2 ± 11.1	72.9 ± 10.4	77.2 ± 10.9
Total cholesterol, mmol/L	5.3 ± 1.1	5.7 ± 1.2	5.5 ± 1.0	5.7 ± 1.1	5.5 ± 1.0	5.6 ± 1.1
HDL cholesterol, mmol/L	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	1.1 ± 0.3
Triglycerides, mmol/L	1.1 ± 0.6	1.8 ± 0.9	1.3 ± 0.7	2.1 ± 1.1	1.3 ± 0.5	2.4 ± 1.2
Diabetes mellitus, *n* (%)	185 (1.3)	135 (6.6)	128 (1.1)	674 (7.1)	20 (0.7)	878 (11.2)
Abdominal obesity, *n* (%)	1,071 (7.5)	626 (30.6)	4,117(36.6)	5,348 (56.5)	2,699 (91.3)	7,331 (93.8)
CRP, mg/L	1.9 ± 5.4	3.0 ± 6.5	2.2 ± 4.7	2.8 ± 5.7	3.6 ± 5.2	3.9 ± 6.1
Time since last meal, h	2.8 ± 2.1	2.5 ± 1.8	2.9 ± 2.2	2.6 ± 1.9	3.1 ± 2.3	2.9 ± 2.2
Blood pressure medication, *n* (%)	1,253 (8.8)	557 (27.2)	1,357 (12.1)	3,125 (33.0)	472 (15.9)	3,276 (41.9)
Current smoker, *n* (%)	2,837(20.3)	545 (27.7)	1,594 (14.5)	1,651 (17.9)	399 (13.9)	1,185 (15.6)
Heavy drinker, *n* (%)	209 (1.5)	39 (1.9)	157 (1.4)	150 (1.6)	29 (1.0)	93 (1.2)
Desk work, *n* (%)	3,401 (30.0)	371 (30.8)	2,937 (32.3)	2,250 (35.6)	673 (30.0)	1,799 (35.0)
Physically inactive, *n* (%)	3,437 (30.9)	707 (43.5)	2,938 (33.3)	3,357 (44.4)	966 (42.3)	3,086 (50.5)
Unmarried, *n* (%)	4,518 (31.6)	272 (13.3)	2,707 (24.1)	1,431 (15.1)	760 (25.7)	1,543 (19.7)

Values are means ± SDs or *n* (%).
AF, atrial fibrillation; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

TABLE 2 Hazard ratios (HRs) of atrial fibrillation, by categories of BMI and metabolic status

BMI (kg/m^2)	Metabolic status	*N*	Events	Person-years	Incidence rate[a]	Crude HR	95% CI	HR[b]	95% CI	HR[c]	95% CI
<25	Healthy	14,325	322	109,068	2.6	1.0	(Ref.)	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	2,049	92	15,232	6.0	2.0	(1.6-2.6)	1.0	(0.8-1.3)	1.0	(0.8-1.4)
25-29.9	Healthy	11,257	295	87,421	3.4	1.1	(1.0-1.3)	1.0	(0.9-1.2)	1.1	(0.9-1.4)
	Unhealthy	9,464	514	71,876	7.2	2.4	(2.1-2.8)	1.3	(1.2-1.5)	1.3	(1.1-1.6)
≥30	Healthy	2,956	112	22,854	5.0	1.7	(1.3-2.1)	1.7	(1.4-2.2)	1.6	(1.2-2.1)
	Unhealthy	7,819	423	59,945	7.1	2.4	(2.1-2.8)	1.6	(1.4-1.9)	1.6	(1.3-1.9)

N: total numbers within each category.
[a]Incidence rate per 1,000 person-years.
[b]HR adjusted for age at baseline (continuous) and sex.
[c]HR adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry work, construction work, heavy physical labor), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein, and sex.

Several previous studies have found that metabolically healthy obesity is a relatively benign condition in relation to cardiovascular diseases (9,23,24), but our findings indicate that there is no "harmless" obesity regarding AF risk.

To our knowledge, only two studies have investigated AF risk in relation to metabolically healthy obesity (11,12). A Swedish study followed up 4,021 participants for a mean of 13.6 years. Consistent with the results from our study, metabolically healthy obesity and unhealthy obesity were associated with similarly increased AF risk (HRs were 1.8, 95% CI: 1.1-2.7 and 1.9, 95% CI: 1.3-2.7 when compared with metabolically healthy normal weight). Another study based on a Korean health insurance database included 389,321 participants with a follow-up of 11 years. The relative risks for AF among metabolically healthy and unhealthy obesity were 1.3 (95% CI: 1.1-1.5) and 1.7 (95% CI: 1.6-1.9) when compared with metabolically healthy

TABLE 3 Hazard ratios (HRs) of atrial fibrillation, by four categories of BMI and metabolic status

BMI (kg/m^2)	Metabolic status	*N*	Events	Person-years	Incidence rate[a]	HR[b]	95% CI	HR[c]	95% CI
<25	Healthy	13,989	307	106,693	2.9	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	1,935	92	14,424	6.4	1.1	(0.9-1.4)	1.1	(0.8-1.5)
25-29.9	Healthy	11,593	310	90,169	3.4	1.1	(0.9-1.2)	1.1	(0.9-1.4)
	Unhealthy	9,578	514	73,140	7.0	1.3	(1.2-1.5)	1.3	(1.1-1.6)
30-34.9	Healthy	2,423	91	18,820	4.8	1.7	(1.3-2.1)	1.6	(1.1-2.1)
	Unhealthy	5,912	300	45,535	6.6	1.4	(1.2-1.7)	1.4	(1.2-1.7)
≥35	Healthy	533	21	4,082	5.1	2.4	(1.5-3.7)	1.7	(0.8-3.4)
	Unhealthy	1,907	123	14,651	8.4	2.5	(2.0-3.0)	2.5	(1.9-3.3)

N: total numbers within each category.
[a]Incidence rate per 1,000 person-years.
[b]HR adjusted for age at baseline (continuous) and sex.
[c]HR adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry work, construction work, heavy physical labor), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein, and sex.

TABLE 4 Hazard ratios (HRs) of atrial fibrillation, by trajectories of BMI and metabolic status

BMI	Metabolic status	*N*	Events	Person-years	Incidence rate[a]	HR[b]	95% CI	HR[c]	95% CI
Long-term normal weight	Healthy	2,676	147	20,330	7.2	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	699	38	5,098	7.5	1.0	(0.7-1.4)	1.1	(0.7-1.6)
Long-term overweight/obesity	Healthy	364	54	2,580	20.9	1.6	(1.2-2.2)	1.6	(1.1-2.4)
	Unhealthy	776	112	5,449	20.6	1.5	(1.2-1.9)	1.4	(1.1-1.9)
Recently developed overweight/obesity	Healthy	946	43	7,354	5.9	0.9	(0.7-1.3)	0.9	(0.6-1.4)
	Unhealthy	906	54	6,922	7.8	1.2	(0.9-1.6)	1.3	(0.9-1.8)
Varying body mass	Healthy	3,139	218	23,841	9.1	1.2	(0.9-1.5)	1.3	(0.9-1.6)
	Unhealthy	5,494	460	41,016	11.2	1.4	(1.2-1.7)	1.4	(1.1-1.7)

N: total numbers within each category.
[a]Incidence rate per 1,000 person-years.
[b]HR adjusted for age at baseline (continuous) and sex.
[c]HR adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry work, construction work, heavy physical labor), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein, and sex.

normal weight, respectively. In these two prior studies, AF diagnoses were based strictly on administrative health data without further validation. However, the specificity of an AF diagnosis can be compromised in such settings (18,25,26), which is usually a greater threat to validity than imperfect sensitivity (27).

We were able to explore the association between severity of obesity according to metabolic status and AF risk in greater depth than has been achieved in previous studies. Several findings from these analyses bear mention. First, AF risk was associated with the severity of obesity regardless of metabolic status. Second, long-term overweight/obesity was associated with similarly increased AF risk among metabolically healthy and unhealthy participants. However, among those who had only recently developed overweight or obesity, only metabolically unhealthy participants had higher AF risk. This may suggest that metabolically healthy overweight/obesity represents an initially benign condition but exacts a greater toll with continued duration.

Our results suggest that obesity may increase AF risk via other mechanisms in addition to its impact on metabolic status, the latter of which appears to occur largely through increased blood pressure. Such mechanisms might include obesity causing left atrial structural changes leading to enlargement, increased fibrosis, impaired diastolic function, inflammation, and accumulation of pericardial fat (28). In particular, obesity appears to be associated with left atrial structural changes, regardless of metabolic factors (29), and may be the strongest risk factor for left atrial enlargement besides aging (30). Given that left atrial enlargement is a key risk factor for AF, it may play a central role in the association between obesity and AF beyond metabolic status.

In addition, our results showed that obesity with hypertension carried a much higher AF risk compared with obesity without hypertension, which largely echoes previous literature that has documented the important role of hypertension in the development of AF (28). Nonetheless, when we combined hypertension with other metabolic

components together, metabolically healthy and unhealthy obesity was associated with similar AF risk. The latter finding might well be due to dilution of the effect of hypertension when combined with other metabolic components that are unimportant for AF risk. If so, our results emphasize the distinct role that the hemodynamic changes of obesity play in AF development. On the other hand, although hypertension seems to play an important role in AF development, previous literature has suggested that each component of the metabolic syndrome may contribute to AF risk (31). Because our results suggest otherwise, it remains important to investigate the differential AF risk between metabolically obesity phenotypes and their potential for targeted preventive strategies in the future.

Our study was a large population-based study with a stable (a net out migration of 0.3% per year) (13) and homogeneous (less than 3% non-Caucasian) (13) study population. We relied on carefully validated AF diagnoses. We were able to analyze the role of both duration and severity of obesity. In addition, we had information on and could consider the role of a wide range of covariates.

Apart from its strengths, our study also has several limitations. First, BMI does not differentiate between fat tissue and muscle mass and does not evaluate fat distribution. Second, we used nonfasting blood samples. Glucose and triglyceride levels are usually higher in nonfasting than in fasting samples, which could result in misclassification of metabolic status. However, other determinants of metabolic status, such as HDL cholesterol, WC, and blood pressure, are not likely to be affected by fasting status. Moreover, time since last meal was accounted for in all analyses. Third, echocardiography data were available only in a small subset of very healthy individuals in HUNT, and hence we could not determine whether echocardiographic parameters mediate the observed associations. Third, only a fraction of the total population had data at all time points, which limited our possibility of analyzing the role of obesity duration. The main reason for incomplete data was the exceptionally long time window. The tuberculosis screening was conducted approximately 40 years before the baseline and was mandatory only for those who were at least 15 years old at that time (14). Thus, a great proportion of the participants at the baseline were too young to participate at the tuberculosis survey 40 years earlier. Since AF mainly occurs among the elderly (32), the loss in statistical power was limited. Lastly, individuals with metabolically unhealthy obesity may tend to have a higher detection rate of AF due to comorbidity demanding check-ups or hospitalizations, compared with metabolically healthy counterparts. Thus, there may exist a higher degree of underestimation of incident AF among metabolically healthy participants than among unhealthy participants.

Conclusion

In this population-based study, metabolically healthy obesity and unhealthy obesity were associated with similarly increased AF risk, especially when obesity was long-term. Obesity severity was positively associated with AF risk regardless of metabolic status. Our findings may have important public health implications and may highlight the potential for weight control strategies to decrease the increasing AF incidence.O

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Supplementary Material

Table S1. Hazard ratios of atrial fibrillation, by categories of BMI and metabolic status, excluding 21,807 participants with chronic disease at baseline

BMI	Metabolic status	Events	HR*	95% CI	HR†	95% CI
<25.0	Healthy	122	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	19	0.8	(0.5-1.3)	1.0	(0.6-1.9)
25.0-29.9	Healthy	118	1.0	(0.8-1.3)	1.2	(0.8-1.6)
	Unhealthy	156	1.2	(0.9-1.6)	1.2	(0.9-1.6)
≥30.0	Healthy	35	1.8	(1.2-2.6)	1.8	(1.1-2.9)
	Unhealthy	118	1.5	(1.2-1.9)	1.7	(1.2-2.4)

*Hazard ratio adjusted for age at baseline (continuous) and sex. †Hazard ratio adjusted for age at baseline (continuous),height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow(er), divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

CI= confidence interval; BMI=Body Mass Index; HR= hazard ratio.

Table S2. Hazard ratios of atrial fibrillation, by categories of BMI and metabolic status, including 120 participants with possible or single-episode AF as event during follow-up

BMI (kg/m^2)	Metabolic Status	Events	HR*	95% CI	HR†	95% CI
<25.0	Healthy	344	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	104	1.1	(0.9-1.4)	1.1	(0.8-1.4)
25.0-29.9	Healthy	317	1.0	(0.9-1.2)	1.1	(0.9-1.4)
	Unhealthy	552	1.3	(1.2-1.5)	1.3	(1.1-1.6)
≥30.0	Healthy	118	1.7	(1.4-2.1)	1.6	(1.2-2.1)
	Unhealthy	443	1.6	(1.4-1.8)	1.5	(1.3-1.8)

*Hazard ratio adjusted for age at baseline (continuous) and sex. † Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex. BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S3. Relative risk of atrial fibrillation per 5-unit increase of baseline body mass index, with and without adjustment for metabolic status

	HR	95% CI
Model 1	1.3	(1.2-1.4)
Model 2	1.3	(1.2-1.3)
Model 3	1.3	(1.2-1.4)
Model 4	1.3	(1.2-1.4)

Model 1:body mass index, age and sex.

Model 2:body mass index, age, sex, and metabolic status.

Model 3:body mass index, age, sex, height , smoking status (never, former, current), time since last meal , type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein .

Model 4:body mass index, age, sex, metabolic status, height , smoking status (never, former, current), time since last meal , type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein .

CI = confidence interval; HR= hazard ratio.

Table S4. Hazard ratios of atrial fibrillation, by categories of BMI and strict metabolic criteria

BMI (kg/m^2)	Metabolic Status	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
<25.0	Healthy	33	40226	0.8	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	378	82249	4.6	1.7	(1.2-2.5)	1.8	(1.1-3.0)
25.0-29.9	Healthy	22	14935	1.5	1.1	(0.7-2.0)	1.5	(0.8-2.9)
	Unhealthy	785	144250	5.4	2.0	(1.4-2.8)	2.2	(1.3-3.5)
≥30.0	Healthy	1	469	2.1	2.6	(0.4-18.9)	7.2	(1.0-54.0)
	Unhealthy	534	82619	6.5	2.6	(1.9-3.8)	2.7	(1.7-4.4)

[#]Incidence rate per 1000 persons-years .[*]Hazard ratio adjusted for age at baseline (continuous) and sex. [†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex. BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Stricter metabolic criteria: only those were regarded metabolically healthy who had all their metabolic parameters within the normal range.

Table S5. Hazard ratios of atrial fibrillation by BMI category and presence of each one of the components of metabolic syndrome.

BMI (kg/m^2)	Metabolic component	HR*	95% CI	HR†	95% CI
<25.0	Without Hypertension	1.0	(Ref.)	1.0	(Ref.)
	Hypertension	1.5	(1.2-1.9)	1.6	(1.2-2.1)
25.0-29.9	Without Hypertension	1.2	(1.0-1.4)	1.3	(1.0-1.7)
	Hypertension	1.7	(1.4-2.0)	1.7	(1.4-2.2)
≥30.0	Without Hypertension	1.6	(1.2-2.1)	1.3	(0.9-1.9)
	Hypertension	2.2	(1.8-2.6)	2.1	(1.6-2.8)
<25.0	Normal glucose	1.0	(Ref.)	1.0	(Ref.)
	Elevated glucose	1.0	(0.8-1.2)	1.1	(0.8-1.4)
25.0-29.9	Normal glucose	1.1	(1.0-1.3)	1.1	(0.9-1.4)
	Elevated glucose	1.3	(1.1-1.5)	1.2	(1.0-1.5)
≥30.0	Normal glucose	1.7	(1.4-2.0)	1.4	(1.1-1.9)
	Elevated glucose	1.6	(1.3-1.9)	1.4	(1.0-1.8)
<25.0	Normal triglycerides	1.0	(Ref.)	1.0	(Ref.)
	Elevated triglycerides	0.9	(0.7-1.2)	0.9	(0.7-1.2)
25.0-29.9	Normal triglycerides	1.2	(1.0-1.3)	1.1	(0.9-1.4)
	Elevated triglycerides	1.2	(1.0-1.4)	1.0	(0.8-1.3)
≥30.0	Normal triglycerides	1.6	(1.4-1.9)	1.3	(1.0-1.7)
	Elevated triglycerides	1.6	(1.3-1.8)	1.2	(0.9-1.5)
<25.0	Normal HDL-C	1.0	(Ref.)	1.0	(Ref.)
	Reduced HDL-C	0.9	(0.7-1.2)	1.0	(0.7-1.4)
25.0-29.9	Normal HDL-C	1.1	(1.0-1.3)	1.1	(0.9-1.4)
	Reduced HDL-C	1.4	(1.2-1.6)	1.2	(1.0-1.5)
≥30.0	Normal HDL-C	1.6	(1.3-1.8)	1.3	(1.0-1.7)
	Reduced HDL-C	1.7	(1.4-2.0)	1.4	(1.1-1.9)
<25.0	No abdominal obesity	1.0	(Ref.)	1.0	(Ref.)
	Abdominal obesity	1.0	(0.8-1.6)	1.2	(0.8-1.7)
25.0-29.9	No abdominal obesity	1.0	(0.9-1.2)	1.1	(0.9-1.4)
	Abdominal obesity	1.4	(1.2-1.6)	1.3	(1.1-1.6)
≥30.0	No abdominal obesity	1.5	(1.0-2.1)	1.8	(1.1-2.9)
	Abdominal obesity	1.6	(1.4-1.9)	1.5	(1.2-1.8)

HDL-C, high-density lipoprotein-cholesterol

Cox proportional hazards model was conducted for each metabolic component separately.

The reference group are participants with BMI<25 and without the respective metabolic component.*Hazard ratio adjusted for age at baseline (continuous) and sex. † Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein , sex and other components of metabolic syndrome. BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S6. Hazard ratios of atrial fibrillation by categories of BMI and metabolic status, excluding the first 2 years of follow-up

BMI (kg/m^2)	Metabolic Status	Events	Person-years	Incidence rate[#]	Crude HR	95% CI	HR[*]	95% CI	HR[†]	95% CI
<25.0	Healthy	263	81057	3.2	1.0	(Ref.)	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	77	11306	6.8	2.1	(1.6-2.7)	1.1	(0.8-1.4)	1.1	(0.8-1.5)
25.0-29.9	Healthy	238	65370	3.6	1.1	(0.9-1.3)	1.0	(0.8-1.2)	1.1	(0.9-1.3)
	Unhealthy	421	53640	7.8	2.4	(2.1-2.8)	1.3	(1.1-1.5)	1.3	(1.1-1.6)
≥30.0	Healthy	93	17056	5.5	1.7	(1.3-2.1)	1.7	(1.4-2.2)	1.6	(1.1-2.1)
	Unhealthy	339	44747	7.6	2.3	(2.0-2.7)	1.6	(1.3-1.8)	1.5	(1.2-1.9)

[#]Incidence rate per 1000 persons-years .[*]Hazard ratio adjusted for age at baseline (continuous) and sex. [†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S7. Hazard ratios of atrial fibrillation, by categories of abdominal obesity and metabolic status

Abdominal Obesity	Metabolic Status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
No	Healthy	20,651	492	158513	3.1	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	6,027	271	46109	5.9	1.1	(1.0-1.3)	1.1	(0.9-1.3)
Yes	Healthy	7,887	237	61252	3.9	1.4	(1.2-1.6)	1.3	(1.1-1.6)
	Unhealthy	13,305	758	101640	7.5	1.5	(1.4-1.7)	1.4	(1.2-1.6)

Abdominal obesity was defined as increased waist circumference (≥102 cm for men, ≥88 cm for women).
Ns: total numbers within each category.
#Incidence rate per 1000 persons-years .
*Hazard ratio adjusted for age at baseline (continuous) and sex.
†Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.
BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S8. Hazard ratios of atrial fibrillation, by categories of obesity which was defined by both body mass index and waist circumference

Obesity	Metabolic Status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
No	Healthy	25,839	628	198819	3.2	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	12,001	624	91335	6.8	1.2	(1.1-1.4)	1.2	(1.0-1.3)
Yes	Healthy	2,699	101	20946	4.8	1.7	(1.3-2.0)	1.6	(1.2-2.0)
	Unhealthy	7,331	405	56415	7.2	1.6	(1.4-1.8)	1.4	(1.2-1.6)

Obesity was defined by body mass index ≥30 kg/m^2 and waist circumference ≥102 cm for men, ≥88 cm for women simultaneously.

Ns: total numbers within each category.

[#]Incidence rate per 1000 persons-years .

[*]Hazard ratio adjusted for age at baseline (continuous) and sex.

[†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S9. Hazard ratios for atrial fibrillation by trajectories of body mass index and metabolic status

BMI Trajectory	Metabolic status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
Normal weight	Healthy	4,648	258	35403	7.2	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	2,179	138	16438	8.4	1.2	(0.9-1.4)	1.1	(0.8-1.4)
Overweight	Healthy	2,254	174	17070	10.2	1.2	(1.0-1.4)	1.3	(1.0-1.5)
	Unhealthy	4,502	380	33469	11.4	1.3	(1.1-1.5)	1.2	(1.0-1.5)
Obesity	Healthy	223	30	1633	18.4	2.2	(1.5-3.2)	1.9	(1.2-3.1)
	Unhealthy	1,164	146	8577	17.0	2.0	(1.6-2.4)	1.8	(1.4-2.3)

BMI trajectories were identified based on group-based trajectory modeling.
[#]Incidence rate per 1000 persons-years .
[*]Hazard ratio adjusted for age and sex.
[†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.
BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Table S10. Hazard ratios of atrial fibrillation, by trajectories of body mass index and metabolic status using multiple imputation

BMI	Metabolic Status	Ns	Events	Person-years	Incidence rate[#]	HR[*]	95% CI	HR[†]	95% CI
Long-term normal weight	Healthy	9,212	225	70955	3.2	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	1,921	63	14889	4.2	1.1	(0.8-1.6)	1.0	(0.6-1.6)
Long-term overweight/ obesity	Healthy	607	75	4380	17.1	1.7	(1.1-2.5)	1.8	(1.2-2.6)
	Unhealthy	1,253	149	8977	16.6	1.6	(1.3-2.0)	1.5	(1.1-2.0)
Recently developed overweight /obesity	Healthy	5,504	82	42631	1.9	0.9	(0.5-1.6)	1.0	(0.6-1.6)
	Unhealthy	3,522	88	27236	3.2	1.2	(0.8-1.8)	1.2	(0.8-1.7)
Varying body mass	Healthy	9,811	347	75831	4.6	1.2	(1.0-1.5)	1.2	(1.0-1.5)
	Unhealthy	16,040	729	122617	5.9	1.5	(1.2-1.8)	1.4	(1.1-1.8)

Multiple imputations (n=5) were used to account for missing data. The imputed variable was trajectory of BMI.

[#]Incidence rate per 1000 persons-years.

[*]Hazard ratio adjusted for age at baseline (continuous) and sex.

[†]Hazard ratio adjusted for age at baseline (continuous), height (continuous), smoking status (never, former, current), time since last meal (continuous), type of work (desk work, light industry worker, construction worker, heavy physical labour), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), C-reactive protein and sex.

BMI= body mass index; CI = confidence interval; HR= hazard ratio.

Paper III

Symptoms of anxiety and depression and risk of atrial fibrillation-the HUNT study

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Abstracts

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Anxiety and depression may activate the autonomic nervous system which is likely to play an important role in the etiology of AF. However, little is known about the association between symptoms of anxiety and depression and risk of AF.

Objective: This study aimed to assess the association between symptoms of anxiety and depression and risk of AF.

Methods: In a population-based study, 37,402 adult residents were followed for incident AF from 2006-2008 until 2015. Participants were classified according to data on anxiety and depression symptoms. Cox proportional regression models were used to adjust for common AF risk factors.

Results: During a median follow-up of 8.1 years, 1,433 (3.8 %) participants developed AF. In comparisons with no anxiety, the multivariable-adjusted hazard ratios (HRs) were 1.1 (95% CI: 0.9-1.5) for mild to moderate anxiety and 1.0 (95% CI: 0.8-1.4) for severe anxiety. In comparisons with no depression, the multivariable-adjusted HRs were 1.5 (95% CI: 1.2-1.8) for mild to moderate depression and 0.9 (95% CI: 0.6-1.3) for severe depression. Recurrent anxiety/depression was not associated with increased AF risk.

Conclusions: In this large, population-based study, we found no evidence of an association between anxiety or severe depression and AF risk, even for recurrent anxiety or depression. An unexpected association of mild to moderate depression with increased AF risk requires confirmation in other studies. Our findings add to the sparse literature on symptoms of anxiety and depression and risk of AF.

Keywords: Atrial fibrillation; depression; anxiety.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with increased risk of mortality and stroke as well as increased health care costs.[1] To be able to better prevent and treat AF, it is important to identify its modifiable risk factors.[2] Symptoms of depression and anxiety have been relatively strongly associated with cardiac diseases, including coronary heart disease,[3] acute myocardial infarction [4] and heart failure.[5] Furthermore, depression and anxiety may activate the autonomic nervous system [6] which is likely to play an important role in the etiology of AF.[7] However, only limited research has explored the effect of psychological distress on AF onset.[8, 9]

Therefore, the aim of this large population-based study was to assess the prospective association of anxiety and depression with AF risk.

Methods

Study population. All 93,860 residents ≥20 years of age in Nord-Trøndelag County in Norway were invited to participate in the third Nord-Trøndelag Health (HUNT 3) study from October 2006 to June 2008. Of these, 50,804 participants (54%) answered questionnaires and underwent a clinical examination. Holmen et al. have described the HUNT study in more detail.[10]

We excluded 1,598 participants from the analysis who had a history of AF at baseline and 11,804 participants with missing response for depression or anxiety symptoms, although we tested the inclusion of participants with missing data in imputation analyses described below. Details about inclusions are provided in Figure 1.

Measures of depression and anxiety symptoms

The Norwegian version of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety (HADS-A) and depression (HADS-D) during the previous week.[11] The HADS is a valid and reliable instrument across various patient samples and settings.[12]

It comprises 14 self-rated items, with seven items forming the Anxiety subscale (HADS-A) and seven items forming the Depression subscale (HADS-D). The HADS-A reflects symptoms of worry and tension, while HADS-D reflects symptoms of anhedonia and loss of interest. Responses are rated on a 4-point Likert scale ranging from 0 (no symptom) to 3 (highest symptom level). Participants were included in the subsequent analyses only if they answered all of the 14 items. The two subscales were divided into 3 categories: (1) having no symptoms of depression or anxiety (score < 8), (2) having mild to moderate symptoms (score 8–10), and (3) having severe symptoms (score ≥ 11), respectively.[13]

Among the 37,402 eligible participants in HUNT 3, 24,706 individuals had available information on HADS from the second wave of the HUNT Study (HUNT 2) conducted between 1995 and 1997.[10] A combined burden of anxiety in HUNT 2 and 3 was categorized into 3 groups: (1) no anxiety (scoring < 11 on HADS-A in HUNT 2 and 3), (2) anxiety at one time (scoring ≥ 11 on HADS-A in one of the HUNT studies), and (3) anxiety at both times (scoring ≥ 11 on HADS-A in both HUNT studies). A combined burden of depression in HUNT 2 and 3 was categorized into 3 groups: (1) no depression (scoring < 11 on HADS-D in HUNT 2 and 3), (2) depression at one time (scoring ≥ 11 on HADS-D in one of the HUNT studies), and (3) depression at both times (scoring ≥ 11 on HADS-D in both HUNT studies).

Atrial fibrillation. From the baseline examination until November 30, 2015, AF diagnoses were retrieved from discharge registers at two hospitals that together serve the entire population of

Nord-Trøndelag County. We used code I48 from the International Classification of Diseases Tenth Revision to screen for patients with possible AF. Medical records of these patients were then reviewed by experts, and AF was adjudicated based on electrocardiographic criteria recommended by the European Society of Cardiology.[14] Persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of hemodynamic instability (e.g., sepsis or non-cardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of the diagnosis, two physicians (HE and JPL) evaluated the available information separately. Only cases where both physicians concurred were regarded as AF. The rest were classified as possible AF and were not regarded as AF cases in the main analyses. The validation process is described in more detail elsewhere.[15]

Covariates. A clinical examination was conducted by trained nurses. Height and weight were measured barefoot and wearing light clothing; height was measured to the nearest cm and weight to the nearest 0.5 kg. Body mass index was calculated as body weight in kilograms divided by the squared value of height in meters. Non-fasting blood samples were analyzed for glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C) and high-sensitivity C-reactive protein (CRP).[10] Self-reported data obtained at the baseline included smoking status (never, former, or current), alcohol consumption (abstainers, light drinkers, moderate drinkers, or heavy drinkers), physical activity (inactivity, moderate activity or high activity), occupation (desk work, light industry work, technicians or heavy physical work), and marital status (cohabitation or no cohabitation). Information on common chronic disorders was self-reported and included: angina pectoris, stroke, asthma, osteoarthritis, kidney disease, hyperthyroidism, rheumatoid arthritis, sarcoidosis, ankylosing spondylitis, cancer, epilepsy, chronic bronchitis, emphysema or

COPD, psoriasis, diabetes, sleep apnea, acute myocardial infarction, and heart failure. Apart from self-report, information on history of acute myocardial infarction and heart failure was also retrieved from hospital registers.[16]

Statistical analyses. Baseline characteristics were presented as mean ± standard deviation for continuous variables and percentages for categorical variables. Cox proportional regression models were used to assess the association of symptoms of depression and anxiety with subsequent risk of AF. Participants who reported no symptoms (i.e., scoring < 8 on HADS-A or HADS-D) were regarded as the reference group. Time was defined as days from inclusion to either incident AF or censoring due to death from other causes (n=2,457), emigration from the county (n=82) or end of follow-up. We calculated hazard ratios (HRs) and 95% confidence intervals (CI). We included age and sex in model 1; in addition, weight, height, smoking, occupation type, marital status, physical activity, and alcohol consumption were added as potential confounders in model 2. In further analyses, we also adjusted for chronic disorders (model 3) and for metabolic components (i.e., blood glucose, blood pressure, triglycerides, HDL-C and CRP) (model 4). We tested linear as well as quadratic trends for the associations of symptoms of anxiety and depression with AF risk.

In separate analyses, we assessed the relative risk of AF according to episodes of anxiety and depression in HUNT 2 and 3. Participants without symptoms in any of the HUNT studies were regarded as the reference group.

The proportional hazards assumption was tested by comparing -ln-ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption.

To assess effect modification, we conducted analyses stratified by age, sex, and chronic diseases.

In sensitivity analyses, we regarded possible or single-episode AF during follow-up as events. Furthermore, to address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 2 years of follow-up and repeated the analyses. Lastly, we used multiple imputation with five imputations (mi command in Stata) to examine whether the complete-case approach yielded biased estimates.[17] All statistical analyses were conducted using Stata/MP 15.1 for Windows (College Station, TX: StataCorp LLC).

Results

Baseline characteristics

Characteristics of participants with and without subsequent AF are presented in Table 1. During a median follow-up of 8.1 years (288,460 person-years), 1,433 (3.8 %) participants developed AF. Using a cutoff score of 11 and above for severe symptoms, 2.2% of the participants reported depression and 4.9% reported anxiety. The participants that developed AF were older and more likely to be men, inactive, heavy drinkers, and score higher on the HADS-D subscale.

Relative risk of atrial fibrillation in relation to anxiety and depression

Table 2 shows HRs for incident AF according to symptoms of depression and anxiety in HUNT 3. In comparisons with no anxiety, the multivariable-adjusted HRs (model 2) were 1.1 (95% CI: 0.9-1.5) for mild to moderate anxiety and 1.0 (95% CI: 0.8-1.4) for severe anxiety, respectively. In comparisons with no depression, the multivariable-adjusted HRs were 1.5 (95% CI: 1.2-1.8) for mild to moderate depression and 0.9 (95% CI: 0.6-1.3) for severe depression, respectively (P = 0.002 for quadratic trend). Additional adjustment for chronic disorders or metabolic status did not materially change the estimates.

Table 3 shows the HRs for AF according to episodes of anxiety and depression in HUNT 2 and 3. Participants with recurrent anxiety or depression did not have higher relative risks of incident AF compared to those without anxiety or depression at any of the HUNT studies.

Effect modification

Overall, we found limited evidence of major effect modification by age, sex, or chronic disease (eTable 1-3). In general, the HRs tended to be higher among younger individuals, men, and participants without chronic disease.

Sensitivity analyses

We documented 1,165 AF cases after the second year of follow-up. Exclusion of the first 2 years of follow-up had little effect on the results (eTable 4). The results were also consistent with the main analyses when possible or single-episode AF events (n=99) were regarded as AF during follow-up. Finally, when we performed multiple imputation, the results were similar to those in the primary analysis (Table 5S).

Discussion

In this large, population-based study, we found no evidence of an association between severe depression and AF risk, even when depression was recurrent. We also found no association of anxiety with AF risk. Unexpectedly, only mild to moderate depression was associated with an increased AF risk.

Only four previous studies have assessed the prospective association of anxiety or depression with AF risk, and all had potential limitations in their assessments of exposure or outcome, and none had repeated measures of anxiety or depression. In the Framingham Offspring study which

had a relatively small sample size (n=3,682) and a 10-year follow-up,[9] anxiety in men (HR:1.1; 95% CI, 1.0 –1.3) had a weak association with AF risk while there was no such an association in women (HR:1.0; 95% CI, 0.8–1.3). In the Multi-Ethnic Study of Atherosclerosis (n=6,644),[18] depression was associated with higher AF risk (HR:1.3; 95% CI, 1.0-1.7). However, few details of these results are available, since these were published only as an abstract. Furthermore, both the Framingham Offspring study and the Multi-Ethnic Study of Atherosclerosis used instruments (i.e., the Tension and Symptoms of Anxiety Scales[9] and Depression Scale of Epidemiologic Studies[19], respectively) that include somatic symptoms. Consequently, the potential overlap of somatic symptoms caused by physical illness with that of psychological distress limited the ability of these studies to examine the genuine effects of core psychological and cognitive symptoms of anxiety and depression on AF risk. On the other hand, our study used the HADS scale, which replaces somatic symptoms with non-somatic alternatives.[11] Thus, in our study, we were able to examine the association of core psychological and cognitive symptoms of anxiety and depression with AF risk. In the Women's Health Study,[8] depression was unrelated to AF risk (HR:1.0; 95% CI, 0.8-1.3). The Mental Health Inventory-5, which has similar features as HADS in terms of exclusion of somatic symptoms, was used to assess depression.[8] However, AF events were self-reported in this study, which would tend to lower the specificity of the AF diagnoses. A Danish matched cohort study compared AF risk in all Danes initiating antidepressant medication (n= 785,254) with that in a 1:5-matched sample from the general population.[20] The study defined depression as the condition within the month before initiation of antidepressant medication. Substantially increased AF risk was observed even before antidepressant medication (HR = 3.18; 95% CI: 2.98–3.39) and within the first month (4.29; 95% CI: 3.94–4.67) after antidepressant initiation, but AF risk decreased 6–12 months after antidepressant initiation (HR =

1.11; 95% CI: 1.06–1.16). However, antidepressant medication is only a proxy for depression and these medications have common indications beyond depression as well,[21] such as pain or insomnia. Furthermore, the study retrieved AF diagnosis from registers without further manual verification, which could have resulted in misclassification.

Our study revealed an unexpected inverted U-shaped association between depression and AF risk, which is inconsistent with the limited previous research. The underlying mechanism is unclear. Depression may lead to increased inflammation,[22] oxidative stress[23] and sympathetic activation which in turn could increase the risk for AF. However, depression has also been associated with parasympathetic suppression,[24] which might actually reduce AF risk, thus potentially explaining the null effects of severe depression. It is also possible that the null effect for anxiety and for severe depression may be related to cardiac effects of different antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs) seem to have a cardio-protective profile.[25] SSRIs have been documented to improve glucose metabolism, dyslipidemia, and reduce inflammatory markers, which may contribute to reduced AF risk.[26] In the absence of any evidence of a dose-response relationship based on time or severity, our results clearly require confirmation in other cohort before the play of chance can be confidently excluded.

Strengths and limitations

The strengths of our study derive from the population-based design, the homogeneity of the population (eliminating confounding by racial differences in AF risk[27]), its high stability (less than 0.3% net migration/ year), the uniformly organized health care system which was equally available for every citizen and the relatively high response rate. Comprehensive data including those on a wide range of chronic disorders allowed us to thoroughly characterize participants and

minimize confounding. We had data on repeated assessments of anxiety and depression, which offered a unique opportunity to examine how AF risk was related to changes in anxiety or depression over time. Furthermore, careful verification of AF diagnoses ensured the minimization of the misclassification of endpoints.

Some limitations warrant discussion. First, we relied on a self-reported scale to measure anxiety and depression and lacked a clinician-administered interview to establish psychiatric diagnoses. This may have led to some misclassification of symptoms of depression and anxiety. However, the HADS has been documented to be a valid and reliable instrument among a wide variety of patient samples and settings.[12] Second, we lacked data on antidepressant medication. Third, AF can be occult and we only identified AF cases that came to clinical attention. Therefore, under-detection of AF, particularly when paroxysmal, is likely to exist in our findings. However, the consequence of under-detection, namely lower sensitivity, is generally less threatening to the validity of an epidemiological study than is lower specificity.[15, 28] Nonetheless, this may have precluded us from identifying a true association between depression or anxiety and risk of AF if one exists.

Conclusion

In this large, population-based study, we found no evidence of an association between anxiety or severe depression and AF risk, even for recurrent anxiety or depression. An unexpected association of mild to moderate depression with increased AF risk requires confirmation in other studies.

Conflict of interest statement:. None of the authors have any conflicts of interest.

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Figure 1. Flow chart for the participants

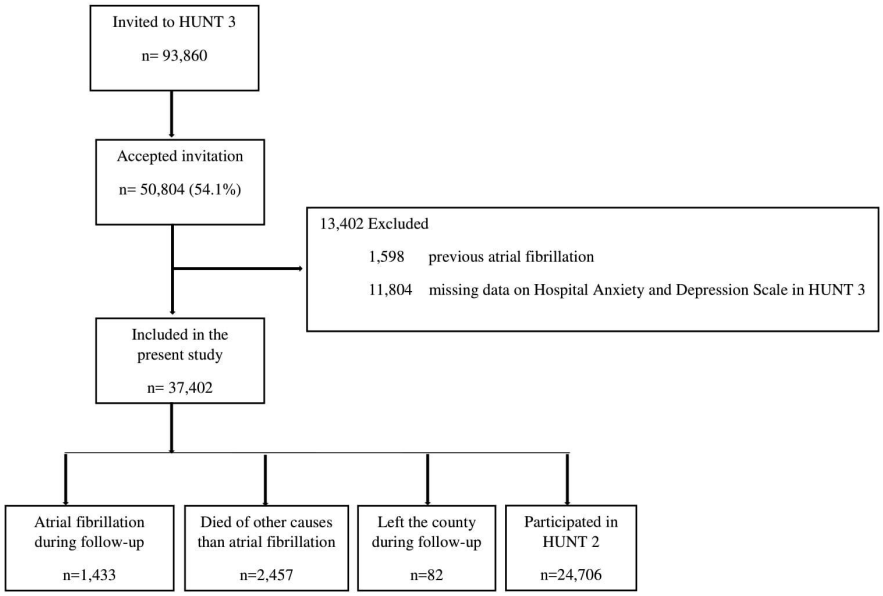

Table 1. Baseline characteristics of participants in the total population according to atrial fibrillation vs. no atrial fibrillation during follow-up

Variable	**No. of subjects**	**Total population**	**AF during follow-up**	**No AF during follow-up**
Total % (n)	37,402	%	3.8 (1,433)	96.2 (35,969)
Variables, % (n)				
Female	21,122	56.5	41.5 (595)	57.1 (20,527)
Diabetes mellitus	1,636	4.4	10.3 (148)	4.1 (1,488)
Current smoker	6,081	16.7	12.5 (173)	16.8 (5,908)
Heavy drinkers	523	1.4	2.5 (35)	1.4 (488)
Technicians	7,234	20.2	12.3 (164)	20.5 (7,070)
Physically inactive	7,470	20.3	24.1 (336)	20.1 (7,134)
Cohabitation	22,798	61.0	64.7 (927)	60.9 (21,871)
Mean (SD)				

Age, years	37,402	53.4 (15.2)	70.1 (10.9)	52.8 (15.0)
Body mass index, kg/m^2	37,289	27.2 (4.4)	28.2 (4.6)	27.1 (4.4)
HADS—depression score (HUNT 3)	37,402	3.3 (2.9)	4.0 (2.9)	3.3 (2.9)
HADS—anxiety score (HUNT 3)	37,402	4.0 (3.3)	3.7 (3.0)	4.0 (3.3)

AF: atrial fibrillation; HADS: Hospital Anxiety and Depression Scale

Table 2. Hazard ratios (95% confidence intervals) for atrial fibrillation during follow up according to symptoms of anxiety (HADS-A) and depression (HADS-D) in HUNT 3

	Model 1	**Model 2**	**Model 3**	**Model 4**
Events/person-years	1,433/ 288,460	1,235/ 266,671	1,186/ 256,765	1,205/ 260,753
HADS-A				
0–7	Reference	Reference	Reference	Reference
8–10	1.0 (0.8-1.3)	1.1 (0.9-1.5)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
≥11	1.1 (0.8-1.4)	1.0 (0.8-1.4)	1.0 (0.7-1.4)	1.1 (0.8-1.5)
***P* for linear trend**	0.5092	0.7865	0.9603	0.6695
***P* for quadratic trend**	0.8193	0.5454	0.5736	0.7501
HADS-D				
0–7	Reference	Reference	Reference	Reference
8–10	1.3 (1.0-1.6)	1.5 (1.2-1.8)	1.4 (1.1-1.7)	1.5 (1.2-1.8)
≥11	0.9 (0.7-1.3)	0.9 (0.6-1.3)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
***P* for linear trend**	0.6503	0.4552	0.3942	0.3648
***P* for quadratic trend**	0.0371	0.0021	0.0070	0.0014

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.

Model 1: adjusted for age and sex.

Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.

Model 3: Model 2 + chronic disorders.

Model 4: Model 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein.).

Table 3. Episodes of anxiety and depression in HUNT 2 and 3, and risk for atrial fibrillation

	Model 1	**Model 2**	**Model 3**	**Model 4**
Episodes of anxiety **Events/person-years**	1,064/ 197,659	941/185,194	905/178,283	919/181,398
No anxiety	Reference	Reference	Reference	Reference
Anxiety at one time	1.2 (0.9-1.6)	1.1 (0.9-1.5)	1.1 (0.8-1.4)	1.2 (0.9-1.6)
Anxiety at two times	0.9 (0.5-1.6)	1.0 (0.5-1.9)	0.9 (0.5-1.8)	1.0 (0.5-2.0)
***P* for linear trend**	0.6947	0.8987	0.8585	0.9624
***P* for quadratic trend**	0.2050	0.5131	0.7950	0.5304
Episodes of depression **Events/person-years**	1,189/209,075	1,039/194,757	998/187,170	1,015/190,694
No depression	Reference	Reference	Reference	Reference
Depression at one time	1.2 (0.9-1.6)	1.2 (0.9-1.6)	1.1 (0.8-1.6)	1.2 (0.9-1.6)
Depression at two times	0.9 (0.4-1.9)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.8 (0.3-1.9)
***P* for linear trend**	0.8137	0.7818	0.8480	0.5888
***P* for quadratic trend**	0.3748	0.3898	0.4934	0.2843

Model 1: adjusted for age and sex.

Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.

Model 3: Model 2 + chronic disorders.

Model 4: Model 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein.).

Supplemental material

eTable 1. Hazard ratios (95% confidence intervals) for atrial fibrillation associated with symptoms of anxiety and depression, stratified by age at 65 years

	< 65 years	≥ 65 years	*P* for interaction Anxiety/depression ×age
HADS—anxiety			
0–7	Reference	Reference	
8–10	1.0 (0.6-1.6)	1.1 (0.8-1.6)	0.271
≥11	1.0 (0.6-1.7)	1.0 (0.6-1.5)	0.609
***P* for linear trend**	0.8763	0.8799	
***P* for quadratic trend**	0.9236	0.5138	
HADS—depression			
0–7	Reference	Reference	
8–10	1.3 (0.8-2.1)	1.4 (1.1-1.9)	0.887
≥11	1.0 (0.6-2.0)	0.7 (0.4-1.2)	0.501
***P* for linear trend**	0.8902	0.1627	
***P* for quadratic trend**	0.3372	0.0037	
Episodes of anxiety			
No anxiety	Reference	Reference	
Anxiety at one time	1.0 (0.6-1.7)	1.0 (0.7-1.6)	0.486
Anxiety at two times	1.3 (0.5-3.6)	0.8 (0.3-1.9)	0.689
***P* for linear trend**	0.5770	0.5547	
***P* for quadratic trend**	0.6771	0.5766	
Episodes of depression			
No depression	Reference	Reference	

Depression at one time	0.8 (0.4-1.5)	1.3 (0.9-1.9)	0.206
Depression at two times	1.4 (0.4-4.3)	0.7 (0.2-2.0)	0.275
***P* for linear trend**	0.5916	0.4668	
***P* for quadratic trend**	0.3393	0.1550	

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.

Hazard ratios adjusted for age, sex, weight, height, smoking status, profession, marital status, physical activity and alcohol consumption, and chronic disorders.

eTable 2. Hazard ratios (95% confidence intervals) for atrial fibrillation associated with symptoms of anxiety and depression, stratified by sex

	Women	**Men**	**P for interaction Anxiety/depression ×sex**
HADS—anxiety			
0–7	Reference	Reference	
8–10	1.0 (0.6-1.4)	1.2 (0.8-1.8)	0.381
≥11	0.9 (0.5-1.4)	1.1 (0.7-1.8)	0.274
***P* for linear trend**	0.5143	0.5665	
***P* for quadratic trend**	0.8993	0.5547	
HADS—depression			
0–7	Reference	Reference	
8–10	1.0 (0.7-1.6)	1.6 (1.2-2.1)	0.429
≥11	0.6 (0.3-1.3)	1.0 (0.6-1.5)	0.558
***P* for linear trend**	0.1882	0.9018	
***P* for quadratic trend**	0.3254	0.0088	
Episodes of anxiety			
No anxiety	Reference	Reference	
Anxiety at one time	0.9 (0.5-1.5)	1.2(0.8-1.8)	0.271
Anxiety at two times	0.7 (0.3-1.9)	1.3 (0.5-3.2)	0.396
***P* for linear trend**	0.4584	0.5592	
***P* for quadratic trend**	0.8469	0.8974	
Episodes of depression			
No depression	Reference	Reference	

Depression at one time	1.2 (0.7-2.0)	1.1 (0.8-1.7)	0.816
Depression at two times	0.9 (0.2-3.6)	1.0 (0.4-2.7)	0.999
***P* for linear trend**	0.8771	0.9829	
***P* for quadratic trend**	0.6133	0.6819	

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.

Hazard ratios adjusted for age, weight, height, smoking status, profession, marital status, physical activity and alcohol consumption, and chronic disorders.

eTable 3. Hazard ratios (95% confidence intervals) for atrial fibrillation associated with symptoms of anxiety and depression, stratified by chronic disease

	Without chronic disease	Chronic disease	P value for interaction Anxiety/depression ×chronic disease
HADS—anxiety			
0–7	Reference	Reference	
8–10	0.9 (0.6-1.4)	1.2 (0.9-1.6)	0.181
≥11	0.9 (0.6-1.5)	0.9 (0.6-1.3)	0.321
***P* for linear trend**	0.3161	0.5363	
***P* for quadratic trend**	0.2433	0.2056	
HADS—depression			
0–7	Reference	Reference	
8–10	1.2 (0.7-2.1)	1.4 (1.1-1.8)	0.686
≥11	1.5 (0.6-3.3)	0.8 (0.5-1.2)	0.156
***P* for linear trend**	0.3552	0.2210	
***P* for quadratic trend**	0.9377	0.0031	
Episodes of anxiety			
No anxiety	Reference	Reference	
Anxiety at one time	1.3 (0.7-2.5)	0.9 (0.7-1.3)	0.404
Anxiety at two times	1.1 (0.2-8.2)	0.9 (0.4-1.8)	0.942
***P* for linear trend**	0.8924	0.7578	
***P* for quadratic trend**	0.7382	0.9709	
Episodes of depression			
No depression	Reference	Reference	

Depression at one time	1.1 (0.5-2.4)	1.1 (0.8-1.6)	0.943
Depression at two times	2.5 (0.6-10.2)	0.7 (0.3-1.9)	0.177
***P* for linear trend**	0.2027	0.5014	
***P* for quadratic trend**	0.4959	0.3165	

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.

Hazard ratios adjusted for age, sex, weight, height, smoking status, profession, marital status, physical activity and alcohol consumption.

eTable 4. Hazard ratios (95% confidence intervals) for atrial fibrillation associated with symptoms of anxiety and depression in different sensitivity analyses

	Exclusion of first 2 years of follow-up	**Inclusion of possible or single-episode AF as events**
HADS—anxiety		
0–7	Reference	Reference
8–10	1.0 (0.7-1.4)	1.1 (0.8-1.4)
≥11	1.1 (0.8-1.6)	1.1 (0.8-1.5)
***P* for linear trend**	0.4556	0.6351
***P* for quadratic trend**	0.8501	0.9468
HADS—depression		
0–7	Reference	Reference
8–10	1.5 (1.1-1.9)	1.4 (1.1-1.7)
≥11	0.8 (0.5-1.2)	0.7 (0.5-1.1)
***P* for linear trend**	0.2627	0.1581
***P* for quadratic trend**	0.0028	0.0024
Episodes of anxiety		
No anxiety	Reference	Reference
Anxiety at one time	1.1 (0.8-1.6)	1.1 (0.8-1.5)
Anxiety at two times	1.2 (0.6-2.3)	1.0 (0.5-1.9)
***P* for linear trend**	0.5865	0.8987
***P* for quadratic trend**	0.9325	0.5131
Episodes of depression		

No depression	Reference	Reference
Depression at one time	0.9 (0.6-1.3)	1.2 (0.9-1.6)
Depression at two times	1.1 (0.5-2.5)	0.9 (0.4-2.0)
***P* for linear trend**	0.8046	0.7818
***P* for quadratic trend**	0.6258	0.3898

HADS-D and HADS-A score: < 8: no symptoms of depression or anxiety, 8–10: mild to moderate symptoms, ≥ 11: severe symptoms.

Hazard ratios adjusted for age, sex, weight, height, smoking status, profession, marital status, physical activity and alcohol consumption.

eTable 5. Hazard ratios (95% confidence intervals) for atrial fibrillation associated with symptoms of anxiety and depression, using multiple imputation

	Model 1	Model 2	Model 3	Model 4
HADS-A (n= 43474)				
0–7	Reference	Reference	Reference	Reference
8–10	1.0 (0.8-1.3)	1.1 (0.8-1.5)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
≥11	1.1 (0.8-1.4)	1.0 (0.8-1.4)	1.0 (0.7-1.3)	1.0 (0.8-1.4)
HADS-D (n=43329)				
0–7	Reference	Reference	Reference	Reference
8–10	1.3 (1.1-1.6)	1.5 (1.2-1.8)	1.4 (1.1-1.8)	1.5 (1.2-1.8)
≥11	0.9 (0.7-1.2)	0.8 (0.6-1.2)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
Episodes of anxiety (n= 37926)				
No anxiety	Reference	Reference	Reference	Reference
Anxiety at one time	1.2 (0.9-1.5)	1.1 (0.8-1.4)	1.0 (0.7-1.4)	1.1 (0.8-1.5)
Anxiety at two times	0.9 (0.5-1.6)	0.9 (0.5-1.8)	0.9 (0.5-1.8)	1.0 (0.5-1.9)
Episodes of depression (n=36995)				
No depression	Reference	Reference	Reference	Reference
Depression at one time	1.2 (0.9-1.6)	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.2 (0.9-1.6)
Depression at two times	1.0 (0.5-2.1)	0.9 (0.4-2.0)	0.9 (0.4-2.1)	0.8 (0.3-1.9)

Multiple imputations (n=5) were used to account for missing data. The imputed variables were HADS-A, HADS-D, episodes of anxiety and episodes of depression.

Model 1: adjusted for age and sex.

Model 2: Model 1 + weight, height, smoking status, occupation, marital status, physical activity and alcohol consumption.

Model 3: Model 2 + chronic disorders.

Model 4: Model 2 + metabolic components (i.e., blood glucose, blood pressure, triglycerides, high-density lipoproteins and C-reactive protein).