HEIGHT, WEIGHT, AND AEROBIC FITNESS IN RELATION TO RISK OF ATRIAL FIBRILLATION

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Running head: Body Size, Aerobic Fitness and Atrial Fibrillation

Abbreviations: AF (atrial fibrillation), BMI (body mass index), CI (confidence interval), HR (hazard ratio), ICD (International Classification of Diseases), RERI (relative excess risk due to interaction), SD (standard deviation), SES (socioeconomic status)

ABSTRACT

Tall stature or obesity has been associated with higher risk of atrial fibrillation (AF), but reported effects of aerobic fitness have been conflicting. A national cohort study was conducted to examine interactions between height or weight and aerobic fitness among 1,547,478 Swedish military conscripts during 1969-1997 (97-98% of all 18-year-old males) in relation to AF identified from nationwide inpatient and outpatient diagnoses through 2012 (maximum age 62). Increased height, weight, or aerobic fitness (but not muscular strength) at age 18 was associated with higher AF risk in adulthood. Positive additive and multiplicative interactions were found between height or weight and aerobic fitness (relative excess risk due to interaction between height and aerobic fitness, highest vs. lowest tertiles: 0.51; 95% CI, 0.40-0.62; ratio of hazard ratios: 1.50; 95% CI, 1.34-1.65). High aerobic fitness was associated with increased risk among men with height ≥186 cm (6 feet 1 inch), but was protective among shorter men. Men with the combination of tall stature and high aerobic fitness had the highest risk (highest vs. lowest tertiles: adjusted hazard ratio, 1.70; 95% CI, 1.61-1.80). These findings suggest important interactions between body size and aerobic fitness in relation to AF and may help identify high-risk subgroups.

Key words: atrial fibrillation, body height, body mass index, body size, body weight, muscle strength, physical fitness

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 30 million people worldwide (1), and is an important cause of stroke and mortality (2, 3). AF is more common with increasing age or underlying heart disease (4, 5). However, many cases also occur among younger adults without known heart disease (6), prompting investigations to identify other risk factors and potential targets for intervention. Prior studies have established that tall stature (7-11) and obesity (11-18) are associated with higher risk of developing AF. However, the reported effects of aerobic fitness have been conflicting. A number of studies have reported an increased risk of AF among competitive athletes or individuals who report high levels of exercise (19-24). In contrast, several (12, 25-27) but not all (28) studies with objectively measured aerobic fitness have suggested that high aerobic fitness is protective against AF.

We hypothesized that these conflicting findings may be due to interactions between height or weight and aerobic fitness that are previously unexamined. The pathogenesis of AF is a heterogeneous process that involves myocardial structural, hemodynamic, electrical, and neural factors (29). Exercise may potentially influence this process through its contribution to left ventricular hypertrophy, leading to diastolic dysfunction and left atrial stretch (30). Because height and weight are positively correlated with left atrial size (31), they may potentially modify the hemodynamic and autonomic effects of aerobic fitness on atrial remodeling and the development of AF (32). If so, elucidation of interactions among these factors may help identify high-risk subgroups and provide new insights into underlying mechanisms.

We examined interactions between height, weight, and aerobic fitness in relation to the risk of AF in a large national cohort. Standardized measurements of these factors were obtained in ~1.5 million 18-year-old male military conscripts in Sweden who were subsequently followed up for AF in adulthood. Our aims were to determine the interactive effects of these common factors at age 18 on the long-term risk of AF in a large population-based cohort.

METHODS

Study population

We identified 1,547,478 males (age ~18 years) who underwent a military conscription examination in Sweden during 1969-1997. All 18-year-old males nationally were conscripted each year except for 2-3% who either were incarcerated or had severe chronic medical conditions or disabilities documented by a physician. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Height, weight, and aerobic fitness ascertainment

Height, weight, and aerobic fitness measurements were obtained using the Swedish Military Conscription Registry, which contains information from a 2-day standardized physical and psychological examination required for all conscripts starting in 1969 (33-37). Height and weight were measured using standard protocols and examined alternatively as continuous variables or categorical variables in tertiles (height in cm: low [<175.0], medium [175.0-181.4], high [≥181.5]; weight in kg: low [<64.0], medium [64.0-71.3], high [≥71.4]). Categorizations for these and other predictors were based on dose-response analyses indicating that they well characterized the underlying relationships with AF risk, as well as having good interpretability.

Body mass index (BMI) was examined as an alternative to height and weight. BMI was calculated as weight in kilograms divided by the square of height in meters, and was examined alternatively as a continuous or categorical variable using Centers for Disease Control and

Prevention definitions for children and adolescents aged 2 to 19 years to facilitate comparability with US studies: "overweight" is defined as ≥85th and <95th percentile and "obesity" as ≥95th percentile on the 2000 sex-specific BMI-for-age growth charts, which correspond to BMI ≥25.6 and <29.0 and BMI ≥29.0, respectively, for 18-year-old males (38).

Aerobic fitness was measured as the maximal aerobic workload in Watts, using a well-validated electrically-braked stationary bicycle ergometer test (39). Following a warm-up period, each conscript performed 5-10 minutes of exercise on a stationary bicycle at a starting work rate of 75 to 175 Watts (determined by a sliding scale based on body weight), and increasing by 25 Watts/minute until volitional exhaustion. Maximal aerobic workload was calculated as the power output in Watts before the last intensity increase, plus the prorated output for the last stage (39). Maximal aerobic workload is highly correlated with maximal oxygen uptake (VO_2 max; correlation ~0.9) (40), and its measurement using this bicycle ergometer test is highly reproducible, with a test-retest correlation of 0.95 (41). This aerobic fitness measurement was examined alternatively as a continuous variable or categorical variable in tertiles (Watts: low [<240], medium [240-288], high [≥289]) (33-37).

In addition to aerobic fitness, we examined muscular strength as a secondary predictor of interest because it represents a different aspect of physical fitness. Muscular strength was measured in Newtons using well-validated isometric dynamometer tests, and calculated as the weighted sum of maximal knee extension (weighted × 1.3), elbow flexion (weighted × 0.8), and hand grip (weighted × 1.7) (42). Each dynamometer test was performed three times and the maximum value was recorded for analysis, except when the last value was highest, in which case testing was repeated until strength values stopped increasing. All testing equipment was calibrated daily (42). Muscular strength was examined alternatively as a continuous variable or categorical variable in tertiles (Newtons: low [<1900], medium [1900-2170], high [≥2171]) (33-37).

Atrial fibrillation ascertainment

The study cohort was followed up for the earliest diagnosis of AF from the date of the military conscription examination through December 31, 2012. AF was identified based on any primary or secondary diagnosis using *International Classification of Diseases* (*ICD*) codes in the Swedish Hospital and Outpatient Registries (427.4 in *ICD*-8, 427.3 in *ICD*-9, and I48 in *ICD*-10). The Swedish Hospital Registry contains all primary and secondary hospital discharge diagnoses from six populous counties in southern Sweden starting in 1964, and with nationwide coverage starting in 1987; and the Swedish Outpatient Registry contains outpatient diagnoses from all specialty clinics nationwide starting in 2001 (33-37). Diagnoses in the Hospital Registry are currently >99% complete and have a reported positive predictive value of 97% for either primary or secondary diagnoses of AF (43).

Adjustment variables

Other variables that may be associated with body size or physical fitness and risk of AF were obtained from the Swedish Military Conscription Registry and national census data, which were linked using an anonymous personal identification number (33-37). The following were used as adjustment variables: year of the military conscription examination (as a continuous variable); highest education level attained during the study period (<12, 12-14, ≥15 years); neighborhood socioeconomic status at baseline (SES, included because neighborhood SES characteristics have been associated with obesity and physical fitness (44) and with cardiovascular disease risk (45); composed of an index that includes low education level, low income, unemployment, and social welfare receipt, as previously described (46), and categorized as low [<-1 SD from the mean], medium [-1 to 1 SD], or high [>1 SD]); and family history of AF in a parent or sibling (yes or no, identified from the Swedish Hospital Registry during 1965-2012 and the Swedish Outpatient Registry during 2001-2012, using the same diagnosis codes noted above).

Because low aerobic fitness and high BMI are known to be associated with hypertension (33), diabetes mellitus (34), and ischemic heart disease (35), which are established risk factors for AF (47), we were interested in whether aerobic fitness and BMI (or height and weight) are associated with AF independently of these conditions. To assess this, we further adjusted for hypertension (400-401 in *ICD*-8, 401 in *ICD*-9, I10 in *ICD*-10), diabetes mellitus (250 in *ICD*-8/9, E10-E14 in *ICD*-10), and ischemic heart disease (410-414 in *ICD*-8/9, I20-I25 in *ICD*-10) as time-dependent variables.

Missing data for each variable were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates and AF (48). Missing data were relatively infrequent for height (7.2%), weight (7.3%), aerobic fitness (5.7%), muscular strength (5.0%), education level (0.4%), and neighborhood SES (9.1%). Data were 100% complete for all other variables.

Statistical analysis

Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between height, weight, aerobic fitness, or muscular strength and risk of AF. The Cox model time scale was elapsed time since the military conscription examination, which also corresponds to attained age because baseline age was the same (18 years) for all conscripts. Individuals were censored at emigration (n=87,450; 5.7%) or death (n=58,835; 3.8%).

Three adjusted models were performed: the first was adjusted for attained age (as the time scale) and year of the military conscription examination; the second additionally included height, weight, aerobic fitness, muscular strength, education, neighborhood SES, and family history of AF; and the third was further adjusted for hypertension, diabetes mellitus, and ischemic heart disease (as defined above). All time-varying factors were modeled as time-dependent covariates. The proportional hazards assumption was evaluated by graphical assessment of log-log plots, which showed a good fit in all models.

Interactions among height, weight, aerobic fitness, and muscular strength were examined on both the additive and multiplicative scale in relation to risk of AF. Additive interactions were assessed using the "relative excess risk due to interaction" (RERI), which is computed for binary variables as: $RERI_{HR} = HR_{11} - HR_{10} - HR_{01} + 1$ (49, 50). Multiplicative interactions were assessed using the ratio of HRs: $HR_{11} / (HR_{10} \times HR_{01})$ (49, 50). These estimates and their respective 95% CIs were determined using maximum likelihood estimation (49-51). A positive additive interaction is indicated if RERI >0, and a positive multiplicative interaction is indicated if the ratio of HRs >1. See the Web Appendix for more details on these methods.

Two sensitivity analyses were performed. First, as an alternative to multiple imputation for missing data, all analyses were repeated after restricting to men with complete data for all variables (N=1 361 083; 88.0%). Second, because of changes in AF ascertainment over time, we assessed different starting points for the follow-up period, alternatively starting in 1987 (at which time inpatient diagnoses were available nationwide instead of only for the most populous counties) or in 2001 (at which time both inpatient and outpatient diagnoses were available nationwide). All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 14.1.

RESULTS

Among the 1,547,478 males in this cohort, 23 600 (1.5%) were diagnosed with AF in 43.7 million person-years of follow-up (mean follow-up, 28.2 years). The median age at the end of follow-up was 47.2 years (mean 47.4, SD 7.9, range 19.0 to 62.0). The median age at diagnosis of AF was 48.2 years (mean 47.1, SD 7.8, range 18.2 to 62.0). Table 1 shows AF incidence rates by height, weight, aerobic fitness, and other factors.

Main effects of height, weight, and aerobic fitness

Tall stature was associated with increased risk of AF, after adjusting for weight and all other covariates (Table 2, Model 3, highest vs. lowest tertile: HR, 1.53; 95% CI, 1.48-1.59; $P<0.001$). High (but not medium) weight was associated with a modestly increased risk of AF compared to low weight, after adjusting for height and all other covariates (highest vs. lowest tertile: HR, 1.18; 95% CI, 1.13-1.23; $P<0.001$). Both height and weight had strongly positive linear associations with AF risk across their full distribution (height per 5 cm: fully adjusted HR, 1.11; 95% CI, 1.10-1.12; $P_{\text{trend}}<0.001$; weight per 5 kg: fully adjusted HR, 1.05; 95% CI, 1.04-1.06; $P_{\text{trend}}<0.001$), but height was a stronger risk factor than weight ($P_{\text{heterogeneity}}<0.001$). Obesity (but not overweight) also was associated with increased risk of AF in the fully adjusted model (Table 2, Model 3).

High aerobic fitness was associated with a modestly increased risk of AF, after adjusting for height, weight, and all other covariates (highest vs. lowest tertile: HR, 1.14; 95% CI, 1.09-1.19; *P*<0.001). In contrast, muscular strength was not clearly associated with AF risk (Table 2). A first-degree family history of AF was associated with a 1.7-fold risk of AF. Sensitivity analyses that were restricted to men with complete data, or that examined different follow-up periods (as noted above), yielded similar risk estimates as the main analyses and the overall conclusions were unchanged.

Interactions among height, weight, and aerobic fitness

The interaction between height and aerobic fitness in relation to AF risk is shown in Table 3. High aerobic fitness was protective against AF among shorter men (lowest tertile for height), but was associated with increased risk among taller men (medium or highest tertiles; see Web Table 1 for more complete reporting of stratum-specific HRs). Men with the combination of tall height and high aerobic fitness had the highest AF risk, which was 70% higher relative to those with short height and low aerobic fitness (highest vs. lowest tertiles for both variables: adjusted HR, 1.70; 95% CI, 1.61-1.80; *P*<0.001). There was a significant positive interaction between height and aerobic fitness on both the additive and multiplicative scales (i.e., the association of both factors together with AF risk exceeded the sum or product of their associations considered separately; *P*<0.001). Figure 1 shows the probability of AF among men at the 25th, 50th, and 75th percentiles of aerobic fitness across the full distribution of height, after adjusting for all covariates. The non-parallel lines reflect a positive interaction. Specifically, high aerobic fitness was associated with increased risk of AF among men with height ≥186 cm (6 feet 1 inch), but was protective among men below this height.

A similar overall pattern was seen for the interaction between weight and aerobic fitness (Table 4). High aerobic fitness was protective among men in the lowest tertile for weight, but was associated with increased risk of AF among those in the medium or highest tertiles (Table 4 and Web Table 2). The combination of high weight and high aerobic fitness was associated with highest AF risk (highest vs. lowest tertiles for both variables: adjusted HR, 1.34; 95% CI, 1.27-1.42; *P*<0.001). These factors had a significant positive interaction on both the additive and multiplicative scales (*P*<0.001). Figure 2 shows the probability of AF among men at the 25th, 50th, and 75th percentiles of aerobic fitness across the full distribution of weight, after adjusting for height and other covariates.

In secondary analyses, we also found positive additive and multiplicative interactions between muscular strength and either height (Web Table 3) or weight (Web Table 4) in relation to AF risk, although smaller in magnitude than the interactions between aerobic fitness and height or weight.

DISCUSSION

In this large national cohort study, we found that increased height or weight at age 18 years was associated with higher risk of developing AF in adulthood, and had interactions with aerobic fitness. High aerobic fitness was associated with increased risk of AF among men with height ≥186 cm (6 feet 1 inch), but was protective among shorter men. Similarly, high aerobic fitness was associated with increased risk among men with high but not low weight. The association between both exposures together (i.e., the combination of increased height or weight and aerobic fitness) and risk of AF exceeded the sum or product of their associations considered separately. These findings suggest that the underlying mechanisms for AF may include important interactions between height or weight and aerobic fitness.

The main associations we observed between tall stature or obesity and AF are overall consistent with previous findings. Prior studies have reported that increased height (7-11), or high BMI and other measures of obesity (11-18), are associated with increased risk of AF among men and women. Although most studies have focused on middle-aged or older adults, one study of 12,850 young Danish men (median age 19 years) reported that overweight or obesity was associated with increased risk of AF in early adulthood (13). Other studies have suggested that high lean body mass (rather than body fat) may also be associated with higher risk of AF (17, 52).

In contrast, previous findings for aerobic fitness or exercise in relation to AF risk have been conflicting. Some (19-24) but not all (53-55) studies have reported a higher risk of AF among athletes or other individuals who report high levels of exercise. A meta-analysis of 6 case-control studies that included 655 athletes and 895 controls reported that athletes had more than a 5-fold odds of AF (odds ratio, 5.29; 95% CI, 3.57-7.85) (56). However, most studies that examined objectively measured aerobic fitness (rather than self-reported exercise) have suggested that high aerobic fitness is protective against AF (12, 25-27). The largest of these was a US cohort study of 64,561 middle-aged adults with median follow-up of 5.4 years, which reported that each 1 higher metabolic equivalent achieved during treadmill testing was associated with a 7% lower risk of developing AF (HR, 0.93; 95% CI, 0.92–0.94; $P<0.001$). In contrast, a Swedish study that included a subset of the present cohort (N=1.1 million) suggested that aerobic fitness was positively associated with AF risk, but did not report potential interactions with height (28).

These discrepancies in reported associations between aerobic fitness or exercise and AF risk may potentially be related to other modifying factors, such as body size. To our knowledge, the present study is the first to examine not only the independent associations between height, weight, or aerobic fitness and risk of AF, but potential additive and multiplicative interactions. We found that the associations between aerobic fitness and risk of AF varied substantially depending on height or weight. High aerobic fitness was associated with increased AF risk among men with height ≥186 cm (6 feet 1 inch), but was protective among men who were below this height. The interactions between height or weight and aerobic fitness were strongly positive on both the additive and multiplicative scales. These findings suggest that high aerobic fitness accounted for significantly more AF cases among tall compared to short men, or those with high compared to low weight.

These results may provide additional insights into underlying mechanisms for AF. AF is a heterogeneous disease process influenced by structural (e.g., left atrial size), hemodynamic (e.g., left atrial stretch), electrical (e.g., altered conduction patterns due to atrial myocardium fibrosis), and neural (e.g., autonomic dysregulation) factors (29). Exercise may influence this process through its contribution to left ventricular hypertrophy, leading to some degree of diastolic dysfunction and left atrial stretch, which may increase the risk of AF in susceptible subgroups (30). Height and weight are known to be positively correlated with left atrial and ventricular size (8, 31). Our findings suggest that these factors may potentially influence the hemodynamic or autonomic effects of aerobic fitness on atrial remodeling and the development of AF. However, left atrial and ventricular size have been reported to only partly explain the association between tall stature and risk of AF (8), suggesting also the possibility of other mechanisms such as common genetic factors (e.g., PITX2 (57) and ZFHX3 (58)) that are associated with growth pathways and with AF. Additional clinical and experimental studies are needed to elucidate these complex pathways, which may help further identify high-risk subgroups and ultimately new targets for intervention.

Strengths of the present study include its large national cohort design with follow-up from age 18 years into adulthood. The national cohort design minimized the potential for selection bias, and the use of registry data with prospectively measured exposures prevented bias that may result from self-reporting. We examined well-validated, objective measurements of aerobic fitness and muscular strength. We were able to adjust for other common risk factors that also were prospectively ascertained and not self-reported, including family history of AF, individual and neighborhood-level socioeconomic factors, and chronic diseases that are associated with AF.

Limitations included measurement of the study exposures at only one age (18 years), and hence we were unable to examine changes in these factors over time. Additional studies with longitudinal exposure data are needed to delineate more specific age windows of susceptibility in relation to AF risk. The study cohort also was relatively young and all male. The median age at the end of follow-up was 47 years (maximum 62), and hence the findings may not necessarily apply to AF in older adults. The risk of AF is estimated to double with each decade of life (47), and 70% of prevalent cases are in adults aged 65 years or older (59). Further studies will be needed to assess our findings in older adults and in women.

In summary, this large national cohort study found that tall stature or high weight at age 18 years was independently associated with higher risk of developing AF in adulthood, and had interactions with aerobic fitness. High aerobic fitness was associated with increased risk of AF among tall men, but was protective among shorter men. These findings suggest important interactive effects of body size and aerobic fitness on the development of AF. Tall, aerobically fit persons may be a relatively high-risk subgroup.

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FIGURE LEGENDS

Figure 1. Probability of atrial fibrillation by height and aerobic fitness at age 18 years (median attained age 47 years, maximum 62 years), adjusted for weight, muscular strength, and other covariates, Sweden, 1969-2012.

Figure 2. Probability of atrial fibrillation by weight and aerobic fitness at age 18 years (median attained age 47 years, maximum 62 years), adjusted for height, muscular strength, and other covariates, Sweden, 1969-2012.

Table 1. Characteristics of Men Who Were or Were Not Subsequently Diagnosed With AF, Sweden, 1969-2012.

Variable	No AF		AF		Rate[a]
	No.	%	No.	%	
Total	1,523,818	100.0	23,660	100.0	54.3
Height, cm					
Lowest tertile (<175.0)	527,967	34.6	6,888	29.1	44.8
Middle tertile (175.0-181.4)	504,217	33.1	6,801	28.7	47.4
Highest tertile (≥181.5)	491,634	32.3	9,971	42.1	71.9
Weight, kg					
Lowest tertile (<64.0)	500,063	32.8	6,784	28.7	45.1
Middle tertile (64.0-71.3)	506,366	33.2	7,061	29.8	49.2
Highest tertile (≥71.4)	517,389	34.0	9,815	41.5	69.1
Body mass index[b]					
Normal	1,406,267	92.3	21,248	89.8	52.6
Overweight	83,124	5.4	1,544	6.5	68.8
Obesity	34,427	2.3	868	3.7	96.2
Aerobic fitness, Watts					
Lowest tertile (<240)	501,335	32.9	10,015	42.3	60.3
Middle tertile (240-288)	511,945	33.6	8,602	36.4	57.4
Highest tertile (≥289)	510,538	33.5	5,043	21.3	42.0
Muscular strength, Newtons					
Lowest tertile (<1900)	504,507	33.1	6,418	27.1	46.4
Middle tertile (1900-2170)	515,024	33.8	8,528	36.0	55.2
Highest tertile (≥2171)	504,287	33.1	8,714	36.8	60.9
Education (years)					
<12	232,151	15.2	4,693	19.8	65.9
12-14	674,001	44.2	9,626	40.7	51.0
≥15	617,666	40.5	9,341	39.5	53.2
Neighborhood SES					
Low	235,421	15.5	3,973	16.8	57.4
Medium	1,006,116	66.0	16,119	68.1	55.4
High	282,281	18.5	3,568	15.1	47.1
Hypertension					
No	1,438,676	94.4	15,478	65.4	37.7
Yes	85,142	5.6	8,182	34.6	257.5
Diabetes mellitus					
No	1,475,411	96.8	20,836	88.1	49.7
Yes	48,407	3.2	2,824	11.9	169.2
Ischemic heart disease					
No	1,488,996	97.7	20,269	85.7	48.0
Yes	34,822	2.3	3,391	14.3	255.8
Family history of AF					
No	1,223,751	80.3	14,986	63.3	44.0
Yes	300,067	19.7	8,674	36.7	91.2

AF = atrial fibrillation, BMI = body mass index, SES = socioeconomic status.

[a] AF incidence rate per 100,000 person-years.

[b] Weight (kg)/height (m)^2.

Table 2. Associations Between Height, Weight, Aerobic Fitness, or Other Factors and Risk of AF, Sweden, 1969-2012.

Variable	Model 1[a]			Model 2[b]			Model 3[c]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Height (tertiles)									
Low	1.00			1.00			1.00		
Medium	1.09	1.05, 1.13	<0.001	1.00	0.96, 1.03	0.85	1.05	1.01, 1.09	0.006
High	1.70	1.65, 1.75	<0.001	1.47	1.42, 1.52	<0.001	1.53	1.48, 1.59	<0.001
Per 5 cm (trend test)	1.14	1.13, 1.15	<0.001	1.04	1.03, 1.05	<0.001	1.11	1.10, 1.12	<0.001
Weight (tertiles)									
Low	1.00			1.00			1.00		
Medium	1.18	1.14, 1.22	<0.001	1.19	1.15, 1.24	<0.001	0.98	0.94, 1.02	0.28
High	1.79	1.74, 1.85	<0.001	1.75	1.68, 1.82	<0.001	1.18	1.13, 1.23	<0.001
Per 5 kg (trend test)	1.14	1.13, 1.15	<0.001	1.13	1.12, 1.13	<0.001	1.05	1.04, 1.06	<0.001
BMI[d]									
Normal	1.00			1.00			1.00		
Overweight	1.47	1.40, 1.55	<0.001	1.35	1.28, 1.42	<0.001	1.05	0.99, 1.10	0.09
Obesity	2.22	2.07, 2.38	<0.001	2.04	1.91, 2.19	<0.001	1.31	1.22, 1.41	<0.001
Per 1 BMI unit (trend test)	1.06	1.05, 1.06	<0.001	1.05	1.05, 1.06	<0.001	1.02	1.01, 1.03	<0.001
Aerobic fitness (tertiles)									
Low	1.00			1.00			1.00		
Medium	1.14	1.11, 1.18	<0.001	0.94	0.91, 0.97	<0.001	1.02	0.99, 1.05	0.31
High	1.36	1.31, 1.41	<0.001	1.00	0.96, 1.05	0.84	1.14	1.09, 1.19	<0.001
Per 100 Watts (trend test)	1.31	1.27, 1.35	<0.001	0.99	0.95, 1.02	0.41	1.12	1.08, 1.16	<0.001
Muscular strength (tertiles)									
Low	1.00			1.00			1.00		
Medium	1.14	1.10, 1.17	<0.001	1.01	0.98, 1.05	0.42	1.04	1.00, 1.07	0.04
High	1.37	1.33, 1.42	<0.001	0.99	0.96, 1.03	0.66	1.03	0.99, 1.07	0.13
Per 1000 Newtons (trend test)	1.44	1.39, 1.50	<0.001	0.94	0.90, 0.98	0.006	1.00	0.95, 1.04	0.88
Education (years)									
<12	1.00			1.00			1.00		
12-14	0.92	0.89, 0.95	<0.001	0.89	0.86, 0.92	<0.001	0.90	0.87, 0.94	<0.001
≥15	0.93	0.89, 0.96	<0.001	0.89	0.86, 0.92	<0.001	0.95	0.91, 0.98	0.02
Per higher category (trend test)	0.97	0.95, 0.99	<0.001	0.95	0.93, 0.97	<0.001	0.98	0.96, 1.00	0.06
Neighborhood SES									
Low	1.00			1.00			1.00		
Medium	1.01	0.98, 1.05	0.48	1.04	1.00, 1.08	0.03	1.06	1.03, 1.10	0.001
High	0.96	0.92, 1.01	0.10	0.95	0.91, 1.00	0.04	0.98	0.93, 1.02	0.36
Per higher category (trend test)	0.98	0.96, 1.00	0.12	0.98	0.96, 1.00	0.06	0.99	0.97, 1.01	0.50
Hypertension									
No	1.00						1.00		

Yes	5.67	5.52, 5.83	<0.001				4.59	4.45, 4.74	<0.001
Diabetes mellitus									
No	1.00						1.00		
Yes	2.89	2.77, 3.00	<0.001				1.21	1.16, 2.26	<0.001
Ischemic heart disease									
No	1.00						1.00		
Yes	4.25	4.10, 4.42	<0.001				2.09	2.01, 2.18	<0.001
Family history of AF									
No	1.00			1.00			1.00		
Yes	1.80	1.76, 1.85	<0.001	1.73	1.68, 1.78	<0.001	1.72	1.67, 1.77	<0.001

AF = atrial fibrillation, BMI = body mass index, HR = hazard ratio, SES = socioeconomic status.

[a] Adjusted for age and year of military conscription examination.

[b] Adjusted for age, year of military conscription examination, height, weight, aerobic fitness, muscular strength, education, neighborhood SES, and family history of AF.

[c] Adjusted for age, year of military conscription examination, height, weight, aerobic fitness, muscular strength, education, neighborhood SES, hypertension, diabetes mellitus, ischemic heart disease, and family history of AF.

[d] Weight (kg)/height (m)^2, examined as an alternative to height and weight in a separate model. The reference category for all variables is indicated by an HR of 1.00.

Table 3. Interaction Between Height and Aerobic Fitness in Relation to Risk of AF,[a] Adjusted for Weight and Other Factors,[b] Sweden, 1969-2012.

Height (tertiles)	Aerobic fitness (tertiles)											
	Low				Medium				High			
	No. cases	Rate[c]	HR	95% CI	No. cases	Rate[c]	HR	95% CI	No. cases	Rate[c]	HR	95% CI
Low	4,569	54.1	1.00		1,756	39.3	0.89	0.84, 0.94	565	23.0	0.85	0.77, 0.93
Medium	2,633	55.3	0.95	0.90, 0.99	2,707	50.4	1.03	0.98, 1.09	1,460	34.6	1.15	1.07, 1.23
High	2,813	82.7	1.34	1.28, 1.41	4,139	80.5	1.49	1.42, 1.57	3,018	56.6	1.70	1.61, 1.80

AF = atrial fibrillation, HR = hazard ratio, RERI = relative excess risk due to interaction, SES = socioeconomic status.

[a] Interaction on additive scale, highest vs. lowest tertiles: RERI, 0.51 (95% CI, 0.40-0.62; *P*<0.001); interaction on multiplicative scale, highest vs. lowest tertiles: ratio of HRs, 1.50 (95% CI, 1.34-1.65; *P*<0.001).

[b] HRs are adjusted for age, year of military conscription examination, weight, muscular strength, education, neighborhood SES, hypertension, diabetes mellitus, ischemic heart disease, and family history of AF.

[c] AF incidence rate per 100,000 person-years.

Table 4. Interaction Between Weight and Aerobic Fitness in Relation to Risk of AF,[a] Adjusted for Height and Other Factors,[b] Sweden, 1969-2012.

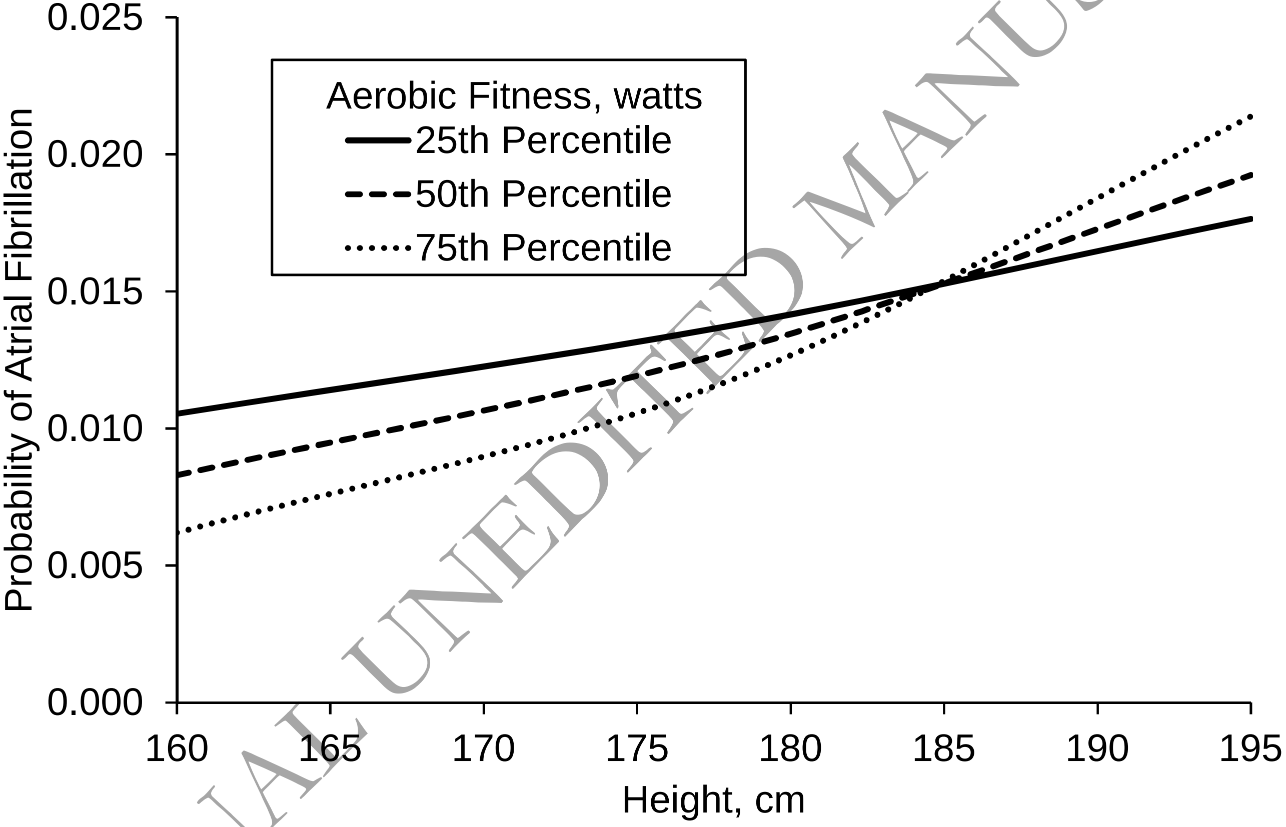
Weight (tertiles)	Aerobic fitness (tertiles)											
	Low				Medium				High			
	No. cases	Rate[c]	HR	95% CI	No. cases	Rate[c]	HR	95% CI	No. cases	Rate[c]	HR	95% CI
Low	5,213	53.0	1.00		1,309	33.9	0.86	0.80, 0.91	264	19.6	0.75	0.66, 0.86
Medium	2,643	62.0	0.90	0.86, 0.95	3,075	52.6	0.99	0.95, 1.04	1,342	31.7	1.01	0.94, 1.08
High	2,159	86.3	1.02	0.96, 1.07	4,218	80.1	1.15	1.09, 1.21	3,437	53.4	1.34	1.27, 1.42

AF = atrial fibrillation, HR = hazard ratio, RERI = relative excess risk due to interaction, SES = socioeconomic status.

[a] Interaction on additive scale, highest vs. lowest tertiles: RERI, 0.57 (95% CI, 0.46-0.68; *P*<0.001); interaction on multiplicative scale, highest vs. lowest tertiles: ratio of HRs, 1.75 (95% CI, 1.51-1.98; *P*<0.001).

[b] HRs are adjusted for age, year of military conscription examination, height, muscular strength, education, neighborhood SES, hypertension, diabetes mellitus, ischemic heart disease, and family history of AF.

[c] AF incidence rate per 100,000 person-years.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Probability of Atrial Fibrillation
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165
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180
185
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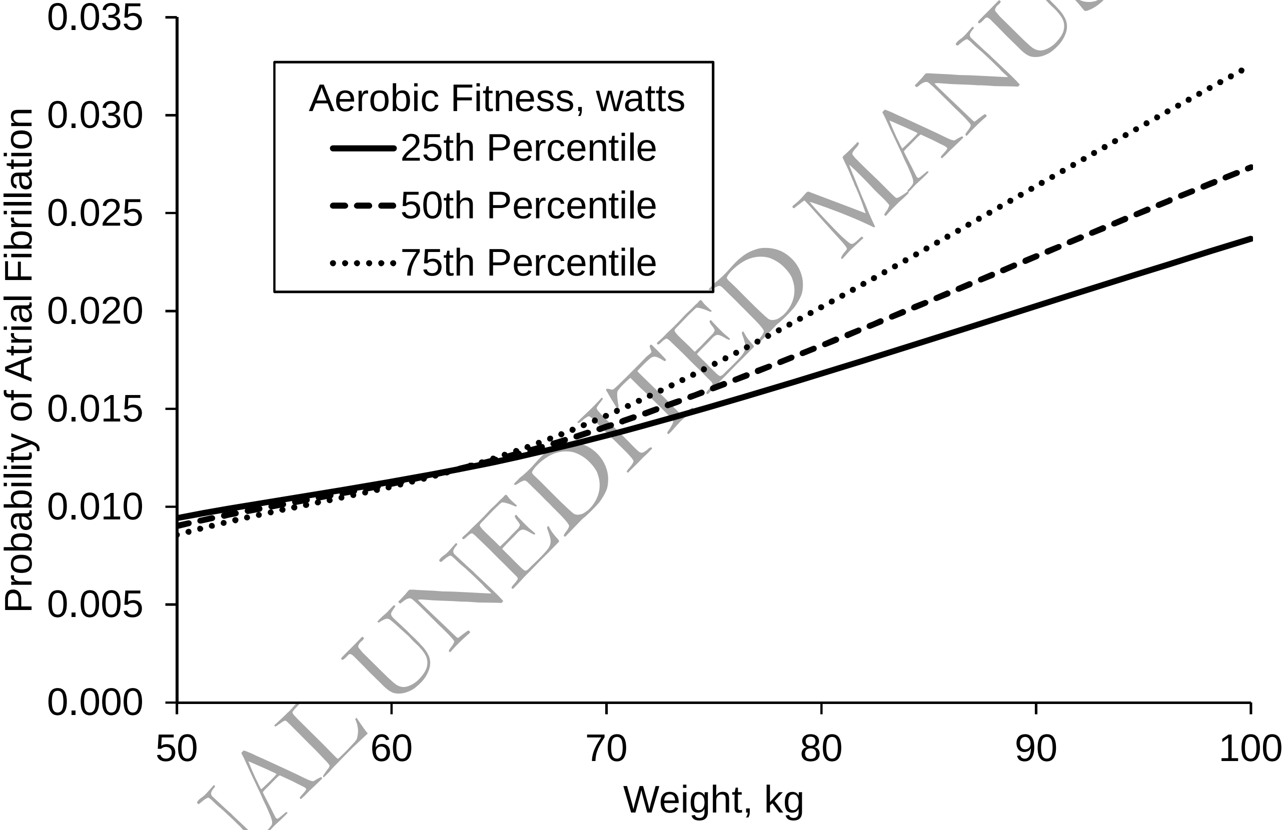
Height, cm
Aerobic Fitness, watts
25th Percentile
50th Percentile
75th Percentile


Aerobic Fitness, watts
25th Percentile
50th Percentile
75th Percentile
Probability of Atrial Fibrillation
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0.030
0.025
0.020
0.015
0.010
0.005
0.000
50
60
70
80
90
100
Weight, kg