Levels and Changes in Childhood Body Mass Index in Relation to Risk of Atrial Fibrillation and Atrial Flutter in Adulthood

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Running head: Child BMI and adulthood atrial fibrillation

Abstract

Children with obesity have a cardio-metabolic risk profile that may predispose them to cardiovascular diseases. We examined the associations between childhood body mass index (BMI) levels and changes on the risk of atrial fibrillation and flutter (AFF) in adulthood.

We conducted a population-based cohort study of Danish schoolchildren aged 7-13 years born from 1930−1989. Among 314,140 children, 17,594 were diagnosed with AFF as adults. In both men and women, above-average BMIs in childhood were associated with increased risks of AFF. Children who were persistently heavy at ages 7 and 13 years, and children whose BMI increased from the internal 25th-75th percentiles or from the internal 75.1th-90th percentiles between ages 7 and 13 years had higher risks of AFF in adulthood than children whose BMIs remained in the internal 25th-75th percentiles at both ages. A decrease in BMI percentile categories between 7 and 13 years of age reduced risks of AFF in adulthood, with risks of AFF reverting to levels similar to those in the reference group for women, but not for men.

In conclusion, risks of AFF in adulthood increased with higher childhood BMIs. Remission from overweight by age 13 years reduced AFF risks, especially in women.

Keywords: Childhood BMI, atrial fibrillation, cohort study

Worldwide, the prevalence of childhood obesity has increased by about 50% between 1980 and 2013.(1) While the most marked rise occurred in high-income countries, substantial increases also were observed in low- and middle-income countries.(1, 2) With the rise in the number of children affected by overweight and obesity, the prevalence of long-term complications such as weight-related orthopedic problems, diabetes, social stigmatization, and cardiovascular diseases also have increased.(3)

Atrial fibrillation and atrial flutter (AFF), the most frequent chronic cardiac arrhythmias, have increased in incidence and prevalence in recent years.(4) The potentially serious consequences of AFF include increased rates of death, hospitalization, reduced quality of life, stroke, and heart failure.(5) Thus AFF represents a major and growing health care burden for Western countries.(6) The lifetime risk of AFF is approximately 30%-40%, with a 1.5 fold higher risk in men than in women.(7, 8)

The pathogenesis of adult cardiovascular diseases involves a complex interplay between genetic and environmental factors, including early life determinants, some operating already *in utero*,(9-14) which may also influence the risk of AFF. Childhood body size has plausible links with AFF as well, since high childhood body mass index (BMI) values are associated with coronary heart disease,(15) ischemic stroke,(16) and type II diabetes.(17) We examined associations of levels and changes in BMI among children ages 7 to 13 years and their subsequent risk of AFF in adulthood. If levels and changes in BMI during childhood are associated with later AFF risk, the rationale for early strategies to prevent overweight in childhood becomes even more compelling.

METHODS

Setting, design, and study population

This population-based cohort study included children born between 1930 and 1989 who participated in mandatory annual health examinations at public and private schools in the Municipality of Copenhagen, Denmark. The Danish Civil Registration System, established in 1968,(18) maintains vital statistics records with daily updates. The Civil Registration System also assigns a unique personal identification number to each Danish resident at birth or upon immigration. This identifier allows linkage of individual-level data across Danish registries.(18)

Body mass index

At the health examinations, children's height and weight were measured without or with light clothing. Each child's height and weight measurements (annually until 1984, at school entry and exit thereafter) were documented on a personal health card also containing the child's name, date of birth, and birth weight (obtained from health records or reported by the children's parents or guardians at school entry since the birth year of 1936). Data on the personal health cards have been computerized and recorded in the Copenhagen School Health Records Register.(19) Linkages to the Civil Registration System succeeded in 88% of these records. Missing linkages were primarily due to death or emigration before 1968.(19)

We used the data recorded in the Copenhagen School Health Records Register to calculate each child's BMI as the weight (kg) divided by height (m^2). Data from 1955−1960 were used to create internal age- and sex-specific BMI reference values. BMI z-scores were calculated according to the Lambda-Mu-Sigma method.(20) Z-scores were interpolated or extrapolated in a ±12 month time window unless the measurements were taken at the exact age.

Atrial fibrillation and atrial flutter

Using personal identification numbers, we linked the cohort of children to the Danish National Patient Registry (DNPR). We then obtained information for each child on any new-onset AFF diagnosis in adulthood (from age 25 years and onwards, as diagnoses of AFF at younger ages are relatively uncommon, and likely linked to rare diseases not related to BMI). AFF was defined using *International Classification of Diseases Eighth Revision* codes 42793 and 42794 and *International Classification of Diseases Tenth Revision* code I48.(21) We used all recorded inpatient and outpatient AFF diagnoses in the DNPR, collapsing atrial fibrillation and atrial flutter into one group. The reasons for this were lack of differentiation of these diagnoses in *International Classification of Diseases Tenth Revision*, and, furthermore, the collapse of the groups is justified because the two conditions share risk factors, pathophysiology, and treatment.(22) The DNPR has recorded information on all inpatient contacts at non-psychiatric hospitals since 1977 and on all outpatient clinic contacts since 1995.(21)

Statistical analyses

We followed all children who were linked successfully to the Civil Registration System starting on the date of their 25th birthday or when the DNPR was established on January 1, 1977, whichever occurred later. The index date was defined as the date of commencement of follow-up. Follow-up continued until a first inpatient or outpatient contact date for AFF, death, emigration, loss to follow-up, or 31 December 2014, whichever came first.

We computed incidence rates of AFF by sex. Sex-specific Cox proportional-hazard regression analyses were used to examine associations between BMI z-scores and risk of AFF, using age as the underlying time scale. All models were stratified by birth cohort (1930-1939, 1940–1949, 1950–1959, 1960–1969, 1970–1979, and 1980–1989). We tested potential non-linearity in the associations between BMI z-score and AFF against a restricted cubic spline with

5 knots.(23) We found indications of non-linearity for both men and women (all p-values <0.04 for men and all but two p-values <0.01 for women). The statistical significance in the men is likely due to the large number of cases; a visual inspection of the association showed that the deviation from linearity was limited (Web Figure 1), thus linear models are presented in the manuscript. For women, the non-linearity was subsequently modelled using linear splines with a knot at a BMI z-score of 0 as the associations showed a linear pattern below and above this point. As the patterns of associations were comparable at all ages, we present the results only for ages 7 years, 10 years, and 13 years. Other ages are shown in Web Tables 1-2. We also performed categorical analyses based on <10th, 10th-24.9th, 25th-75th (reference group), 75.1th-90th, and >90th percentiles of the age- and sex-specific BMI distributions. To enhance interpretability of the estimates we included US Centers for Disease Control (CDC) percentile equivalents to our z-scores in the tables (24). To put these results into perspective, we calculated the incidence rate of AFF given a child's category of BMI at age 13 years.

Because we had long-term follow-up, we performed a sensitivity analysis, accounting for the competing risk of death using Fine and Grey regression models (25). We also calculated E-values for selected estimates and the corresponding lower limit of the 95% confidence interval for men and women aged 13 years, in a sensitivity analysis, to assess how strong an unmeasured confounder would have to be to potentially be able to explain away our observed exposure–outcome association (26, 27). Given that birth weight, reflecting intrauterine growth, may influence the risk of AFF,(28, 29) we performed additional analyses in the sub-cohort of individuals for whom birth weight was available. We adjusted our categorical BMI analyses for birth weight as a categorical variable (five categories) and evaluated potential interactions between birth weight and childhood BMI with AFF using a Wald test.

Potential interactions between birth cohorts, 1930–1951 and 1952–1989 (this cut point was chosen to ensure that all participants in the later cohort were followed up from age 25 years) and BMI z-scores or birth weight on the risk of AFF were examined in stratified models. The proportional hazard assumptions were assessed by stratifying the age-at-risk into categories, based upon quartiles of ages at diagnosis and including a time-varying covariate in the model. For men, the strength of the BMI z-score and AFF associations appeared to decrease with older age-at-risk, but the associations remained statistically significant at all ages (all p-values <0.04). Therefore, age-combined results are presented in the Results section and age-specific results are available in Web Table 3. For women, there were no significant differences in the associations by increasing age-at-risk (all p-values >0.12).

Finally, we computed hazard ratios for the effects of different patterns of BMI percentile changes between ages 7 years and 13 years on risk of AFF using categorical analyses with children who had BMIs within the 25^{th}-75^{th} at both ages as the reference.

The study was approved by the Danish Data Protection Agency (record number: 2012-58-0004). All analyses were conducted using Stata statistical software version 14.2 (StataCorp LP, College Station, Texas; www.stata.com).

RESULTS

The total study population consisted of 372,636 children. After excluding those missing identification numbers, an early diagnosis of AFF before 25 years of age, or missing BMI information, 314,140 children (159,036 boys and 155,104 girls) were included in the analytic dataset (Figure 1). As expected, the incidence rate of AFF increased with advancing age and the rate was higher in men than in women (Web Figure 2). During 8,565,403 person-years of follow-up, with a median follow-up time of 27.3 (25^{th}-75^{th} percentile, 19.0-38.0) years, 17,594 individuals were diagnosed with AFF.

Childhood body mass index and risk of atrial fibrillation and atrial flutter

In men, BMIs at all ages from 7 to 13 years were positively associated with an AFF diagnosis in adulthood (Figures 2A, 2C, and 2E). In women, patterns were similar to those observed for men, but below-average childhood BMI values generally were not associated with AFF in adulthood (Figures 2B, 2D, 2F). However, above-average BMI values in women were positively associated with AFF and consistently reached statistical significance.

In categorical analyses, using BMIs in the internal 25^{th}-75^{th} percentiles as the reference group, BMIs in the internal 75.1^{th}-90^{th} percentiles and particularly BMIs >internal 90^{th} percentile in children were associated with an increased risk of AFF at all ages over age 25 years (Table 1). For men with a childhood BMI >internal 90^{th} percentile at ages 7, 10 and 13 years, risks of AFF were 35% to 46% higher than boys with BMIs in the reference group. Similarly, for women with a childhood BMI >internal 90^{th} percentile at ages 7,10 and 13 years, risks of AFF were 26% to 38% higher than for girls with BMIs in the reference group. In men and women older than 55 years, the incidence rate of AFF was higher in those who had higher childhood BMIs (Figures 3A and 3B).

In the sensitivity analysis we accounted for the competing risk of dying, which changed the results very little (Web Table 2). For men aged 13 years (hazard ratio, 1.19, 95% confidence interval, 1.16-1.22), the E-value was 1.66 (E-value for lower limit of 95% confidence interval, 1.59). In women aged 13 years (hazard ratio, 1.24, confidence interval 1.18-1.30), for positive z-scores, the E-value was 1.79 (E-value for lower limit of 95% confidence interval=1.64). In the subset of 242,981 individuals who had available data on birth weight, 10,475 were diagnosed with AFF. When the associations between BMIs and AFF were adjusted for birth weight, the results remained largely unchanged (Web Table 4). We observed no interactions between birth weight with BMI on the association with later AFF risk at any ages. There were no birth cohort effects for the main analysis (Web Table 5).

BMI percentile change during childhood and risk of atrial fibrillation and atrial flutter

The analyses of BMI change included 253,664 children (127,321 boys and 126,343 girls), and children with BMIs from the 25th-75th percentiles at ages 7 and 13 years were the reference group. Compared with the reference group, persistently heavier children had 15% to 60% increased risks of AFF in adulthood (Table 2). Children who increased their BMIs from the internal 25th-75th percentile at 7 years to either the internal 75.1th-90th or >internal 90th groups at age 13 years had 13% to 53% higher risks of AFF during adulthood than children in the reference group. Women with a BMI in either the internal 75.1th-90th or >internal 90th percentile at age 7 who then reduced their BMIs to the internal 25th-75th group by age 13 years did not have different risks of AFF in adulthood than women in the reference group. For men with a BMI within internal 75.1th-90th percentiles at age 7 years reducing their BMI to the internal 25th-75th percentiles at age 13 years, there also was no association with future AFF. However, men in >internal 90th BMI percentile group at age 7 years with decreasing BMI to the internal 25th-75th group at age 13 years had a 23% increased risk of AFF compared with men in the reference group. There were no interactions of birth weight with change in BMI percentiles in their association with later AFF risk.

DISCUSSION

In this population-based cohort study of 314,140 schoolchildren aged 7-13 years, above-average BMIs were positively associated with AFF at all adult ages above age 25 years in both sexes. These associations remained after adjustment for birth weight, and were consistent across birth cohorts. In addition, being persistently heavier than average and gaining more BMI than average between the ages of 7 and 13 years were associated with an increased risk of AFF in adulthood. Among children with BMIs >75th percentiles at age 7 years, reducing their BMI during childhood decreased risks of AFF, particularly for women.

Adult obesity is a well-established risk factor for AFF.(30) In a Danish cohort study of 12,850 men undergoing examination for army conscription (median age, 19 years), those with overweight (BMI 25-<30 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) and had 2-fold and 3-fold higher risks of AFF later in life, respectively, than young men with BMI between 18.5-25 kg/m^2).(31) In line with this finding, a Danish study of women at time of childbirth found a 2-fold higher risk of AFF among those with a BMI between 30 and 35 kg/m^2 compared to those with a normal BMI.(32) Similarly, a Swedish study of young women (mean age, 28 years) reported a 2-3 fold increased risk of atrial fibrillation in those with BMI >27.5 kg/m^2 relative to those with normal range BMI.(33) None of these studies included data on associations between obesity in childhood and future AFF. Thus, observations from the current study extend this literature, indicating an increased risk of AFF in adulthood associated with childhood overweight, especially for children with above-average BMIs (BMI z-score>0). In support of this finding, childhood obesity was recently found to be associated with ischemic stroke in adulthood,(16) which in turn is caused by underlying AFF in up to 20% of cases.(34) Notably, we found a relatively low and almost unchanged AFF incidence across the BMI categories for nearly 40 years of age for men and 50 years of age for women. Thus, differences in absolute AFF risks as a result of childhood BMI first become apparent in late adulthood.

In our categorical analysis, we observed increased risks of future AFF among children with BMI values starting at the 75th percentile, and markedly elevated risks for children above the 90th percentile, compared with children with BMI values in the 25th-75th percentile range. Based on the current childhood BMI classification used by the CDC in the United States, the 90th percentile of BMI in our study is equivalent to its classification of “overweight”.(35) Thus our findings suggest that an elevated BMI in childhood, even at values below those classified as overweight by the CDC, should be considered an important risk factor for AFF. This finding reinforces the justification of developing strategies for screening and primary prevention of childhood overweight and obesity.

Our analysis also revealed that BMI percentile change during childhood changed the risk of AFF in adulthood. In the multifactor Swedish Primary Prevention Study, weight change from age 20 years to midlife was calculated as the ratio between measured weight at midlife and recalled weight at age 20 years. A multivariable analysis indicated that weight gain of 5% to 15% was not associated with AFF, while weight gains of 16% to 35% and >35% were associated with 46% and 90% increased risks of AFF, respectively.(36) This is in accord with our analysis demonstrating that gains in BMI percentiles during childhood was associated with increased risks of AFF in adulthood. The associations weakened with declines in BMI percentiles from ages 7 to 13 years in women, while the association persisted in men reducing their weight from the >90th percentile to the reference group. Therefore, our data suggest that overweight and obesity in childhood may be a modifiable risk factor with the potential to prevent AFF.

Several mechanisms could underlie our results. Genes and environmental changes *in utero* may produce long lasting changes in physiology and metabolism,(11) increasing the likelihood of AFF later in life. Moreover, since childhood obesity is linked to young adult obesity,(37) obesity in young adulthood could serve as a mediator of increased AFF risk. It must be noted, however, that correlations between BMI in childhood and in late adulthood when AFF typically occurs are weak.(37) Although our data suggest that the heaviest children were at particularly high risk of AFF, we found an increased risk of AFF across all above-average BMI levels, suggesting that tracking of BMI from childhood to adulthood cannot fully explain our study findings. The underlying pathways are likely multifactorial, as children with obesity have a high prevalence of cardio-metabolic risk factors such as high cholesterol, triglycerides, blood pressure, and glycated hemoglobin,(38) which also are risk factors for AFF.(22) Interestingly, in comparison with normal weight children, children with obesity have larger left atrial and ventricular dimensions, increased left ventricular mass, subclinical myocardial dysfunction (39), and altered left ventricular geometry,(40) which could lower the threshold for AFF occurrence. Because most previous studies compared obese children to non-obese children, it is unknown whether these associations reflect a dose-response relation.

Strengths of our study are its access to prospectively collected data on virtually all school-children in the Copenhagen municipality, as well as long-term follow-up and minimal loss to follow-up. The diagnosis of AFF in the DNPR is valid, with positive predictive values between 92% and 99%.(21, 41) Relying solely on hospital-based (inpatient and outpatient) diagnoses may have underestimated the observed AFF incidence rate. However, such misclassification would likely be non-differential (*i.e*. AFF outcomes are presumably not related to childhood BMI), and thus cannot explain the observed associations. Although we had information on birth weight, we lacked information on potential confounders such as parental socioeconomic status and smoking habits. However, socioeconomic differences may change over time, and because our results were consistent across birth cohorts, confounding by socioeconomic factors is unlikely to explain our findings. The derived E-values indicating the association strength needed by an unmeasured confounder - both with the exposure and the outcome – to potentially (as a maximum) be able to explain away, some representative findings (hazard ratios: 1.19-1.24), were large (E-values: 1.66-1.79) thus suggesting that our findings may be robust to effects of potential unmeasured and uncontrolled confounding. We assessed the long-term risk associated with childhood BMI, and we did not explore the underlying mechanisms, as many mediators such as adult weight and cardiovascular risk factors have complex patterns over time and could not be subtracted for this study. Because occurrence of cardiovascular conditions such as hypertension, type 2 diabetes, coronary artery disease, and heart failure are on the causal pathway from childhood BMI through AFF in adulthood,(16, 17, 42-44) they were not accounted for in the main analysis.

In this population-based cohort study, we found a clear association between BMIs above average and increases in BMI percentiles from ages 7 to 13 years with increased risks of AFF in adulthood. Risks of adult AFF decreased in women who reduced their BMI during childhood. This pattern was also observed for men, but to a lesser degree. Our study suggests that childhood obesity may be an important risk factor for AFF.

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Table 1. Body Mass Index Category and Risk of Atrial Fibrillation and Atrial Flutter in Adulthood, by Age and Sex, in Children Born from 1930−1989, Denmark. All Analyses Are Stratified by Birth Cohort.

	Men					Women				
BMI percentile[a]	**BMI value (kg/m^2)[a]**	**CDC percentile**	**No. events**	**HR**	**95% CI**	**BMI value (kg/m^2)[a]**	**CDC percentile**	**No. events**	**HR**	**95% CI**
7 years										
<10th	<14.0	<9.3th	762	0.85	0.79,0.92	<13.8	<10.3th	495	0.93	0.84,1.02
10th-24.9th	14.0-14.5	9.3th -23.5th	1,414	0.90	0.85,0.96	13.8-14.4	10.3th-25.5th	914	0.91	0.85,0.98
25th-75th	14.6-16.3	23.6th -69.3th	5,774	1.00	Referent	14.5-16.3	25.6th -68.4th	3,415	1.00	Referent
75.1th-90th	16.4-17.2	69.4th-82.9th	1,483	1.10	1.04,1.16	16.4-17.3	68.5th -82.2th	802	1.11	1.02,1.19
>90th	>17.2	>82.9th	781	1.35	1.25,1.45	>17.3	>82.2th	475	1.26	1.14,1.38
10 years										
<10th	<14.7	<11.1th	654	0.83	0.77,0.90	<14.4	<8.5th	363	0.87	0.78,0.96
10th-24.9th	14.7-15.4	11.1th-25.9th	1,417	0.89	0.84,0.94	14.4-15.2	8.5th-21.5th	879	0.91	0.85,0.98
25th-75th	15.5-17.7	26.0th -68.3th	6,109	1.00	Referent	15.3-17.8	21.6th-64.7th	3,625	1.00	Referent
75.1th-90th	17.8-19.1	68.4th -83.1th	1,379	1.15	1.09,1.22	17.9-19.4	64.8th -81.3th	879	1.12	1.04,1.20
>90th	>19.1	>83.1th	781	1.42	1.32,1.53	>19.4	>81.3th	518	1.32	1.20,1.45
13 years										
<10th	<15.6	<6.2th	563	0.79	0.73,0.86	<15.7	<8.2th	358	0.90	0.81,1.01
10th-24.9th	15.6-16.4	6.2th -14.4th	1,356	0.91	0.85,0.96	15.7-16.6	8.2th -19.7th	769	0.92	0.85,0.99
25th-75th	16.5-19.4	14.5th -63.9th	5,751	1.00	Referent	16.7-19.9	19.8th-65.0th	3,425	1.00	Referent
75.1th-90th	19.5-21.1	64.0th-80.5th	1,516	1.18	1.11,1.25	20.0-21.9	65.1th-81.5th	1,057	1.19	1.11,1.27
>90th	>21.1	>80.5th	876	1.46	1.36,1.56	>21.9	>81.5th	598	1.38	1.27,1.51

[a]Approximate values, corresponding to BMI percentiles of <10th, 10th-24.9th, 25th-75th, 75.1th-90th, and >90th of the internal age- and sex-specific BMI distributions. BMI was calculated as the weight (kg) / height (m^2)

Abbreviations: BMI, body mass index; CDC: Center for Disease Control and Prevention; CI, confidence interval; HR, hazard ratio.

Table 2. Hazard Ratios (95% Confidence Intervals) for the Association between Different Patterns of Change in Body Mass Index between Ages 7 and 13 Years and Adulthood Atrial Fibrillation and Atrial Flutter, in Children Born from 1930−1989, Denmark. All Analyses Are Stratified by Birth Cohort.

		BMI percentile at age 13[a]															
		<25th				25th-75th				75.1th-90th				>90th			
BMI percentile at age 7[a]		**BMI value (CDC percentiles) at age 13[a]**															
Men	**BMI value (CDC percentile) at age 7[a]**	<16.5 (<17.8th)				16.5-19.4 (17.8th-63.3 th)				19.5-21.1 (63.4th-80.8th)				>21.1 (>80.8th)			
		No.	No. events	HR	95% CI	No.	No. events	HR	95% CI	No.	No. events	HR	95% CI	No.	No. events	HR	95% CI
<25th	<14.6 (<24.7th)	17,248	1143	0.85	0.80,0.91	10,404	796	0.95	0.88,1.03	618	50	1.23	0.93,1.62	140	10	1.49	0.80,2.78
25th-75th	14.6-16.3 (24.7th-69.0th)	8,835	616	0.89	0.81,0.97	45,346	3,784	1.00	Referent	7,627	692	1.22	1.13,1.33	2,362	218	1.53	1.34,1.76
75.1th-90th	16.4-17.2 (70.0th-83.1th)	122	8	1.02	0.51,2.04	7,769	654	1.04	0.96,1.13	5,526	481	1.18	1.07,1.29	2,876	225	1.30	1.14,1.49
>90th	>17.2 (>83.1th)	18	2	(.-.)[b]	(.-.)	1,340	113	1.23	1.02,1.48	2,753	216	1.15	1.00,1.32	4,949	380	1.57	1.41,1.74
Women		**BMI value (CDC percentiles) at age 13[a]**															
		<16.7 (<20.5th)				16.7-19.9 (20.5th-65.3th)				>20.0-21.9 (65.4th-81.4th)				>21.9 (>81.4th)			
		No.	No. events	HR	95% CI	No.	No. events	HR	95% CI	No.	No. events	HR	95% CI	No.	No. events	HR	95% CI
<25th	<14.5 (<24.4th)	16,980	692	0.91	0.83,0.99	12,392	606	0.98	0.90,1.08	684	37	1.20	0.86,1.66	120	5	1.27	0.53-3.06
25th-75th	14.5-16.3 (24.4th-68.3th)	8,620	349	0.92	0.82,1.03	44,460	2,195	1.00	Referent	9,358	496	1.13	1.03,1.25	2,658	144	1.44	1.21-1.70
75.1th-90th	16.4-17.3 (68.4th-82.5th)	145	4	(.-.)	(.-.)	6,613	308	1.06	0.94,1.19	5,427	304	1.24	1.10,1.40	3,222	147	1.19	1.01-1.41
>90th	>17.3 (>82.5th)	20	0	(.-.)	(.-.)	1,405	52	0.93	0.70-1.22	2,772	135	1.26	1.06-1.50	5,730	262	1.46	1.28-1.66

[a]Approximate values.

Abbreviations: BMI, body mass index (kg/m^2); CDC: Center for Disease Control and Prevention

[b](.-.) Insufficient data for conducting analyses

Figure 1. Flow Chart of Children born from 1930−1989, Denmark.

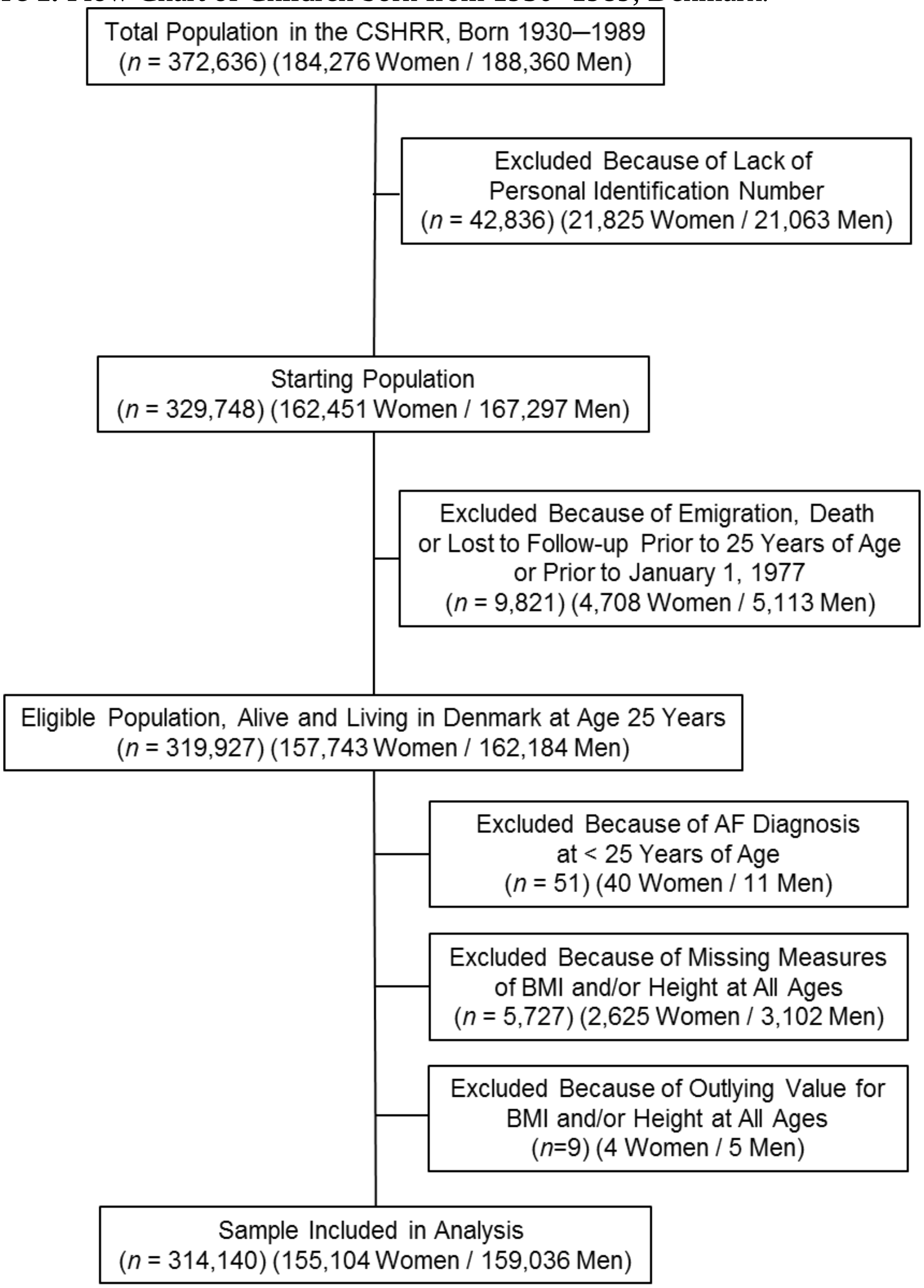
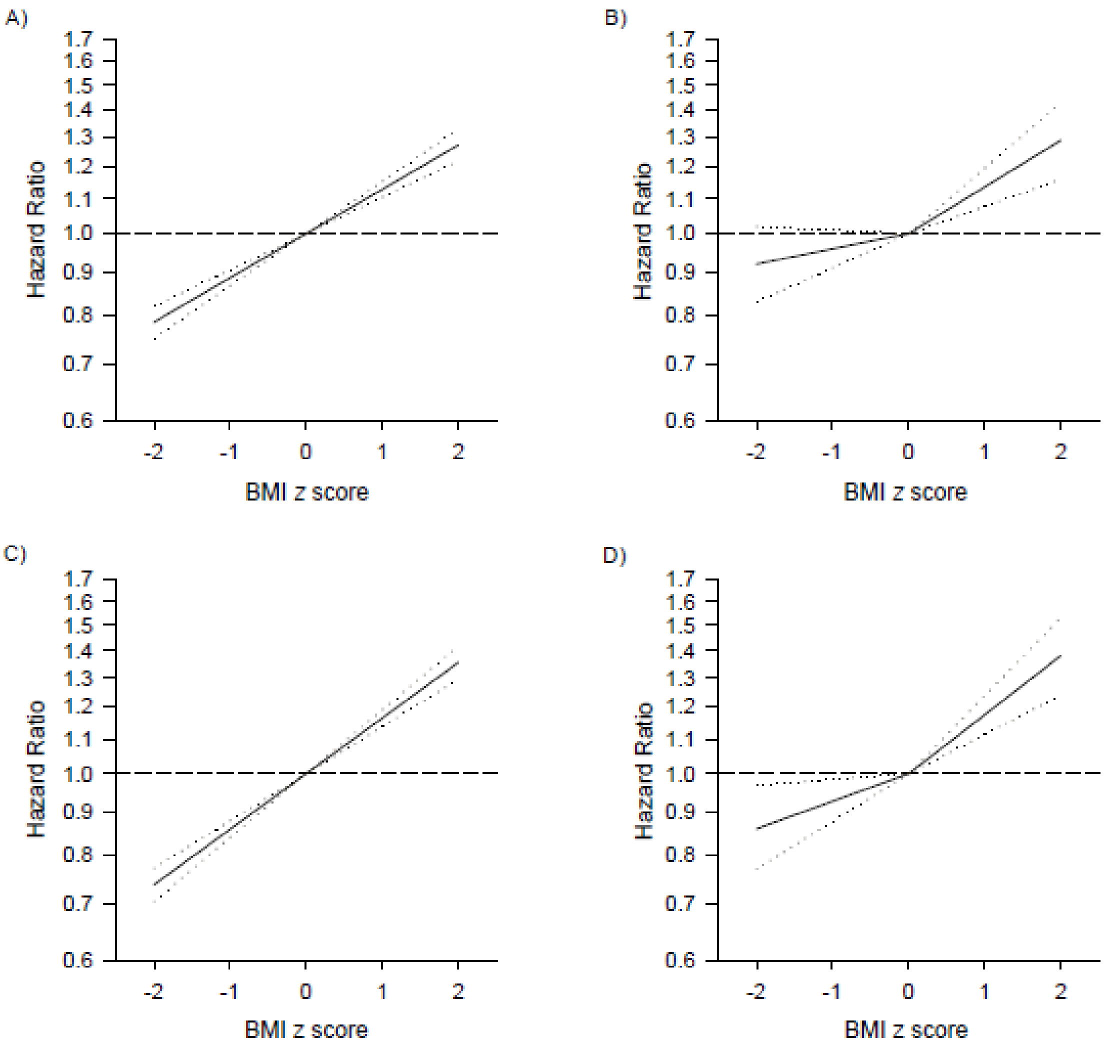
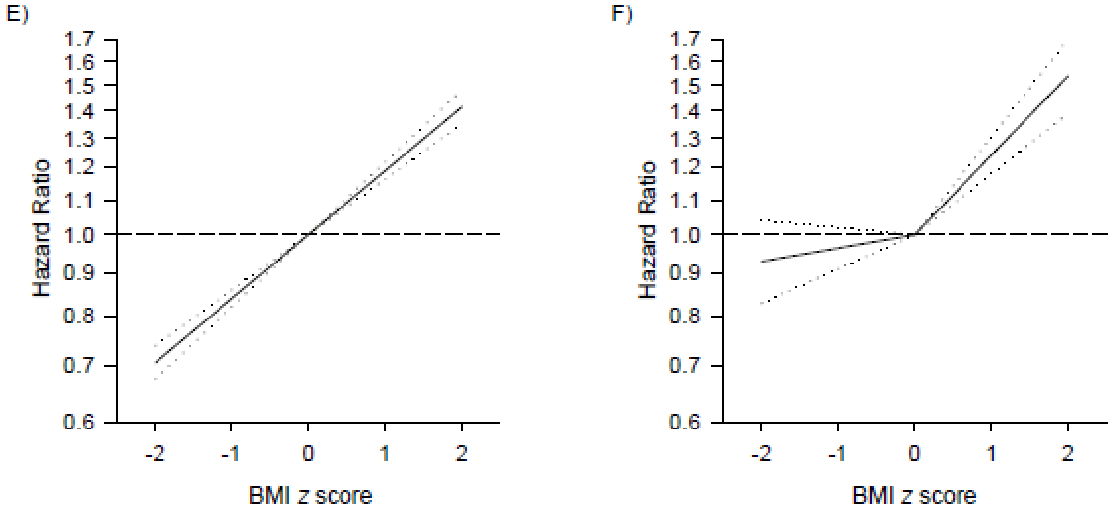


Figure 2. The Association between Body Mass Index Z-Score, CDC percentiles, and Atrial Fibrillation and Atrial Flutter at ages 7, 10, and 13 Years of Age, in Children Born from 1930−1989, Denmark..

A) Men, age 7 years
B) Women, age 7 years
C) Men, age 10 years
D) Women, age 10 years
E) Men, age 13 years
F) Women, age 13 years

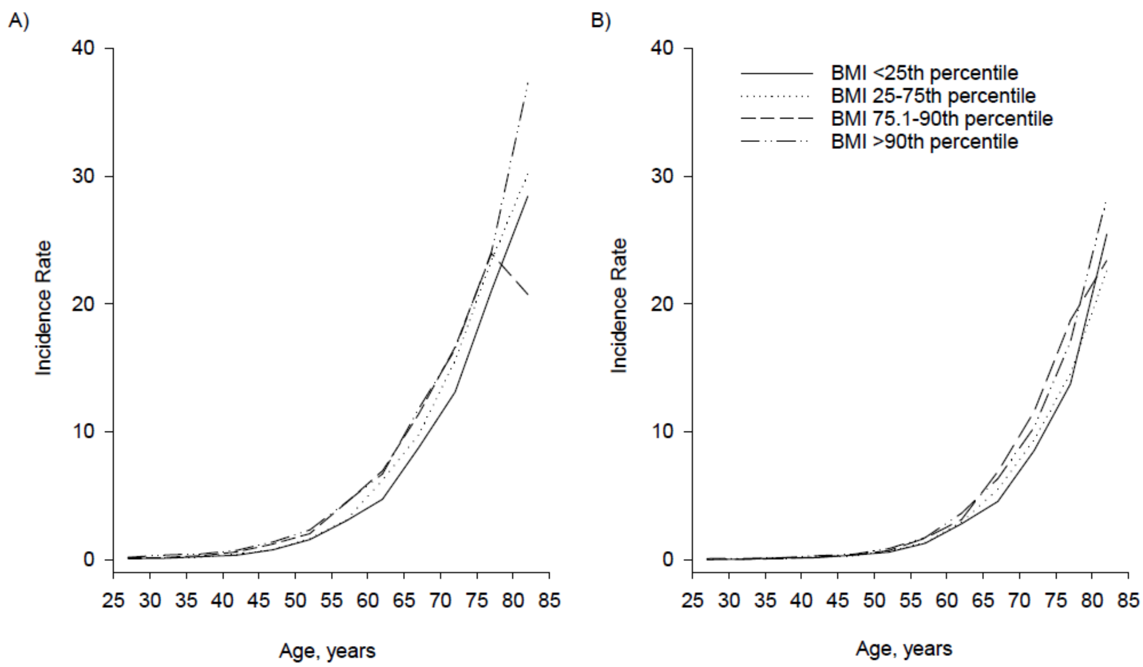




For men the associations were illustrated using linear models, while the associations in women were modelled using linear splines with a knot at a body mass index z-score of 0.
Abbreviations: BMI, body mass index (kg/m^2); CDC: Center for Disease Control and Prevention; CI, confidence interval

Figure 3. The Incidence Rate of Atrial Fibrillation and Atrial Flutter, According to Categories of Childhood Body Mass Index (at age 13 years), in Children Born from 1930−1989, Denmark.

A) Men
B) Women



Abbreviations: BMI, body mass index (kg/m^2)

Web materials

Levels and Changes in Childhood Body Mass Index in Relation to Risk of Atrial Fibrillation and Atrial Flutter in Adulthood

Contents

Web Table 1. Body mass index category and risk of future atrial fibrillation and atrial flutter, by age and sex for children ages 8, 9, 11, and 12 years.

		Men				**Women**			
Age, years	**BMI percentile**[a]	**BMI value (kg/m^2)**[a]	**CDC percentile**	**No. events**	**HR (95% CI)**	**BMI value (kg/m^2)**[a]	**CDC percentile**	**No. events**	**HR (95% CI)**
8	<10th	<14.2	<11.0th	626	0.81 (0.74-0.87)	<14.0	<11.0th	437	0.97 (0.87-1.07)
	10th-24.9th	14.2-14.8	11.0th -26.9th	1,376	0.89 (0.84-0.95)	14.0-14.6	11.0th-24.6th	887	0.89 (0.82-0.96)
	25th-75th	14.9-16.7	27.0th-69.6th	6,140	Reference	14.7-16.7	24.7th -66.8th	3,590	Reference
	75.1th-90th	16.8-17.8	69.7th-83.7th	1,511	1.12 (1.06-1.18)	16.8-17.9	66.9th-81.8th	838	1.10 (1.02-1.19)
	>90th	>17.8	>83.7th	762	1.37 (1.27-1.48)	>17.9	>81.8th	505	1.31 (1.19-1.44)
9	<10th	<14.5	<12.7th	648	0.83 (0.76-0.90)	<14.2	<10.2th	417	0.94 (0.85-1.04)
	10th-24.9th	14.5-15.1	12.7th-27.2th	1,353	0.85 (0.81-0.91)	14.2-14.9	10.2th-23.7th	882	0.92 (0.85-0.99)
	25th-75th	15.2-17.2	27.3th -69.7th	6,145	Reference	15.0-17.3	23.8th-67.0th	3,613	Reference
	75.1th-90th	17.3-18.4	69.8th-83.3th	1,438	1.13 (1.06-1.19)	17.4-18.7	67.1th-82.2th	853	1.10 (1.03-1.19)
	>90th	>18.4	>83.3th	778	1.41 (1.31-1.52)	>18.7	>82.2th	509	1.28 (1.16-1.40)
11	<10th	<15.0	<9.8th	626	0.81 (0.75-0.88)	<14.7	<7.7th	381	0.93 (0.84-1.04)
	10th-24.9th	15.0-15.7	9.8th-22.9th	1,406	0.85 (0.80-0.90)	14.7-15.5	7.7th-18.9th	882	0.94 (0.87-1.01)
	25th-75th	15.8-18.2	23.0th-66.4th	6,097	Reference	15.6-18.4	19.0th -63.7th	3,596	Reference
	75.1th-90th	18.3-19.8	66.5th-82.5th	1,383	1.18 (1.12-1.25)	18.5-20.1	63.8th -80.4th	888	1.13 (1.05-1.21)
	>90th	>19.8	>82.5th	790	1.41 (1.31-1.52)	>20.1	>80.4th	526	1.35 (1.23-1.48)
12	<10th	<15.3	<6.1th	591	0.81 (0.74-0.88)	<15.1	<7.2th	357	0.87 (0.78-0.97)
	10th-24.9th	15.3-16.0	6.1th -19.2th	1,453	0.92 (0.87-0.97)	15.1-16.0	7.2th-18.8th	843	0.92 (0.85-0.99)
	25th-75th	16.1-18.8	19.3th-65.4th	5,902	Reference	16.1-19.1	18.9th-63.7th	3,573	Reference
	75.1th-90th	18.9-20.5	65.5th-81.9th	1,418	1.21 (1.14-1.28)	19.2-21.0	63.8th-80.9th	943	1.13 (1.05-1.21)
	>90th	>20.5	>81.9th	859	1.51 (1.41-1.62)	>21.0	>80.9th	544	1.35 (1.23-1.48)

All analyses are stratified by birth cohort.

[a]Approximate values

Abbreviations: BMI, body mass index (kg/m^2); CI, confidence interval; HR, hazard ratio

Web Table 2. The association between body mass index z-score and atrial fibrillation and atrial flutter at all ages. For men the associations were illustrated using linear models, while the associations in women were modelled using linear splines with a knot at a body mass index z-score of 0.

	Age, years	BMI z-score	Standard Cox regression with birth cohort stratification	Standard Cox regression without birth cohort stratification	Subdistribution hazards model[a]
			HR (95% CI)	HR (95% CI)	Subdistribution HR (95% CI)
Men	7		1.13 (1.10-1.15)	1.13 (1.11-1.16)	1.12 (1.09-1.14)
	8		1.15 (1.13-1.18)	1.16 (1.13-1.18)	1.13 (1.11-1.16)
	9		1.16 (1.13-1.19)	1.17 (1.14-1.20)	1.14 (1.12-1.17)
	10		1.16 (1.14-1.19)	1.17 (1.15-1.20)	1.15 (1.12-1.17)
	11		1.18 (1.16-1.21)	1.19 (1.16-1.22)	1.16 (1.13-1.19)
	12		1.19 (1.16-1.22)	1.20 (1.17-1.23)	1.17 (1.14-1.20)
	13		1.19 (1.16-1.22)	1.20 (1.17-1.23)	1.17 (1.14-1.19)
Women	7	-2	0.92 (0.83–1.02)	0.93 (0.84–1.03)	0.93 (0.84–1.03)
		-1	0.96 (0.91–1.01)	0.96 (0.92–1.02)	0.96 (0.92–1.02)
		0	1	1	1
		1	1.13 (1.08–1.19)	1.15 (1.09–1.21)	1.11 (1.05–1.17)
		2	1.29 (1.16–1.43)	1.33 (1.20–1.47)	1.23 (1.11–1.36)
	8	-2	0.91 (0.81–1.01)	0.93 (0.83–1.04)	0.92 (0.83–1.03)
		-1	0.95 (0.90–1.01)	0.96 (0.91–1.02)	0.96 (0.91–1.01)
		0	1	1	1
		1	1.15 (1.09–1.21)	1.17 (1.12–1.24)	1.12 (1.06–1.18)
		2	1.33 (1.20–1.47)	1.38 (1.24–1.53)	1.25 (1.13–1.39)
	9	-2	0.90 (0.80–1.01)	0.93 (0.83–1.04)	0.92 (0.82–1.03)
		-1	0.95 (0.90–1.00)	0.96 (0.91–1.02)	0.96 (0.90–1.01)
		0	1	1	1
		1	1.15 (0.10–1.22)	1.18 (0.12–1.24)	1.12 (1.06–1.18)
		2	1.33 (1.20–1.48)	1.39 (1.25–1.54)	1.25 (1.13–1.39)
	10	-2	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.87 (0.78–0.98)
		-1	0.93 (0.88–0.98)	0.95 (0.89–1.00)	0.93 (0.88–0.99)
		0	1	1	1
		1	1.17 (1.11–1.24)	1.20 (1.14–1.27)	1.13 (1.07–1.19)
		2	1.38 (1.24–1.53)	1.44 (1.30–1.60)	1.28 (1.15–1.43)
	11	-2	0.90 (0.81–1.01)	0.94 (0.84–1.06)	0.91 (0.81–1.02)
		-1	0.95 (0.90–1.01)	0.97 (0.92–1.03)	0.95 (0.90–1.01)
		0	1	1	1
		1	1.21 (1.15–1.27)	1.23 (1.17–1.30)	1.16 (1.10–1.22)
		2	1.46 (1.31–1.62)	1.52 (1.37–1.69)	1.34 (1.20–1.49)
	12	-2	0.91 (0.81–1.02)	0.95 (0.85–1.07)	0.91 (0.81–1.03)
		-1	0.96 (0.90–1.01)	0.97 (0.92–1.03)	0.96 (0.90–1.01)
		0	1	1	1
		1	1.22 (0.16–1.28)	1.24 (1.18–1.31)	1.16 (1.10–1.22)
		2	1.48 (1.34–1.65)	1.55 (1.39–1.72)	1.35 (1.22–1.50)
	13	-2	0.93 (0.83–1.04)	0.96 (0.86–1.08)	0.92 (0.82–1.04)
		-1	0.96 (0.91–1.02)	0.98 (0.92–1.04)	0.96 (0.91–1.02)
		0	1	1	1
		1	1.24 (1.18–1.30)	1.26 (1.20–1.32)	1.18 (1.12–1.24)
		2	1.54 (1.39–1.70)	1.58 (1.43–1.75)	1.39 (1.26–1.54)

Abbreviations: BMI, body mass index (kg/m^2); CI, confidence interval; HR, hazard ratio.
[a]Not stratified by birth year, since this option is not available in the subdistribution model.

Web Table 3. Test of proportional hazards assumptions by investigation within quartiles of age at risk (divided based upon age at diagnosis) and assuming a linear model.

Age, years	**Age-at-risk, years**	**Men HR (95% CI)**	**Women HR (95% CI)**
7	25-59	1.12 (1.13-1.23)	1.11 (1.04-1.18)
	59-67	1.12 (1.08-1.17)	1.14 (1.08-1.20)
	67-73	1.09 (1.04-1.14)	1.04 (0.99-1.10)
	>73	1.10 (1.05-1.16)	1.07 (1.01-1.13)
8	25-59	1.21 (1.16-1.26)	1.13 (1.06-1.20)
	59-67	1.15 (1.10-1.20)	1.13 (1.08-1.20)
	67-73	1.10 (1.05-1.15)	1.07 (1.01-1.13)
	>73	1.13 (1.06-1.19)	1.08 (1.02-1.14)
9	25-59	1.23 (1.18-1.28)	1.14 (1.07-1.21)
	59-67	1.17 (1.12-1.21)	1.12 (1.06-1.18)
	67-73	1.09 (1.04-1.15)	1.09 (1.03-1.16)
	>73	1.11 (1.05-1.18)	1.08 (1.02-1.14)
10	25-59	1.23 (1.18-1.28)	1.15 (1.08-1.23)
	59-67	1.16 (1.11-1.21)	1.14 (1.08-1.21)
	67-73	1.10 (1.05-1.16)	1.12 (1.06-1.19)
	>73	1.13 (1.07-1.20)	1.09 (1.03-1.16)
11	25-59	1.26 (1.21-1.31)	1.16 (1.09-1.24)
	59-67	1.18 (1.13-1.23)	1.15 (1.09-1.22)
	67-73	1.11 (1.06-1.17)	1.12 (1.06-1.18)
	>73	1.13 (1.07-1.20)	1.10 (1.03-1.17)
12	25-59	1.27 (1.22-1.32)	1.15 (1.08-1.23)
	59-67	1.18 (1.13-1.23)	1.17 (1.11-1.23)
	67-73	1.13 (1.08-1.19)	1.13 (1.07-1.20)
	>73	1.14 (1.07-1.21)	1.09 (1.03-1.16)
13	25-59	1.26 (1.21-1.32)	1.13 (1.06-1.21)
	59-67	1.19 (1.14-1.23)	1.20 (1.14-1.27)
	67-73	1.14 (1.08-1.19)	1.13 (1.07-1.19)
	>73	1.14 (1.08-1.21)	1.11 (1.05-1.18)

Abbreviations: CI, confidence interval; HR, hazard ratio
All analyses are stratified by birth cohort.

Web Table 4. Hazard ratios for the risk of atrial fibrillation and atrial flutter according to categories of body mass index in childhood with and without adjustment for birth weight.

		Men		**Women**	
	BMI percentile	**Unadjusted HR (95% CI)**	**BW adjusted HR (95% CI)**	**Unadjusted HR (95% CI)**	**BW adjusted HR (95% CI)**
7 years	<10th	0.84 (0.76-0.92)	0.85 (0.76-0.93)	0.89 (0.78-1.01)	0.89 (0.78-1.01)
	10th-24.9th	0.89 (0.82-0.96)	0.89 (0.83-0.96)	0.90 (0.82-1.00)	0.90 (0.82-1.00)
	25th-75th	Reference	Reference	Reference	Reference
	75.1th-90th	1.08 (1.00-1.16)	1.07 (1.00-1.15)	1.09 (0.99-1.21)	1.09 (0.98-1.20)
	>90th	1.39 (1.27-1.52)	1.38 (1.26-1.51)	1.34 (1.19-1.51)	1.32 (1.17-1.49)
10 years	<10th	0.81 (0.73-0.90)	0.82 (0.74-0.91)	0.85 (0.74-0.99)	0.85 (0.74-0.99)
	10th-24.9th	0.87 (0.81-0.94)	0.88 (0.82-0.95)	0.94 (0.84-1.04)	0.93 (0.84-1.03)
	25th-75th	Reference	Reference	Reference	Reference
	75.1th-90th	1.13 (1.05-1.21)	1.12 (1.05-1.21)	1.14 (1.04-1.26)	1.15 (1.05-1.27)
	>90th	1.45 (1.33-1.58)	1.44 (1.32-1.57)	1.35 (1.21-1.52)	1.36 (1.22-1.53)
13 years	<10th	0.83 (0.74-0.92)	0.83 (0.75-0.93)	0.86 (0.74-0.99)	0.86 (0.74-0.99)
	10th-24.9th	0.92 (0.85-0.99)	0.93 (0.86-1.00)	0.92 (0.83-1.02)	0.92 (0.83-1.03)
	25th-75th	Reference	Reference	Reference	Reference
	75.1th-90th	1.21 (1.13-1.29)	1.20 (1.12-1.29)	1.19 (1.08-1.30)	1.18 (1.08-1.30)
	>90th	1.50 (1.38-1.63)	1.49 (1.38-1.62)	1.39 (1.25-1.56)	1.39 (1.24-1.55)

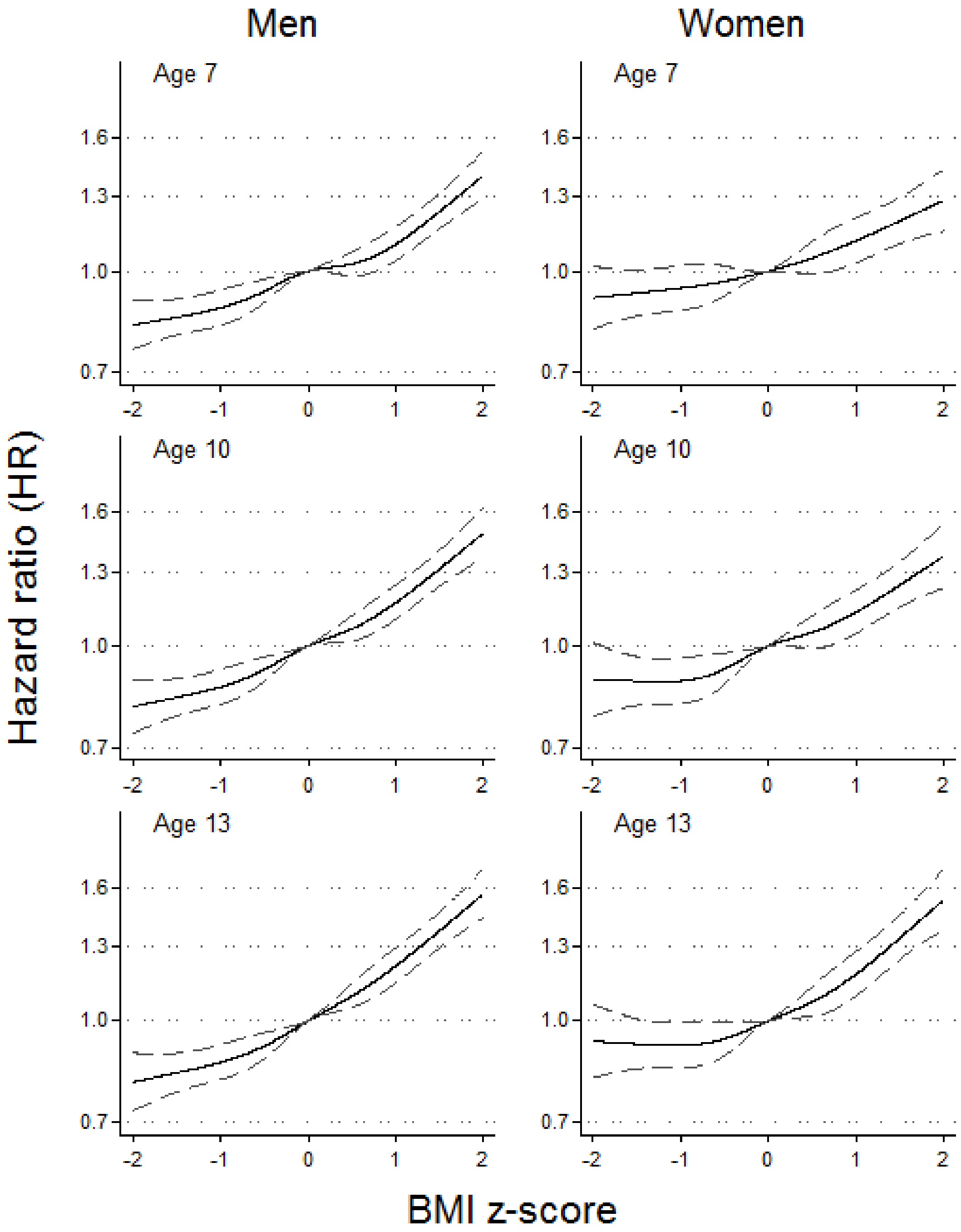
Abbreviations: BMI, body mass index (kg/m^2); BW, birth weight; CI, confidence interval; HR, hazard ratio
All analyses are stratified by birth cohort.

Web Table 5. The association between body mass index z-score and atrial fibrillation and atrial flutter at all ages for men and women, by birth cohort.

Men – linear models		
	HR (95% CI)	
Age, years	**1930-1951**	**1952+**
7	1.12 (1.10-1.15)	1.17 (1.11-1.24)
8	1.14 (1.12-1.17)	1.19 (1.12-1.26)
9	1.15 (1.12-1.18)	1.21 (1.15-1.29)
10	1.15 (1.13-1.18)	1.22 (1.15-1.30)
11	1.17 (1.14-1.20)	1.24 (1.17-1.31)
12	1.18 (1.15-1.21)	1.24 (1.17-1.31)
13	1.19 (1.16-1.22)	1.22 (1.15-1.29)
Women – BMI z-score <0[a]		
	HR (95% CI)	
Age, years	**1930-1951**	**1952+**
7	1.04 (0.99-1.10)	1.05 (0.89-1.23)
8	1.05 (0.99-1.12)	1.03 (0.88-1.21)
9	1.06 (0.99-1.12)	1.05 (0.89-1.24)
10	1.07 (1.01-1.14)	1.14 (0.96-1.35)
11	1.05 (0.99-1.12)	1.08 (0.91-1.28)
12	1.04 (0.98-1.11)	1.10 (0.93-1.30)
13	1.04 (0.98-1.11)	1.04 (0.88-1.23)
Women – BMI z-score >0[a]		
	HR (95% CI)	
Age, years	**1930-1951**	**1952+**
7	1.13 (1.07-1.20)	1.13 (0.98-1.31)
8	1.15 (1.08-1.21)	1.19 (1.03-1.37)
9	1.15 (1.09-1.22)	1.18 (1.01-1.36)
10	1.18 (1.12-1.25)	1.12 (0.96-1.30)
11	1.21 (1.14-1.28)	1.18 (1.02-1.38)
12	1.23 (1.16-1.30)	1.15 (0.99-1.34)
13	1.25 (1.19-1.32)	1.15 (0.99-1.34)

Abbreviations: CI, confidence interval; HR, hazard ratio
[a] Corresponding to slopes as shown in figure 2

Web Figure 1. Illustration of restricted cubic spline models for the associations (hazard ratios with 95% confidence intervals) between body mass index and future atrial fibrillation and atrial flutter in childhood at ages 7, 10, and 13 years for men and women separately.



Web Figure 2. Incidence rate of atrial fibrillation and atrial flutter by sex.