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Original research

Interaction of genetic risk and lifestyle on the incidence of atrial fibrillation

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ABSTRACT

Background The relationship between combined genetic predisposition and lifestyle and the risk of incident atrial fibrillation (AF) is unclear. Therefore, we aimed to assess a possible interaction between lifestyle and genetics on AF risk.

Methods We included AF cases and a randomly drawn subcohort of 4040 participants from the Danish Diet, Cancer and Health cohort. Lifestyle risk factors were assessed, a score was calculated, and participants were categorised as having a poor, intermediate, or ideal lifestyle. We calculated a genetic risk score comprising 142 variants, and categorised participants into low (quintile 1), intermediate (quintiles 2–4) or high (quintile 5) genetic risk of AF.

Results 3094 AF cases occurred during a median follow-up of 12.9 years. Regardless of genetic risk, incidence rates per 1000 person-years were gradually higher with worse lifestyle. For participants with high genetic risk, the incidence rates of AF per 1000 person-years were 5.0 (95% CI 3.4 to 7.3) among individuals with ideal lifestyle, 6.6 (95% CI 5.4 to 8.1) among those with intermediate lifestyle and 10.4 (95% CI 9.2 to 11.8) among participants with poor lifestyle. On an additive scale, there was a positive statistically significant interaction between genetic risk and lifestyle (relative excess risk due to interaction=0.86, 95% CI 0.68 to 1.03, $p<0.001$).

Conclusions The rates of AF increased gradually with worse lifestyle within each category of genetic risk. We found a positive interaction on an additive scale between genetic risk and lifestyle, suggesting that risk factor modification is especially important in individuals with a high genetic risk of AF.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Several lifestyle factors, including alcohol intake, obesity and smoking, are major risk factors for atrial fibrillation (AF).
- ⇒ Genetic predisposition to AF plays an important role in the risk of incident AF.

WHAT THIS STUDY ADDS

- ⇒ The risk of AF increased gradually with worse lifestyle regardless of genetic predisposition, which we assessed a genetic risk score based on multiple risk variants.
- ⇒ There was a positive interaction on an additive scale between genetic risk and lifestyle. The interaction indicates that adherence to a healthy lifestyle is especially beneficial for individuals with a high genetic risk in order to reduce the risk of incident AF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Stratifying individuals according to genetic risk may be useful in directing lifestyle modification strategies for primary prevention of AF.
- ⇒ Future study directions should focus on randomisation to risk factor modification among individuals with high genetic risk for primary and secondary AF prevention.

of unfavourable lifestyle risk factors associates with higher risk of AF compared with a favourable lifestyle.^{4,5} However, the relationship between combined genetic predisposition and lifestyle risk factors on AF risk is unclear.

We set out to assess the associations between genetic risk quantified as a GRS, lifestyle risk factors and risk of incident AF. Furthermore, we aimed to examine a possible interaction between the GRS and lifestyle risk factors in the risk of incident AF.

METHODS

Study population

The study was based on the Danish cohort study Diet, Cancer and Health, which has previously been described in detail.⁶ Briefly, between 1993 and 1997, a total of 160 725 women and men born in Denmark, aged 50–64 years, with no diagnosis of cancer, were invited. A total of 57 053 individuals

INTRODUCTION

The aetiology of atrial fibrillation (AF) is multifactorial.¹ Genetics and lifestyle factors both contribute to disease development. In recent years, several novel genes and variants associated with AF have been identified through genome-wide association studies (GWAS).¹ Studies have shown that the risk of incident AF can be predicted by a genetic risk score (GRS)—a sum of the exposure to several genetic variants associated with AF.^{2,3} In addition to genetic predisposition, several lifestyle factors such as smoking, high alcohol intake, physical inactivity, obesity and high blood pressure are associated with AF.^{1,4} Studies have reported that the accumulation



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accepted participation in a research examination. Participants with missing data were excluded. Participants with a diagnosis of AF at baseline were excluded as well as participants with late registration of prior cancer and participants who withdrew consent. For this study, we used a case-cohort design.⁷ This study design allows for examining the association between an exposure and outcome without all members of the cohort undergoing diagnostic testing,⁷ in this case, genetic testing. All cases of AF, including atrial flutter, between baseline and end of follow-up (December 2009), were identified through the Danish National Patient Register, which includes discharge diagnoses from in-hospital patients, emergency rooms and outpatient visits.⁸ From the cohort, a random subcohort of 4040 participants was chosen (online supplemental figure 1).

Assessment of lifestyle status

At a baseline research examination, participants were asked about smoking status (never, prior or current) and the number of hours per week of physical activities. Height and weight were measured, and body mass index (BMI) was calculated as [weight (kg)]/[height (m)²]. Total cholesterol and blood pressure were measured at the research examination. Before the research examination, a detailed Food Frequency Questionnaire including 192 food items was sent by mail to the participants and filled in. In the Food Frequency Questionnaire, alcohol intake was reported as drinks per day with a definition of a standard drink containing 10 g of alcohol.

To quantify lifestyle risk factors for participants, we used a modification of the Life's Simple 7, a definition of ideal cardiovascular health behaviours proposed by the American Heart Association.⁹ In this study, we were not able to include blood glucose, which is a part of the Life's Simple 7. Instead, we included alcohol intake, which was associated with AF risk in several observational studies and for which causality has further been suggested in Mendelian randomisation studies.^{10,11} For each lifestyle risk factor, participants were given a score (2 for ideal health, 1 for intermediate and 0 for poor health). We categorised the elements of Life's Simple 7 and alcohol consumption as in other previous studies.^{9,12} The categorisation of lifestyle risk factors is shown in online supplemental table 1. The points were summed for a total score of lifestyle risk factors (range 0–14). Scores of 0–8 were considered as poor lifestyle status, 9–10 as intermediate and 11–14 as ideal lifestyle status according to a study from the Multi-Ethnic Study of Atherosclerosis.⁴

Assessment of GRS

Participants had blood samples drawn at study enrolment. For the case group and the random subcohort, DNA was extracted and eluted into a low-salt buffer and stored at –20°C until further analyses. Genotypes were obtained with the Illumina Infinium Human CoreExome BeadChip (CoreExomeChip) using Illumina HiScan system at the Novo Nordisk Foundation Center for Basic Metabolic Research's laboratory, Copenhagen, Denmark. The standard pipeline in Illumina GenomeStudio software was used for the genotype calling. Genotypes were called by the Illumina GenCall algorithm. Individuals were excluded based on the following criteria: missing phenotype, sex mismatch between genotype and phenotype, outlying heterozygosity, non-European ethnicity outliers detected via principal component analysis and call rate <95%. Variants with call rate <98%, out of Hardy-Weinberg equilibrium ($p > 10^{-5}$) and monomorphic variants, were excluded. Genotypes were imputed to the HRC V1.1 reference panel. We calculated an AF GRS, which was

based on a large GWAS performed on individuals of European ancestry, in which 142 risk variants were identified.¹³ The GRS was calculated as the sum of the number of risk alleles (0, 1 or 2) for each of the 142 risk variants weighted by the log of the OR for each allele reported by the GWAS¹³ (online supplemental table 2). Based on existing literature, the GRS was categorised into the following categories: low (quintile 1), intermediate (quintiles 2–4) and high (quintile 5) genetic risk.¹⁴

Assessment of AF and comorbidities from the Danish National Patient Register

We identified all participants with a diagnosis of AF/atrial flutter in the Danish National Patient Register.⁸ For comorbidities, we identified all patients with a diagnosis of heart failure, ischaemic stroke, diabetes mellitus, myocardial infarction and hypertension in the Danish National Patient Register until the time of the research examination. The International Classification of Diseases-10 (ICD-10) codes for the outcome and covariates can be seen in online supplemental table 3. For diabetes mellitus and hypertension, we combined information from the Danish National Patient Register and self-reported information, since these conditions are often diagnosed by a general practitioner and thus not registered in the Danish National Patient Register. Information on vital status was obtained from the National Central Person Register.

Statistical analyses

Descriptive statistics were presented as medians and 25th–75th percentiles or frequency counts and percentage, as appropriate. The participants were followed from time of inclusion into the study until the date of AF diagnosis, death, emigration or end of follow-up in December 2009, whichever came first. Data were analysed using weighted Cox proportional hazards regression with age as the time axis to calculate HRs and 95% CIs. For the random subcohort to represent the entire cohort, weights were assigned to each participant. The cases were assigned a weight of one, while the random subcohort was weighed as $w = 1/p_m$ (one over the sampling fraction of non-cases). The sampling fraction of non-cases (p_m) was assessed as $p_m = (\text{non-cases in the subcohort})/(\text{non-cases in the full cohort})$. The weights were included in the Cox proportional hazards model to account for the under-sampling of non-cases.¹⁵ We assessed the associations between lifestyle status and risk of AF as well as GRS and risk of AF, separately. For each of the models, we calculated Harrell's C-index to assess the predictive power of the models. We stratified the analyses according to sex. In sensitivity analyses, we adjusted for competing risk of death using the Fine and Gray method. In secondary analyses, we assessed weighted HRs according to intermediate and poor status of separate lifestyle risk factors compared with ideal status. The cumulative incidence proportions of AF according to GRS (low, intermediate and high) and lifestyle status (poor, intermediate and ideal) were visualised for the total population and separately for women and men taking into account the competing risk of death.

To assess interaction between GRS and lifestyle status, we used weighted Cox proportional hazards models by combined GRS and lifestyle status with individuals with low GRS and ideal lifestyle as reference. We calculated Harrell's C-index for the model and the differences in C-index between the full model (GRS and lifestyle) compared with the models with only GRS and lifestyle, respectively. In secondary analyses, we stratified according to sex. In a sensitivity analysis, we adjusted for competing risk of death using the Fine and Gray method. To test for interaction

Table 1 Baseline characteristics in cases and the subcohort in the Diet, Cancer and Health cohort

	Cases (N=3094)	Subcohort (N=4036)
Age (years)	58 (54–62)	55 (52–60)
Women	1111 (36%)	2178 (54%)
School education <8 years	1144 (37%)	1275 (32%)
Body mass index (kg/m ²)	26.7 (24.3–29.8)	25.2 (23.1–27.6)
Systolic blood pressure (mm Hg)	144 (131–159)	136 (123–151)
Diastolic blood pressure (mm Hg)	85 (78–92)	82 (75–89)
Total cholesterol (mmol/L)	6.0 (5.3–6.8)	6.0 (5.3–6.8)
Physical activity (hours/week)	14.0 (9.5–22)	14.5 (10–21.5)
Alcohol intake (drinks/week)	11 (5–25)	9 (4–22)
Smoking		
Current	1177 (38%)	1412 (35%)
Prior	991 (32%)	1131 (28%)
Never	923 (30%)	1488 (37%)
Lifestyle status		
Ideal	156 (5%)	402 (10%)
Intermediate	665 (22%)	1185 (29%)
Poor	2273 (73%)	2449 (61%)
Diabetes mellitus	110 (4%)	99 (2.5%)
Heart failure	33 (1%)	18 (0.4%)
Myocardial infarction	147 (5%)	73 (1.8%)
Stroke	65 (2%)	26 (0.6%)

Values are n (%) and median (25th–75th percentile).

between GRS and lifestyle status on an additive scale, we assessed the relative excess risk due to interaction (RERI).¹⁶ The RERI represents the excess risk of two combined risk factors beyond the sum of their individual effects.¹⁶

To assess whether GRS was a modifier of the association between lifestyle status and AF, we stratified analyses of the association between lifestyle status and risk of incident AF, according to GRS. For each group of GRS, individuals with ideal lifestyle status were used as reference.

For all weighted Cox proportional hazards models, we adjusted for the following variables: age, sex, educational level and disease at study entry (heart failure, stroke, diabetes mellitus and myocardial infarction). For all weighted Cox proportional hazards models, the proportional hazards assumption was checked by plotting the observed and fitted curves and by log–log curves. Two-sided *p* values below 0.05 were considered statistically significant. Analyses were performed using the Stata program software V.17.0.

RESULTS

Study participant characteristics

A total of 3094 cases of AF were identified during a median follow-up of 12.9 years (25th–75th percentile 9.8–13.9). The maximum follow-up was 16.1 years. Of the random subcohort, 234 were also cases. Table 1 shows the characteristics of the cases and the random subcohort at the baseline research examination. Among the 4036 participants in the random subcohort, median age was 55 years (25th–75th percentile 52–60) and 2178 (54%) were women. In the random subcohort, 402 (10%) had ideal lifestyle status, 1185 (29%) had intermediate and 2449 (61%) had poor lifestyle status. Characteristics according to lifestyle status in the random subcohort are displayed in online supplemental table 4. There were fewer women in the group of participants with poor lifestyle compared with ideal lifestyle (50% vs 60%). The prevalence of comorbidities was generally

slightly higher among participants with poor lifestyle compared with intermediate and ideal lifestyle.

AF according to GRS

The GRS approximated a normal distribution in the random subcohort (online supplemental figure 2). Cumulative incidence and HR of AF according to GRS categories in sex-pooled and sex-stratified samples are displayed in figure 1. Compared with participants with a low GRS, the risk of incident AF was significantly higher among participants with intermediate GRS (HR 1.97, 95% CI 1.71 to 2.27) and high GRS (HR 4.27, 95% CI 3.61 to 5.06). In analyses stratified by sex, we observed a higher risk of incident AF among both men and women with intermediate and high GRS compared with low GRS. When taking the competing risk of death into account, the results did not differ substantially (online supplemental table 5).

AF according to lifestyle status

Cumulative incidence and HR of AF according to lifestyle status in sex-pooled and sex-stratified samples are displayed in figure 1. Compared with participants with an ideal lifestyle, the risk of AF was higher among participants with both intermediate (HR 1.32, 95% CI 1.05 to 1.65) and poor (HR 1.92, 95% CI 1.56 to 2.36) lifestyle. In analyses stratified by sex, we found no difference between men and women. When taking the competing risk of death into account, the results did not differ substantially (online supplemental table 6).

The risks of incident AF for ideal, intermediate and poor status of each lifestyle risk factor are displayed in online supplemental figure 3. For smoking, BMI and blood pressure, intermediate and poor status were associated with statistically significantly higher risks of AF compared with ideal status.

GRS, lifestyle status and risk of incident AF

Incidences of AF per 1000 person-years and HR according to lifestyle status and GRS are shown in figure 2. Adding lifestyle status to GRS provided a numerical gradient in incidence rates and HR of AF across GRS groups. For individuals with a high GRS, the incidence rate per 1000 person-years was 5.0 (95% CI 3.4 to 7.3) for ideal, 6.6 (95% CI 5.4 to 8.1) for intermediate and 10.4 (95% CI 9.2 to 11.8) for poor lifestyle. Compared with individuals with low GRS and ideal lifestyle, the risk was significantly higher among individuals with high GRS and poor lifestyle (HR 12.33, 95% CI 6.67 to 22.80). The RERI was 0.86 (95% CI 0.68 to 1.03) indicating a positive interaction on an additive scale between GRS and lifestyle status. Adjusting for competing risk of death did not alter the results substantially (online supplemental table 7). Results from analyses stratified by sex are shown in online supplemental figure 4.

In the analyses of risk of AF according to lifestyle status stratified by GRS (online supplemental table 8), poor lifestyle was associated with a higher risk of AF in all GRS groups.

DISCUSSION

In this case-cohort study from the Danish Diet, Cancer and Health cohort, we found that a GRS and lifestyle status were each associated with incident AF for both women and men. A poor lifestyle further augmented the risk of AF in participants with a high genetic risk and there was positive interaction at an additive scale between GRS and lifestyle status. Within any genetic risk category, a poor lifestyle was associated with a higher risk of AF compared with an ideal lifestyle.

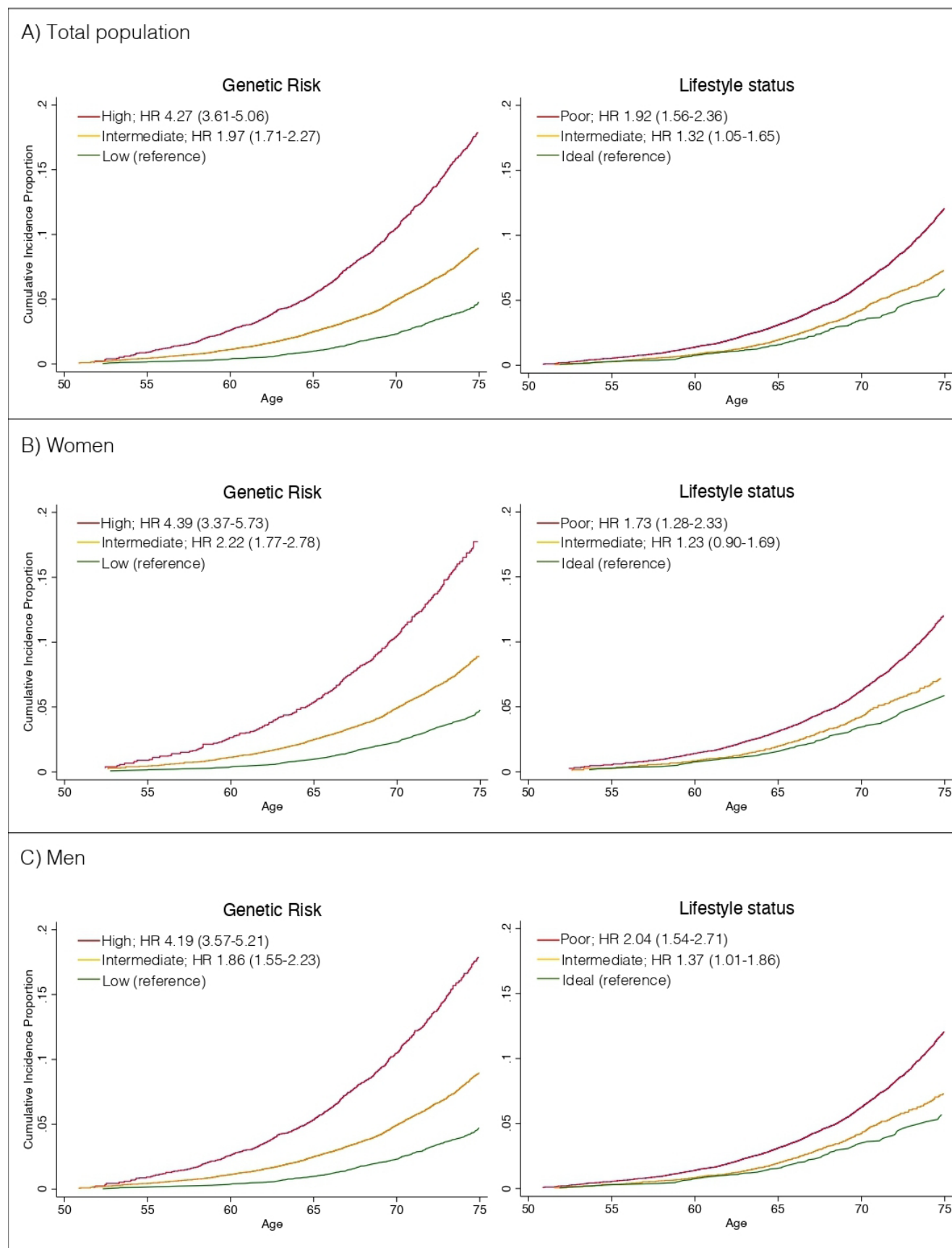


Figure 1 Cumulative incidence proportions and HRs of atrial fibrillation according to genetic risk score and lifestyle status. The figures show the cumulative incidence proportions of atrial fibrillation according to genetic risk score and lifestyle status in the cases and the random subcohort (A) and stratified by sex (B, C). Cumulative incidence proportions are adjusted for competing risk of death. HRs are weighted and adjusted for age, sex, educational level, heart failure, stroke, diabetes mellitus and myocardial infarction.

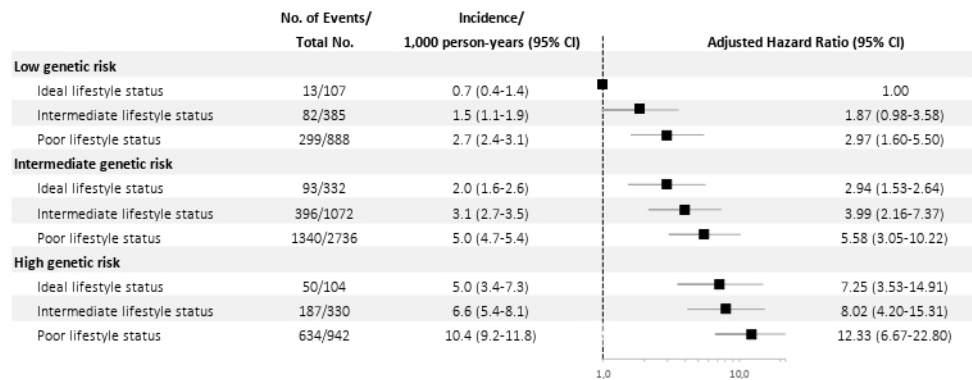


Figure 2 Incidence rates and HRs of atrial fibrillation according to genetic risk score (GRS) and lifestyle status. Multivariable-adjusted models were adjusted for age, sex, educational level, heart failure, stroke, diabetes mellitus and myocardial infarction. Incidence rates and HRs are weighted. The x-axis for forest plot is logarithmic. Harrell's C-index for the model was 0.69 (95% CI 0.68 to 0.70). Compared with the models with GRS and lifestyle only, combining GRS and lifestyle did not change the C-index of the model substantially. The difference from the model with only GRS was 0.0005 (95% CI -0.003 to 0.004) and the difference was 0.02 (95% CI 0.01 to 0.02) comparing the combined model with the model with lifestyle only.

Two large studies from the UK Biobank examined the risk of incident AF according to genetic risk and lifestyle factors, including smoking, BMI, physical activity and diet.^{17 18} Consistent with our results, the authors found that a poor lifestyle status, compared with ideal, was associated with a higher risk of AF across GRS groups. In addition to BMI, diet, physical activity and smoking, we included additional components of Life's Simple 7—total cholesterol and blood pressure—and alcohol consumption. Thus, the categorisation of lifestyle status was substantially different from the two studies from UK Biobank, in which a smaller proportion of participants were categorised as having a poor lifestyle compared with our study.^{17 18}

While the clinical utility of a GRS in risk stratification of AF is still unclear,¹⁹ the importance of modification of lifestyle factors seems evident and is supported by the results of this study. The additive interaction indicated by the positive RERI value implies that a poor lifestyle and a high genetic risk of AF in combination are associated with greater risk of incident AF than just the sum of each. Thus, individuals at high genetic risk of AF may particularly benefit from counselling and lifestyle modification, but further research and replication of these findings are needed before firm conclusions can be made. European and American guidelines suggest modification of lifestyle and management of risk factors for primary and secondary prevention of AF.^{20 21} The positive interaction found in our study further indicates that the benefit may be largest for individuals who are at the genetically highest risk. Our results provide a potential for future research to determine if combining GRS and clinical risk factors can identify individuals at risk who may benefit from targeted screening or risk factor modification. So far, widespread screening for AF has not proven to be substantially clinically beneficial with regard to stroke prevention.^{22 23} However, targeted screening in high-risk individuals, that is, those with high genetic risk, may be of clinical relevance. Although the financial costs of genotyping have reduced significantly in recent years,²⁴ other predictors of AF may be more readily available, such as clinical data, ECG markers, biomarkers and echocardiography.¹ However, the potential benefits of AF screening in selected populations are largely unclear.^{25 26}

Several limitations to this study should be mentioned. First, the study was observational. Thus, we cannot exclude residual confounding and cannot establish causal relations. In addition, lifestyle factors including diet, alcohol intake, physical activity and smoking were based on self-report. Individuals

may underestimate poor lifestyle behaviours which, if non-differential with regard to later outcomes, would most likely bias the results towards the null. Furthermore, lifestyle risk factors were assessed at one point in time. Risk factors may change over the long follow-up period, which we were not able to account for. If participants improved their lifestyle during follow-up, they may experience lower risk of AF than expected, thus also biasing our results towards the null. In 2022, the American Heart Association updated the original Life's Simple 7 to Life's Essential 8, which includes sleep duration.²⁷ Studies have reported an association between short and long sleep duration and risk of incident AF.²⁸ However, information on sleep duration was not available in the Danish Diet, Cancer and Health cohort; thus, we could not include it in our lifestyle score. We categorised participants into three groups of both lifestyle risk factor burden and genetic risk. The somewhat arbitrary categorisations improve comprehensibility and comparability with other studies but limit the details of the data. AF ascertainment was based on diagnosis codes from the Danish National Patient Registry until 2009 when ECG monitoring was primarily based on Holter monitoring.²⁹ Since then, several monitoring devices to detect AF have been made available.²⁹ Thus, the incidence of AF may be underestimated in this study. In addition, data inclusion from private hospitals to the Danish National Patient Registry started in year 2003 but was not complete until 2007.⁸ Cases from private hospitals might have been missed. However, the overall activity of private hospitals in Denmark is low, accounting for 2.2% of all hospital activity in 2010.³⁰ Finally, the study participants were primarily white and middle-aged at baseline and the GRS was based on a GWAS performed on individuals of European ancestry. Therefore, generalisability to other races/ethnicities and ages cannot be assumed.

CONCLUSIONS

A GRS and lifestyle risk factors were each associated with AF risk. The rates of AF increased gradually with cumulation of lifestyle risk factors within each category of the GRS. We found a positive interaction on an additive scale between genetic risk and lifestyle status, indicating that individuals with a high genetic risk of AF may particularly benefit from adherence to a healthy lifestyle. Our data underscore the importance of risk factor modification in primary AF prevention.

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Contributors TCF, CCD, MKC, KO and HKJ contributed to the conception or design of the work. TCF, KO, AQ, MKA, TH, NG and CCD contributed to the acquisition, analysis or interpretation of data for the work. TCF drafted the manuscript. CCD, MKC, AQ, KO, EJB, MKA, TH, NG and HKJ critically revised the manuscript. TCF was responsible for the overall content as guarantor. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Danish Data Protection Agency (reference no. 2012-58-0004 I-Suite nr: 6357, VD-2018-117). All participants gave written informed consent at enrolment.

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Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The data are available from the Diet, Cancer and Health Steering Committee at the Danish Cancer Society (dchdata@cancer.dk).

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