Atrial fibrillation and obesity—results of a meta-analysis

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Background Obesity has been shown to be associated with atrial enlargement and ventricular diastolic dysfunction, both of which are risk factors for atrial fibrillation (AF). However, the role of obesity as a risk factor for the development of AF is unknown. The study aims to evaluate the role of obesity as a risk factor for the development of AF.

Methods The MEDLINE/ PUBMED and Cochrane databases were searched for studies in human subjects published in English language between 1966 and May 2007. Studies were included in our analyses if they were population-based cohort or postcardiac surgery cohort and investigated the incidence of AF in relation to the body mass index (BMI) categories.

Results Of the 468 articles identified, 16 studies that enrolled a total of 123 249 individuals met the inclusion criteria. These 16 articles included 5 population-based cohort studies that enrolled 78 602 adult individuals from the United States and 3 European countries and 11 postcardiac surgery studies that enrolled 44 647 patients. Based on the population-based cohort studies, obese individuals have an associated 49% increased risk of developing AF compared to nonobese individuals (relative risk 1.49, 95% CI 1.36-1.64). The risk of AF increased in parallel with greater BMI in this cohort. In contrast, in the postcardiac surgery studies, obese individuals do not have an associated increased risk of developing AF compared to nonobese individuals (relative risk 1.02, 95% CI 0.99-1.06).

Conclusions Our findings demonstrate that obesity increased the risk of developing AF by 49% in the general population, and the risk escalated in parallel with increased BMI. Thus, AF evolves as yet another pathogenetic factor by which obesity may increase cardiovascular and cerebrovascular events. (Am Heart J 2008;155:310-5.)

The pathogenetic mechanisms tying obesity to an excessive cardiovascular morbidity and mortality are ill understood and may be multifactorial. Obesity has been clearly linked to the development of hypertension, coronary artery disease, diabetes mellitus, left ventricular hypertrophy, left atrial enlargement, ventricular diastolic dysfunction, congestive heart failure, and obstructive sleep apnea.[1-11] Moreover, an association between increased body mass index (BMI) and stroke has been reported in several studies.[12-15] Each 1-unit increase in BMI increased the risk of ischemic stroke by 4% and hemorrhagic stroke by 6%.[15] Obesity may increase the risk of stroke by multiple mechanisms, including by increasing the prevalence of atrial fibrillation (AF).

As the most common arrhythmic condition, currently affecting nearly 2.3 million people in the United States, AF is emerging as a major public health concern.[16-19] It is estimated that slightly <1% of the general population currently has AF, and the prevalence will increase 2.5-fold by the year 2050.[18,19] The prevalence of AF is on the rise, due, in part, to an aging general population and to increased longevity resulting from improved medical care among patients with coronary artery disease, hypertension, and heart failure—all chronic cardiac conditions that predispose to AF.[19] Atrial fibrillation has been established as an independent risk factor for stroke, increasing the risk by 3- to 5-fold.[20] Based on the Framingham Heart Study, AF increased the risk of all-cause mortality by 1.5- to 2-fold after adjusting for the preexisting cardiovascular conditions with which AF was related.[21] Therefore, both obesity and AF have to be considered as 2 contemporary epidemics associated with major morbidity and mortality.

Although obesity has been associated with many factors that contribute to the development of AF, there are only

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limited data available to date investigating the link between obesity and AF. This meta-analysis was designed to quantify the conditions of overweight and obesity as risk factors for AF.

Methods

Search strategy

Comprehensive searches of the MEDLINE and Cochrane databases were performed using Web-based search engines for human studies published in English between 1966 and May 2007. Search terms included *obesity*, *overweight*, *body mass index*, *arrhythmia*, *atrial fibrillation*, and their combinations. We checked the reference lists of reviewed articles, prior meta-analyses, and original studies identified by the search to find other potentially relevant studies.

Study selection

Studies were included in the analysis if they were either population-based cohort studies or postcardiac surgery studies that investigated the incidence of AF in relation to subjects' BMI. We include cardiac surgery studies in this analysis as comparison cohorts. Our hypothesis is that in cardiac surgery cohorts, increased BMI also increased the risk of developing AF as in the general population. However, we analyzed the general population and the postcardiac surgery cohorts separately. To be included, these studies must have used the standard World Health Organization (WHO) criteria to categorize their subjects' BMI or other clearly defined BMI category. Normal weight by the WHO criteria is defined as BMI of <25.0 kg/m^2; overweight, 25.0 to <30.0 kg/m^2; and obese, ≥ 30.0 kg/m^2. Both prospective and retrospective studies were included.

Data extraction and synthesis

We extracted the inclusion/exclusion criteria in each of the studies, publication year, the sample size, baseline characteristics, length of follow-up, and the incidence of AF in each BMI category in each of the studies. In this meta-analysis, we compared the risk of developing AF in the obese cohort (BMI ≥30 kg/m^2) versus the nonobese cohort (normal-weight and overweight individuals; BMI <30 kg/m^2). We also conducted a subanalysis to look into the graded-response relation between 3 BMI categories (normal weight vs overweight vs obese) and the risk of developing AF. Population-based and postoperative cohort studies were analyzed separately.

Statistical analysis

Meta-analysis of summary statistics from individual trials was performed with standard software (Stata 9.0, Stata Corporation, College Station, TX) using the METAN program.[22] The pooled effect of each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). Heterogeneity was assessed visually using Q (χ^2) statistics and/or the I^2 statistics.[23] If trials were homogeneous ($P > .05$), a fixed-effect model was used to calculate pooled effect sizes. Otherwise, a random-effect model of DerSimonian and Laird was applied to calculate overall differences. Publication bias was estimated using the weighted regression test of Egger. P value was considered significant at <.05.

Results

Study selection

Of the 468 identified articles from the search, 16 studies that enrolled a total of 123 249 individuals met the inclusion criteria and were included in the analysis. The rest of the studies did not meet our inclusion criteria because they either did not provide any data regarding the link between BMI categories and incidence of AF or did not provide clear BMI cutoffs for their BMI categories. These 16 articles consisted of 5 population-based cohort studies[24-28] that enrolled 78 602 adults from the United States and 3 European countries and 11 postcardiac surgery studies[29-39] that enrolled 44 647 patients. The average follow-up ranged from 4.7 to 25.2 years in the population-based cohort studies. In the postcardiac surgery studies, the rate of new-onset AF was reported mainly as part of perioperative complications (during index hospitalization).

Characteristics of the trials

Table I shows baseline characteristics of the studies and Table II shows baseline characteristics of the patients in each study that were included in this analysis. As expected, in both population-based cohorts and postcardiac surgery cohorts, diabetes and hypertension were more prevalent in the obese group than in the nonobese group (Table II). The mean age for the population-based cohorts was 56 ± 2 years, and 48% of these individuals were women. As these studies were not randomized controlled trials, the baseline characteristics of each study might not be well matched. The Swedish cohort study by Wilhemsen et al[24] and the postcardiac surgery study by Habib et al[36] were the only 2 studies that did not use the WHO criteria to categorize their subjects' BMI. The BMI cutoff for the obese group in the Swedish cohort study was ≥27 kg/m^2, whereas the BMI of >32 kg/m^2 was the cutoff for the obese group in the study by Habib et al (Table I). The mean age for the postcardiac surgery cohorts was 64 ± 2 years, and 27% of these patients were women.

Obesity and increased risk of developing AF

Based on the population-based cohort studies, obese individuals have an associated 49% increased risk of developing AF compared to nonobese individuals (Figure 1). There was no heterogeneity in this analysis ($P = .31$). In contrast, in the postcardiac surgery cohort, obesity did not confer an increased risk of developing AF, compared to nonobese individuals (Figure 1). Given significant heterogeneity in this analysis ($P = .0002$), we used a random-effects model to calculate effect sizes. There was no publication bias in the analysis based on either the Begg's test ($P = .224$) or the Egger's test ($P = .123$).

Table I. Baseline characteristics of the studies

Study	Year	Design	N	BMI cutoff for obese (kg/m^2)	Definition of AF
Population-based cohorts					
Wilhemsen et al (Swedish)	2001	Prospective	7437	≥27	AF on ECG
Wang et al (Framingham)	2004	Prospective	5282	≥30	AF or atrial flutter on ECG
Frost et al (Danish Diet, Cancer, and Health)	2005	Prospective	47589	≥30	AF or atrial flutter from outpatient or inpatient diagnoses
Murphy et al (Renfrew-Paisley)	2006	Prospective	15144	≥30	AF on ECG
Gami et al (Olmsted County)	2007	Retrospective	3150	>30	AF or atrial flutter on ECG
Postcardiac surgery cohorts					
Moulton et al	1996	Retrospective	2300	>30	Postoperative atrial arrhythmia
Engelman et al	1999	Prospective	5168	>30	Postoperative new-onset AF
Brandt et al	2001	Retrospective	500	≥30	Postoperative atrial arrhythmia
Kuduvalli et al	2002	Retrospective	4713	≥30	Postoperative atrial arrhythmia
Reeves et al	2003	Prospective	4372	≥30	Postoperative arrhythmia *
Orhan et al	2004	Retrospective	1206	>30	Postoperative AF
Zacharias et al	2005	Retrospective	8051	>30	Postoperative new-onset AF
Habib et al	2005	Retrospective	2780	>32	Postoperative AF
Pan et al	2006	Retrospective	9862	≥30	Postoperative AF or atrial flutter
Wigfield et al	2006	Retrospective	1727	>30	Postoperative AF
Yap et al	2007	Retrospective	3968	>30	Postoperative new atrial arrhythmia

ECG, Electrocardiogram.
*Ventricular tachycardia and ventricular fibrillation incidence are reported separately in this study.

Table II. Baseline characteristics of patients in the studies

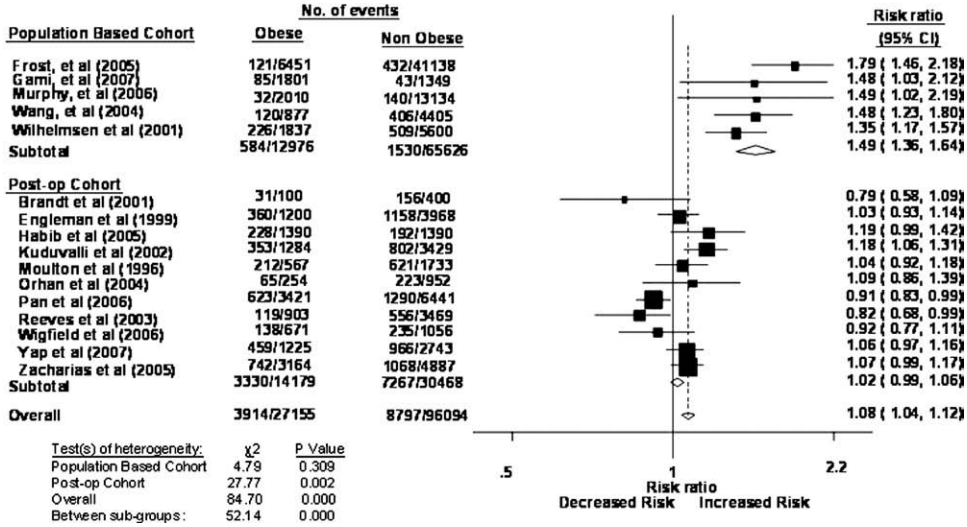
	n				Low EF (%) *		Diabetes (%)		HTN (%)	
Study	Nonobese	Obese	Age	Men (%)	Nonobese	Obese	Nonobese	Obese	Nonobese	Obese
Population-based cohorts										
Wilhemsen et al (Swedish)	5600	1837	NA	100	NA	NA	NA	NA	NA	NA
Wang et al (Framingham)	4405	877	57	45	1.0	1.0	5.7	13.5	NA	NA
Frost et al (Danish Diet, Cancer, and Health)	41138	6451	56	47	NA	NA	NA	NA	9.0	18.9
Murphy et al (Renfrew-Paisley)	13134	2010	54	46	NA	NA	1.1	2.1	NA	NA
Gami et al (Olmsted County)	1349	1801	50	66	NA	NA	5.0	15.3	21.8	41.0
Postcardiac surgery cohorts										
Moulton et al	1733	567	62	65	NA	NA	21.9	40.9	56.6	69.1
Engelman et al	3968	1200	NA	68	7.4	6.0	23.5	40.0	56.2	66.0
Brandt et al	400	100	64	80	NA	NA	18.0	73.0	71.0	85.0
Kuduvalli et al	3429	1284	63	80	8.9	9.7	14.3	22.2	47.2	59.4
Reeves et al	3469	903	68	81	5.4	3.8	14.8	20.2	55.7	61.8
Orhan et al	952	254	60	82	8.6	8.7	21.6	38.6	45.0	50.4
Zacharias et al	4887	3164	64	67	NA	NA	NA	NA	NA	NA
Habib et al	1390	1390	61	67	NA	NA	NA	NA	NA	NA
Pan et al	6441	3421	63	75	38.9	37.1	29.6	42.8	70.3	81.3
Wigfield et al	1056	671	63	73	NA	NA	22.4	39.8	63.3	76.9
Yap et al	2743	1225	65	73	9.2	8.2	20.3	33.1	63.2	74.9

EF, Ejection fraction; *HTN*, hypertension; *NA*, not applicable.
* Defined as prior congestive heart failure diagnosis in Wang et al; EF of <30% in Engelman et al, Kuduvalli et al, Reeves et al, and Yap et al; EF of <40% in Orhan et al; and EF of <50% in Pan et al.

Subgroup analysis

In addition, we performed a subgroup analysis for both population-based studies and postcardiac surgery studies that reported results for the 3 BMI categories.[25-28] The results showed that there was a graded relationship between increased BMI and increased risk of AF in the general population (Table III). In the population-based cohorts, compared to normal-weight cohort, the overweight cohort had a 39% increased risk of developing AF, whereas the obese cohort had an 87% increased risk of

Figure 1



Risk ratio of being obese for developing AF compared to the that of being nonobese. See Table I for expansions of study names. The sizes of the data markers relate to study sample size and the inverse of the SE of each study.

Table III. Graded relationship between increased BMI and increased risk of atrial fibrillation in the general population

	Incidence of AF			RR (95% CI)*	
Parameter	**Normal weight (%)**	**Overweight (%)**	**Obese (%)**	**Overweight**	**Obese**
Overall †	407/30597 (1.3%)	614/29429 (2.1%)	358/11139 (3.2%)	1.39 (1.05-1.83)	1.87 (1.43-2.44)
Men ‡	188/11654 (1.6%)	398/15917 (2.5%)	156/4287 (3.6%)	1.40 (1.04-1.90)	1.71 (1.04-2.84)
Women ‡	201/18464 (1.1%)	191/12642 (1.5%)	117/5051 (2.3%)	1.44 (1.11-1.86)	2.01 (1.61-2.51)

*RR is in reference to the normal-weight cohort.
†Based on data in studies by Frost et al,[26] Gami et al,[28] Murphy et al,[27] and Wang et al.[25]
‡Based on data in studies by Frost et al,[26] Murphy et al,[27] and Wang et al.[25]

developing AF (Table III). When compared to the overweight cohort, the obese cohort has an associated 32% increased risk of developing AF. However, we did not find this graded relationship in the postcardiac surgery cohorts.

Sex differences

In the 3 large population-based cohort studies that reported the sex differences and[25-27] enrolled 68 273 individuals, the relationship between the 3 BMI categories and the risk of developing AF was similar in both women and men. The graded relationship between increasing BMI category and the increased risk of developing AF was also seen in both sex groups, with a somewhat larger effect in obese women than in obese men (Table III). Among men, compared to the normal-weight cohort, the overweight cohort has an associated 40% increased risk of AF, whereas the obese cohort has an associated 71% increased risk of AF (Table III). Similarly among women, compared to the normal-weight cohort, the overweight cohort has an associated 44% increased risk of developing AF, whereas the obese cohort has an associated 101% increased risk of developing AF (Table III). No sex-specific data were available in the postcardiac surgery cohorts.

Discussion

Our meta-analysis of the available data shows that the presence of overweight and obesity increases the risk of AF in the general population. This relationship was strengthened by the finding of a classification-dependent relationship between BMI and the risk of developing AF. Furthermore, these findings were consistent for both men and women.

The electrophysiologic mechanisms by which obesity may lead to AF remain to be elucidated. Traditionally, obesity is thought to be an indirect cause of heart disease

through either hemodynamic (increased heart rate, stroke volume, and blood pressure) or metabolic (dyslipidemic) derangements.[5-7,10,40] It seems likely that eccentric left ventricular hypertrophy (thickening of chamber walls and chamber dilatation) with resultant progressive atrial dilatation may play a role.[3,7,11,40-43] Another potential mechanism for the left atrial enlargement in obese patients is increased total blood volume.[7,40,44] In addition, obesity commonly clusters with the metabolic syndrome, diabetes, hypertension, and obstructive sleep apnea, all of which may contribute to the development of AF.[1,2,5,9,28,40,45] Obstructive sleep apnea may be an important mediator of the risk of AF conferred by obesity.[46] Sleep apnea causes nocturnal oxygen desaturations, significant fluctuations in sympathetic and parasympathetic activity, and changes in intrathoracic pressure. It is associated with increased daytime sympathetic tone, left ventricular dysfunction, and increased left atrial size. Nevertheless, it is difficult to differentiate the effects of obesity from the effects of obstructive sleep apnea. The one study that included patients with overnight sleep studies, and thus was able to confirm or rule out the presence of obstructive sleep apnea, found that BMI and the apnea-hypopnea index contributed to the risk of AF in an additive fashion and that nocturnal oxygen desaturation and BMI both independently increased the risk of AF.[28] Thus, with the limited data available, it seems that obesity may act independently of obstructive sleep apnea but that both are important risk factors or risk markers for AF.

In contrast to these traditional concepts, a more recent theory based on animal studies suggested that excessive deposits of lipids within myocardial tissue (direct cardiac lipotoxicity) may be an important pathogenetic cause of left ventricular remodeling and nonischemic dilated cardiomyopathy.[7] Similar pathology may occur in the atria.

Atrial fibrillation is the most common complication associated with coronary artery bypass graft surgery.[47] Despite significance advances in surgical care, AF incidence remains around 20% to 40%, although this is due, in part, to a somewhat older population of patients undergoing coronary artery bypass graft.[47] Unexpectedly, based on our findings in the postcardiac surgery patient population, obesity did not confer an increased risk of AF. The reason for this is unclear, but it may be related to a selection bias of patients undergoing cardiac surgery. Because obesity per se is considered a major risk for cardiac surgery, obese patients may have been preselected to avoid potential complications. It is also possible that the disease mechanisms for AF are different between the general population and the postcardiac surgery cohorts. Proposed mechanisms for postcardiac surgery AF include neurohormonal activation, volume overload, and inflammation.[48]

Study limitations

As with other meta-analyses, given the lack of data in each trial, we were not able to adjust our overall analysis for concomitant risk factors, medication use, left atrial size, left ventricular ejection fraction, and obstructive sleep apnea. Given the limitations, this study is hypothesis-generating only. A prospective study needs to be conducted to confirm our findings.

Conclusions

Our data demonstrate that obesity increased the risk of developing AF by 49% in the general population. In contrast, in the postcardiac surgery population, obesity was not shown to increase the risk of developing AF. Thus, AF evolves as yet another pathogenetic factor by which obesity may increase cardiovascular and cerebrovascular events.

Drs Wanahita, Bangalore, and Messerli had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Wanahita, Bangalore, and Messerli contributed in the study concept and design, in the analysis and interpretation of data, and in the drafting of the manuscript; Drs Wanahita, Bangalore, Gami, and Somers, in the acquisition of data; Drs Wanahita, Bangalore, Messerli, Gami, Somers, and Steinberg, in the critical revision of the manuscript for important intellectual content; Drs Wanahita and Bangalore, in the statistical analysis; and Drs Messerli and Steinberg, in the study supervision.

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