ASSOCIATIONS OF EPICARDIAL, ABDOMINAL AND OVERALL ADIPOSITY WITH ATRIAL FIBRILLATION

Short Title: Wong *et al. Epicardial Fat & Atrial Fibrillation*

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ABSTRACT

Background: While adiposity is increasingly recognized as a risk factor for atrial fibrillation (AF), the importance of epicardial fat compared to other adipose tissue depots remains uncertain. We sought to characterize and compare the associations of AF with epicardial fat and measures of abdominal and overall adiposity.

Methods and Results: We conducted a meta-analysis of 63 observational studies including 352,275 individuals, comparing AF risk for one-standard deviation (1-SD) increases in epicardial fat, waist circumference (WC), waist-to-hip ratio (WHR) and body mass index (BMI). A 1-SD higher epicardial fat volume was associated with a 2.6-fold higher odds of AF (OR 2.61, 95% CI 1.89-3.60), 2.1-fold higher odds of paroxysmal AF (OR 2.14, 95% CI 1.45-3.16) and 5.4-fold higher odds of persistent AF (OR 5.43, 95% CI 3.24-9.12) compared with sinus rhythm. Likewise, a 1-SD higher epicardial fat volume was associated with 2.2-fold higher odds of persistent compared to paroxysmal AF (OR 2.19, 95% CI 1.66-2.88). Similar associations existed for post-ablation, post-operative and post-cardioversion AF. In contrast, associations of abdominal and overall adiposity with AF were less extreme, with relative risks per 1-SD higher values of 1.32 (95% CI 1.25-1.41) for WC, 1.11 (95% CI 1.08-1.14) for WHR, and 1.22 (95% CI 1.17-1.27) for BMI.

Conclusions: Strong and graded associations were observed between increasing epicardial fat and AF. Moreover, the strength of associations of AF with epicardial fat is greater than for measures of abdominal or overall adiposity. Further studies are needed to assess the mechanisms and clinical relevance of epicardial fat.

Keywords: atrial fibrillation; obesity; epicardial fat; ectopic adipose tissue, visceral adiposity.

INTRODUCTION

Obesity is increasingly recognized as an important and modifiable determinant of atrial fibrillation (AF), which is the most common cardiac arrhythmia.[1-5] However, the mechanisms through which obesity causes AF are not fully understood. Previous studies have demonstrated that obesity is associated with diastolic dysfunction, atrial inflammation, myocardial lipidosis, and atrial contractile dysfunction.[6-10] Such changes may result in atrial structural remodeling (including diffuse atrial fibrosis and dilatation), and electrophysiological abnormalities (including conduction slowing and shortened atrial effective refractory periods).[7, 8] It is possible that these changes may contribute to an arrhythmogenic atrial substrate that promotes AF.

Epicardial fat, an ectopic adipose tissue, is a metabolically active tissue that produces cytokines and chemokines that may enhance atrial arrhythmogenesis. Previous studies have suggested that biomarkers of inflammation (including IL-1β, TNF-α) may promote atrial fibrosis via paracrine effects on the adjacent myocardium, and cause micro-reentry circuits via fatty infiltration that interrupt conduction wavefronts.[11, 12] Population studies have also demonstrated independent associations of epicardial fat with atrial conduction properties.[13] While associations between epicardial fat and AF have been reported, suggesting that epicardial fat may mediate the relationship between overall adiposity and AF, the results of individual studies have not been entirely consistent.[14-17] Hence, we conducted a meta-analysis of all observational studies reporting associations between epicardial fat and AF to clarify the strength of the associations between epicardial fat with AF, to determine the extent to which these associations vary in different clinical settings, and to explore any reasons for between-study heterogeneity. Moreover, we compared the

strength of the associations of AF with other measures of adiposity, including abdominal and overall adiposity.

METHODS

This systematic review and meta-analysis was performed in accordance with both the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Search strategy and eligibility criteria

We performed a systematic search of observational studies in MEDLINE and EMBASE databases available to July 2015. This search was supplemented by manual hand-searching of the reference lists from individual studies, review articles and conference proceedings. Search terms included epicardial, pericardial, fat, adipose, ectopic, visceral, body mass index (BMI), waist circumference (WC), waist-hip ratio, waist-to-hip ratio (WHR), AF and their combinations. Studies were included if they were cross-sectional, case-control or cohort studies that allowed for an assessment of associations between continuous measures of adiposity (epicardial fat, pericardial fat, WC, WHR or BMI) and AF risk. We also included studies reporting data that allowed for an assessment of associations of epicardial fat with the severity of AF (persistent versus paroxysmal) and AF in different clinical settings (post-ablation, post-cardiac surgery or post-cardioversion). Definitions of epicardial and pericardial fat varied between studies.[11] In sub-group analyses, however, we considered studies to have quantified epicardial fat if they described measurement of adiposity between the myocardium and visceral pericardium.[11] Human studies reporting data in any language were included. Two investigators independently performed the

searches and reviewed all identified studies for inclusion. The decision to include studies was hierarchical, initially based on the study title, followed by abstract and then full-text review of each remaining article.

Data extraction

Data from included studies were extracted independently by two investigators using a standard protocol. Data were extracted (where available and applicable) on study data reported (AF risk, AF severity, post-ablation AF, post-operative AF, or post-cardioversion AF), study characteristics (year, region, design), adiposity measurement (epicardial fat, WC, WHR, BMI), epicardial fat type (epicardial fat, pericardial fat, or unspecified), epicardial fat location (total, peri-atrial, peri-ventricular fat, or unspecified), imaging modality (magnetic resonance imaging [MRI], computed tomography [CT], or echocardiography), epicardial fat measurement method (volume, thickness, or area), number of AF cases, mean and variance of epicardial fat in each group, risk estimates and covariates adjusted for in any multivariate models.

Statistical analysis

Risk estimates and confidence intervals (CI) for the associations of AF with adiposity measures were extracted from each study where available and log-transformed. For each study, the risk estimates from the most fully adjusted models were abstracted. For studies that only reported relative risks (RR) in subgroups, we used fixed-effects meta-analysis to generate an overall study-level RR. Where mean and variance for group-specific epicardial fat depots were provided instead of risk estimates, standardized mean differences were computed and log-transformed. To facilitate standardized comparisons, risk estimates and

their CIs were re-scaled to correspond to a one-standard deviation (1-SD) increase where necessary. Overall summary estimates were subsequently calculated using random effects meta-analysis. Overall summary RRs are presented with 95% CI; all other RRs are presented with 99% CIs. For primary epicardial fat analyses, we restricted meta-analysis to studies that used either MRI or CT to measure epicardial fat volumes since echocardiography can only measure pericardial separation, not all of which may be adipose tissue, and epicardial fat thickness and area do not necessarily reflect epicardial fat volume.[1] Heterogeneity across studies was quantified using I^2 statistics and was explored using subgroup analyses, sensitivity analyses and meta-regression techniques. Epicardial fat study characteristics considered as possible sources of heterogeneity included study year, study type, prospective design, study region, imaging modality, measurement method, fat definition, fat location, sample size, publication status and covariate adjustment. As sensitivity epicardial fat analyses, we tested (i) the effect of including studies that used echocardiography; and (ii) the effect of excluding individual studies; and (iii) tested the effect of excluding studies considered to be at higher risk of bias. We screened for small-study effects that might be attributable to publication bias using funnel plots of effect size plotted against standard error, Egger's test, Begg's test; where present, the effect of this was characterized using trim-and-fill procedures. All analyses were performed using Stata 13.0 (Stata Corporation) and R 3.2.1 (R Project), and a 2-tailed value of $p<0.05$ was considered statistically significant.

RESULTS

Included studies

The systematic search of electronic databases identified 3,146 reports, from which we identified 670 potentially relevant studies for full-text review (Figure 1). An additional 12 studies were identified by manual searching of reference lists. A total of 63 eligible studies, involving 352,725 individuals, were included: 34 on epicardial fat (Table 1)[14-47], 5 on WC and/or WHR (Tables 2 & 3 respectively)[48-52], and 24 on BMI (Table 4)[49, 50, 52-72]. From these studies, 34, 5, 4 and 25 separate risk estimates for associations of AF with epicardial fat, WC, WHR and BMI respectively were available for pooling. Among the 34 epicardial fat studies, 23 studies used CT to quantify epicardial fat depots, 3 used MRI and 8 used echocardiography. Among these 34 studies, 21 measured volume, 11 measured thickness and 2 measured area. The primary epicardial fat analysis was restricted to 21 studies involving 16,496 individuals, and the secondary analysis included 13 further studies (that used echocardiography, or measured epicardial fat thickness or area) involving an additional 4,286 individuals.

Associations of epicardial fat with the presence and severity of AF

The overall pooled summary of 10 separate risk estimates from MRI and CT studies indicated that a 1-SD higher in epicardial fat volume was associated with 2.6-fold higher odds of any AF (OR 2.61, 95% CI 1.89-3.60; Figure 2A). A total of 14 risk estimates from MRI and CT studies were available on the association between epicardial fat volume and the presence of paroxysmal and persistent AF compared to sinus rhythm. A 1-SD higher epicardial fat volume was associated with 2.1-fold higher odds of paroxysmal AF (OR 2.14, 95% CI 1.45-3.16) and 5.4-fold higher odds of persistent AF (OR 5.43, 95% CI 3.24-9.12;

Figure 2C) compared to sinus rhythm. Eleven risk estimates from MRI and CT studies were available on the association between epicardial fat volume and persistent AF compared to paroxysmal AF. Likewise, a 1-SD higher epicardial fat volume was associated with 2.2-fold higher odds of persistent AF relative to paroxysmal AF (OR 2.19, 95% CI 1.68-2.88; Figure 2B).

Heterogeneity was observed in some of the above meta-analyses (I^2 statistics: any AF 80% p<0.001, AF severity 28% p=0.18, post-procedural AF 76% p<0.001). Table 5 displays the results of subgroup analyses exploring the sources of this heterogeneity, which suggest that this may reflect differences in fat quantification (epicardial or pericardial fat), covariates used for adjustment, study region, and study type. Sensitivity analyses including studies that either used echocardiography or non-volumetric methods (thickness or area) to quantify epicardial fat resulted in greater heterogeneity and more extreme associations (Table 6). Estimates were consistent in other sensitivity analyses excluding individual studies and those studies at higher risk of bias (Supplementary Tables 1-5). Although meta-regression techniques did not suggest sample size significantly contributed to heterogeneity, funnel plots indicated the presence of small study effects (Supplementary Figures 1-4). Trim and fill methods accounting for these effects attenuated overall estimates though they remained statistically significant.

Associations of epicardial fat with post-procedural AF

A total of 13 post-procedural studies were identified. Among the 11 studies of the association of epicardial fat volume with post-ablation AF, a 1-SD higher epicardial fat volume was associated with 2.7-fold higher odds of post-ablation AF (OR 2.69, 95% CI

1.66-4.07; Figure 2D). Two studies assessed the association between epicardial fat and post-operative AF, where a 1-SD higher epicardial fat volume was associated with 2.2-fold higher odds of post-operative AF (OR 2.24, 95% CI 1.23-4.05; Figure 2D). A single study also reported a significant association between epicardial fat thickness and post-cardioversion AF (OR 2.01, 95% CI 1.15-3.53). Overall, 1-SD higher in epicardial fat volume was associated with 2.5-fold higher odds of any post-procedural AF (OR 2.49, 95% CI 1.72-3.49; Figure 2D).

Heterogeneity was observed in the meta-analysis of post-ablation AF studies (I^2 statistics: post-ablation AF 78% p<0.001, post-operative AF 61% p=0.11). Subgroup analyses exploring this heterogeneity suggested this may be in-part due to study region. Sensitivity analyses including studies that either used echocardiography or non-volumetric methods to quantify epicardial fat similarly increased summary estimates and heterogeneity (Table 6). Estimates were consistent with other sensitivity analyses excluding individual studies and studies at higher risk of bias (Supplementary Tables 6-10). Meta-regression did not suggest sample size significantly contributed to heterogeneity. There was some evidence of small study effects as seen in funnel plot asymmetry, and trim and fill methods accounting for this attenuated overall estimates though they remained significant (Supplementary Figures 5 and 6).

Associations of abdominal and overall adiposity with AF

Five studies examined the associations between abdominal adiposity with any AF; RRs per 1-SD higher measure were 1.32 (95% CI 1.25-1.41) for WC and 1.11 (95% CI 1.08-1.14) for WHR (Figure 3). From 24 separate risk estimates, a 1-SD higher in BMI was similarly

associated with a 1.2-fold greater risk of any AF (RR 1.22, 95% CI-1.17-1.27; Figure 4). There was heterogeneity in associations of BMI (I^2 statistic 81% p<0.001) but not of WC and WHR (I^2 statistics 34% p=0.20 and 0% p=0.65 respectively).

DISCUSSION

Major findings

This meta-analysis of 63 studies, involving 352,275 individuals, demonstrated strong and graded associations between higher epicardial fat volumes and risk of AF. Importantly, higher epicardial fat volume was also associated with greater severity of AF (persistent compared to paroxysmal AF). Similar associations were observed for post-ablation, post-operative and post-cardioversion AF. Moreover, all of these associations with epicardial fat were stronger than those for either abdominal or overall adiposity.

Potential pathogenicity of epicardial fat

The epidemiologic burden of AF is increasing, and previous reports have estimated that obesity may account for one-fifth of cases and 60% of the recent increase in AF cases.[73-77] In view of the substantial attributable risk of AF due to obesity, the potential role of epicardial fat in mediating the relationships between overall adiposity and AF has prompted considerable interest in this hypothesis.[1, 11, 13] The importance of ectopic fat depots has been previously demonstrated in other cardiometabolic disorders.[78] Such ectopic adipose tissue may have distinct biologic properties compared to subcutaneous adiposity, and the unfavorable distribution of such fat depots may in-part explain the variable cardiometabolic risk seen in individuals with similar degrees of overall adiposity. As with other ectopic adipose tissue, there is growing body of evidence from basic and clinical studies

suggesting a role for epicardial fat in arrhythmogenesis.[1, 11, 12] Crucially, the anatomical proximity of the epicardial fat to the adjacent myocardium, given the lack of fascia boundaries, may facilitate pathogenic interaction. Subsequent structural remodeling, similar to that observed in other AF substrates, may create the electrical heterogeneity conducive to arrhythmogenesis.[79, 80]

Epicardial fat and atrial fibrillation

The increasing recognition of the potential pathogenicity of ectopic fat, together with increased availability of imaging modalities, has prompted further studies to quantify ectopic fat depots and characterize clinically relevant disease associations. In an analysis from the Framingham Heart Study, pericardial fat volume was associated with prevalent AF even after adjusting for AF risk factors, body mass index and other ectopic fat depots.[17] Epicardial fat has also been shown to be associated with increasing AF severity and post-ablation AF.[14-16] However, these findings have not been invariably confirmed in other reports. In one large prospective cohort, epicardial fat was not associated with incident AF after adjusting for AF risk factors.[26] Likewise, other investigators have not demonstrated significant associations between epicardial fat and paroxysmal AF or post-ablation AF.[17, 21, 28, 30]

Hence, we conducted this meta-analysis to clarify this uncertainty and confirmed an association between increasing epicardial fat and any AF. Furthermore, there was also an association between epicardial fat and increasing AF burden (i.e., increasing epicardial fat being associated with the presence of more severe persistent AF compared to paroxysmal AF). This may potentially explain why some individual studies failed to demonstrate

significant associations between epicardial fat and the presence of paroxysmal AF compared to sinus rhythm. With greater statistical power than individual studies, our analyses also showed a relationship between epicardial fat and paroxysmal AF, although the effect estimate for this relationship was smaller than the association between epicardial fat and persistent AF, consistent with a dose-response relationship between epicardial fat and the increasingly severe continuum from paroxysmal to persistent AF.

Associations were similarly observed between increasing epicardial fat depots and post-procedural AF, including after catheter ablation, cardiac surgery, and electrical cardioversion. The consistency of associations across different clinical settings may be supportive of a true arrhythmogenic effect of epicardial fat. Furthermore, these associations appeared to be stronger than those of abdominal and overall adiposity. Taken together, these data support the possibility that epicardial fat may mediate observed associations between overall adiposity and AF.

We have shown previously that intensive risk factor modification and weight reduction may be of benefit in both preventing the development of AF and managing patients with established AF.[81-83] The increasing clinical availability of imaging modalities, including those undertaken for other indications, may be opportunities to assess epicardial fat depots that could have cardiometabolic implications beyond AF.[78] It is possible that increased epicardial fat could identify patients who may potentially benefit from intensive risk factor modification and weight reduction, although this remains to be proven and requires further study.[82-85]

In interpreting the above, a number of other findings are worthy of discussion. Effect estimates were smaller in studies quantifying pericardial fat compared to those studies measuring epicardial fat. This is consistent with a more biologically plausible effect of the anatomically contiguous epicardial fat, and the inclusion of less relevant paracardial adiposity in studies that measured pericardial fat may be attenuating associations between epicardial fat and AF. Interestingly, epicardial fat associations also appeared to differ by geographic region, with effect estimates in studies from Asia being stronger than those from North America or Europe. Racial differences in body composition are well-established, and individuals of Asian descent have greater cardiovascular morbidity with lower amounts of overall and abdominal adiposity. It may be possible that ectopic adipose tissue has similar race-specific associations with cardiovascular disease, though this hypothesis requires further exploration in future studies.

Study limitations

The present review had a number of limitations that warrant discussion. We restricted the primary epicardial fat analyses to studies using MRI or CT to measure epicardial fat volume given limitations in echocardiographic and non-volumetric methods of quantifying epicardial fat outlined previously. Additional sensitivity analyses including studies that used such methods were associated with greater heterogeneity and more extreme estimates of risk. Thus, the present study suggests that volumetric quantification of epicardial fat using CT or MRI may be more reliable for studying disease associations. We explored potential reasons between-study heterogeneity in epicardial fat studies where possible, including that due to fat type, study region, study design and covariate adjustment (heterogeneity in overall adiposity studies is explored elsewhere).[3] Associations were more extreme in those

epicardial fat studies that did not adjust for other risk factors for cardiovascular disease, indicating confounding by other AF risk factors. While overall epicardial fat summary estimates were attenuated after adjustment for confounding, the associations remained significant in analyses restricted to studies reporting multivariable-adjusted results, though we cannot exclude residual confounding by unmeasured variables. We suspect that other between-study variation in epicardial fat quantification that we were unable to characterize may be also in-part responsible for heterogeneity. There was also evidence of small study effects, and while trim and fill methods adjusting for these did not materially affect summary estimates, the possibility of publication bias also cannot be eliminated. Given the resource required to image epicardial fat and analyze large datasets for population associations, few included studies had prospective or cohort study designs. While our findings represent the best-available estimates, future cohort studies are warranted to further to evaluate the relative and absolute risks of AF associated with increments in epicardial fat, overall and in age-specific groups after adjustment for known risk factors for vascular disease, to assess the clinical relevance of these associations. Finally, given the variable definition and use of the terms epicardial and pericardial fat, we also chose to include studies purporting to measure either ectopic fat depot. Any true effect is likely to be due to the more biologically plausible epicardial fat though, and sensitivity analyses in the present report support this suggestion. However, these observational studies cannot exclude the possibility that epicardial fat is merely a marker of AF rather than being causal.

Conclusion

The present meta-analysis demonstrated significant and graded associations between increasing epicardial fat and AF in multiple clinical settings. The associations appeared stronger than those of abdominal and overall adiposity with AF. Recognizing the importance of epicardial fat as source of adipokines and cytokines, the results of this meta-analysis support the possibility that epicardial fat may mediate the relationships between overall adiposity and arrhythmogenesis. Further studies are needed to assess causality, potential mechanisms, and the relevance and use of epicardial fat measurement in clinical practice.

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DISCLOSURES

Dr Selvanayagam reports lecture and/or consulting fees from Medtronic, St Jude Medical, Bayer, Siemens, Toshiba and Biotronik. Dr Selvanayagam reports having received research funding from Bayer and Biotronik. Dr Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, and St Jude Medical, and having received lecture and/or consulting fees from Biosense-Webster, Medtronic, and St Jude Medical. Dr Sanders reports having received research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik and Sorin.

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Table 1: Characteristics of epicardial fat studies

Study reference	Year	Number and type of patients included	AF follow-up type	AF at follow-up	Measurement method	Other covariates in model
CT Studies						
Al Chekakie[15]	2010	197 atrial fibrillation (126 paroxysmal, 71 persistent), 76 sinus rhythm	N/A	N/A	Volume	Age, sex, structural heart disease, hypertension, diabetes, left atrial diameter, body mass index, ejection fraction
Batal[16]	2010	96 atrial fibrillation (60 paroxysmal, 36 persistent), 73 sinus rhythm	N/A	N/A	Thickness	N/A
Drossos[18]	2014	83 sinus rhythm	Cardiac surgery	28 (34%)	Volume	Hypertension, peripheral vascular disease, left atrial size, antihypertensive medication use
Evranos[19]	2013	60 atrial fibrillation	Cryoablation	12 (21%)	Thickness	N/A
Girerd[20]	2013	49 atrial fibrillation (25 paroxysmal, 24 persistent)	N/A	N/A	Volume	N/A
Greif[21]	2013	354 atrial fibrillation (223 paroxysmal, 131 persistent), 934 sinus rhythm	N/A	N/A	Volume	N/A
Kanazawa[22]	2014	120 atrial fibrillation (80 paroxysmal, 40 persistent), 120 sinus rhythm	N/A	N/A	Volume	Body mass index, left atrial diameter, brain natriuretic peptide
Kanmanthareddy[23]	2014	522 atrial fibrillation (136 paroxysmal, 386 persistent)	N/A	N/A	Volume	N/A
Kawakami[24]	2013	95 atrial fibrillation	Radiofrequency catheter ablation	43 (45%)	Volume	Not stated
Kim[25]	2014	665 atrial fibrillation (450 paroxysmal, 215 persistent)	N/A	N/A	Volume	N/A
Mahabadi[26]	2014	96 atrial fibrillation, 3371 sinus rhythm	N/A	N/A	Volume	Age, sex, body mass index, antihypertensive treatment, left atrial area
Murakami[27]	2012	38 atrial fibrillation	Radiofrequency catheter ablation	12 (32%)	Volume	N/A
Nagashima[28]	2011	40 atrial fibrillation (24 paroxysmal, 16 persistent), 37 sinus rhythm	Radiofrequency catheter ablation	15 (38%)	Volume	N/A
Nakanishi[29]	2012	17 atrial fibrillation, 262 sinus rhythm	N/A	N/A	Volume	N/A
Nakatani[30]	2011	55 atrial fibrillation	Radiofrequency catheter ablation	10 (18%)	Volume	N/A
Opolski[31]	2015	102 sinus rhythm	Cardiac surgery	24 (24%)	Volume	Body mass index, atrial dimensions, pulmonary vein dimensions
Park[32]	2014	33 atrial fibrillation (13 paroxysmal, 20 persistent)	N/A	N/A	Thickness	N/A
Shin[33]	2011	80 atrial fibrillation (40 paroxysmal, 40	N/A	N/A	Volume	N/A

		persistent), 80 sinus rhythm				
Soucek[34]	2014	102 atrial fibrillation (74 paroxysmal, 28 persistent)	Radiofrequency catheter ablation	27 (26%)	Volume	Not stated
Thanassoulis[17]	2010	54 atrial fibrillation, 3163 sinus rhythm	N/A	N/A	Volume	Age, sex, blood pressure, antihypertensive treatment, PR interval, valvular disease, body mass index, intrathoracic fat, visceral fat
Tsao[35]	2011	68 atrial fibrillation, 34 sinus rhythm	Radiofrequency catheter ablation	24 (35%)	Volume	N/A
Yokoyama[36]	2012	19 atrial fibrillation	Radiofrequency catheter ablation	9 (47%)	Volume	N/A
Yorgun[37]	2014	426 atrial fibrillation (169 paroxysmal, 257 persistent), 192 sinus rhythm	N/A	N/A	Thickness	N/A
MRI Studies						
Muhib[38]	2013	10 atrial fibrillation, 52 sinus rhythm	N/A	N/A	Area	Age, sex, blood pressure, antihypertensive treatment, PR interval, valvular disease, body mass index
Tereshchenko[39]	2014	12 atrial fibrillation, 15 sinus rhythm	N/A	N/A	Area	N/A
Wong[14]	2011	102 atrial fibrillation (38 paroxysmal, 64 persistent), 20 sinus rhythm	Radiofrequency catheter ablation	79 (64%)	Volume	Sex, left atrial volume, left ventricular dysfunction, obstructive sleep apnea, body mass, valvular disease, AF chronicity
Echocardiography Studies						
Acet[40]	2014	154 atrial fibrillation (71 paroxysmal, 63 persistent), 63 sinus rhythm	N/A	N/A	Thickness	N/A
Aribas[41]	2014	54 atrial fibrillation, 60 sinus rhythm	N/A	N/A	Thickness	N/A
Chao[42]	2013	283 atrial fibrillation (227 paroxysmal, 56 persistent)	Radiofrequency catheter ablation	56 (33%)	Thickness	N/A
Cho[43]	2014	163 atrial fibrillation	Electrical cardioversion	85 (52%)	Thickness	N/A
Ekinci[44]	2011	24 atrial fibrillation, 22 sinus rhythm	N/A	N/A	Thickness	N/A
Iacobellis[45]	2014	84 atrial fibrillation (64 paroxysmal, 20 persistent)	N/A	N/A	Thickness	N/A
Kurt[46]	2012	58 atrial fibrillation (17 paroxysmal, 41 persistent), 22 sinus rhythm	N/A	N/A	Thickness	N/A
Yener[47]	2014	80 sinus rhythm	Cardiac surgery	30 (38%)	Thickness	N/A

AF = atrial fibrillation, CT = computed tomography, MRI = magnetic resonance imaging, N/A = not applicable. See Web Appendix for references for included studies.

Table 2: Characteristics of Waist Circumference Studies

Study reference	Year	Cohort source	Study design	Subjects (% women)	Mean age (years)	Mean waist circumference (SD)	AF cases (%)	Other covariates in the model
Frost[48]	2014	Diet, Cancer and Health Study	Prospective cohort	55,273 (52.4)	56.1	88.7 (12.7)	2,581 (4.7)	smoking status, fruit and vegetable intake, alcohol consumption, physical activity, total energy intake, educational level, hypertension, diabetes mellitus, hypercholesterolemia, ischemic heart disease, congestive heart failure, and valvular heart disease
Knuiman[49]	2014	Busselton Health Study	Prospective cohort	4,267 (56.4)	52	83 (13)	343 (8.0)	age, sex, height
Long[50]	2011	Guangzhou Biobank Cohort Study	Nested case-control	20,430 (71.2)	65.7 AF, 62.1 no AF	84.0 (10.2) AF, 81.5 (8.9) no AF	159 (0.8)	sex, age, drinking, smoking, hyperthyroidism, diabetes, hypertension, and total cholesterol
Nystrom[51]	2015	60-year Old Men and Women from Stockholm Study	Prospective cohort	4,021 (52.2)	60	97.5 (10.2) men, 86.5 (11.6) women	285 (7.1)	hypertension, elevated fasting glucose, sex, smoking, alcohol intake, history of myocardial infarction, regular moderate-intensity physical activity, and Swedish-born
Zhang[52]	2009	China Multi-center Collaborative study of Cardiovascular Epidemiology	Cross-sectional	18,615 (55.7)	56	81.9 (9.9)	194 (1.0)	age, electrocardiographic left ventricular hypertrophy, regular use of cigarettes and alcohol, history of myocardial infarction and history of doctor-diagnosed diabetes

AF = atrial fibrillation, SD = standard deviation.

Table 3: Characteristics of Waist-to-Hip Ratio Studies

Study reference	Year	Cohort source	Study design	Subjects (% women)	Mean age (years)	Waist-to-hip ratio (SD)	AF cases (%)	Other covariates in the model
Frost[48]	2014	Diet, Cancer and Health Study	Prospective cohort	55,273 (52.4)	56.1	0.88 (0.10)	2,581 (4.7)	smoking status, fruit and vegetable intake, alcohol consumption, physical activity, total energy intake, educational level, hypertension, diabetes mellitus, hypercholesterolemia, ischemic heart disease, congestive heart failure, and valvular heart disease
Knuiman[49]	2014	Busselton Health Study	Prospective cohort	4,267 (56.4)	52	0.86 (0.09)	343 (8.0)	age, sex, height
Long[50]	2011	Guangzhou Biobank Cohort Study	Nested case-control	10,518 (71.2)	65.7 AF, 62.1 no AF	0.91 (0.06) AF, 0.90 (0.06) no AF	159 (1.5)	sex, age, drinking, smoking, hyperthyroidism, diabetes, hypertension, and total cholesterol
Nystrom[51]	2015	60-year Old Men and Women from Stockholm Study	Prospective cohort	4,021 (52.2)	60	0.90 (0.09) AF, 0.89 (0.09) no AF	285 (7.1)	hypertension, elevated fasting glucose, sex, smoking, alcohol intake, history of myocardial infarction, regular moderate-intensity physical activity, and Swedish-born

AF = atrial fibrillation, SD = standard deviation.

Table 4: Characteristics of Body Mass Index Studies

Study reference	Year	Cohort source	Study design	Subjects (% women)	Mean age (years)	Mean body mass index (SD)	AF cases (%)	Other covariates in the model
Bonhorst[53]	2010	Prevalence of Atrial Fibrillation in the Portuguese population aged 40 and over Study	Cross-sectional	10,447 (55)	59	27.7 (4.4)	261 (2.5)	None
De Bacquer[54]	2007	Belgian Interuniversity Research on Nutrition and Health Survey	Nested case-control	160 (45)	64	29.4 (5.1) AF, 27.2 (4.1) no AF	40 (25)	Systolic blood pressure, ischemic ECG changes, P wave duration, P wave morphology
Dublin[55]	2006	Group Health Cooperative	Case-control	1,132 (58)	71	252 overweight, 308 obese	425 (38)	Age, sex, hypertension, hypertension duration, systolic blood pressure, diastolic blood pressure, diabetes, diabetes duration, hyperlipidemia, total and HDL cholesterol levels
Frost[56]	2005	Danish Diet, Cancer and Health Study	Prospective cohort	47,589 (53)	56	26,403 overweight or obese	553 (1.2)	Age, systolic blood pressure, antihypertensive therapy, serum cholesterol, alcohol consumption, smoking, education, diabetes, ischemic heart disease, heart failure, valve disease
Gami[57]	2007	Mayo Clinic	Retrospective cohort	3,542 (34)	49	33 (9)	133 (3.8)	Age, sex, smoking, hypertension, diabetes, ischemic heart disease, heart failure
Grunvold[58]	2012	Oslo governmental hospitals	Prospective cohort	2,014 (0)	50	25 (2.8)	270 (13.4)	Age, systolic blood pressure, current smoking, total cholesterol, and blood glucose and, at a final step, physical fitness
Hanna[59]	2006	National Registry to Advance Heart Health	Cross-sectional	25,268 (28)	66	28.7 (6.4)	7,027 (28)	Age, sex, hypertension, diabetes, left ventricular ejection fraction, NYHA class, etiology of heart failure, medication use
Karasoy[60]	2013	Nationwide registers in Denmark	Retrospective cohort	271,203	30.6	76,324 overweight or obese	110 (0.0)	Age, hyperthyroidism, previous use of beta-blockers
Knuiman[49]	2014	Busselton Health Study	Prospective cohort	4,267 (56.4)	52	26 (4)	343 (8.0)	Age, sex, height
Long[50]	2011	Guangzhou Biobank Cohort Study	Nested case-control	20,430 (71.2)	65.7 AF, 62.1 no AF	24.2 (3.4) AF, 23.7 (3.3) no AF	159 (0.8)	Age, sex, drinking, smoking, hyperthyroidism, diabetes, hypertension, and total cholesterol
Minami[61]	2009	Kanazawa Social Insurance Hospital	Nested case-control	207 (0)	57	24.2 (3.2) AF, 22.9 (2.8) no AF	69 (33.3)	Age, systolic blood pressure, cardiomegaly, alcohol, total cholesterol, gamma-glutamyl transpeptidase, uric acid, fasting plasma glucose, red blood cell count, hemoglobin, smoking
Murphy[62]	2006	Renfrew-Paisley Study	Prospective cohort	15,402 (54)	53	8,503 overweight or obese	175 (1.1)	Age, sex, systolic blood pressure, diabetes, cholesterol, forced expiratory volume, smoking, social class
Park[63]	2015	YangPyeong Cardiovascular Disease Cohort	Prospective cohort	4,067 (61)	60.2	23.5 (3.2) AF, 24.5 (3.2) no AF	54 (1.3)	Age, gender, left ventricular ejection fraction, peak E, left atrial diameter, uric acid, creatinine, alanine transaminase, total cholesterol, adiponectin, ischemic heart disease
Rosengren[64]	2009	Swedish Primary Prevention Study	Prospective cohort	6,903 (0)	52	22.4 (2.2)	1,253 (18.2)	Age, systolic blood pressure, antihypertensive therapy, diabetes, smoking, alcohol, social class
Schnabel (AGES)[65]	2010	Age, Gene/Environment	Prospective cohort	4,238 (63)	76	27.0 (4.5)	226 (5.3)	Age, sex, antihypertensive therapy, PR interval, heart failure

		Susceptibility-Reykjavik Study						
Schnabel (CHS)[65]	2010	Cardiovascular Health Study	Prospective cohort	9,806 (60)	75	26.4 (4.5) Whites, 28.5 (5.6) African Americans	958 (9.8)	Age, sex, antihypertensive therapy, PR interval, heart failure
Schnabel (GHS)[66]	2015	Gutenberg Health Study	Cross-sectional	10,000 (49)	56	28 (4.4)	309 (3.1)	Age, gender, smoking, alcohol, hypertension, dyslipidemia, diabetes, family history of cardiovascular disease, prevalent cardiovascular disease, heart failure
Shoemaker[67]	2014	Vanderbilt University Medical Center	Cross-sectional	1,341 (76)	47	47 (5.2)	25 (1.9)	Age, gender
Smith[68]	2010	Malmo Diet and Cancer Study	Prospective cohort	30,447 (60)	58	25.8 (4.0)	1,430 (4.7)	Age, sex, myocardial infarction, heart failure, hypertension, diabetes, smoking
Soliman[69]	2010	Chronic Renal Insufficiency Cohort	Cross-sectional	3,267 (46)	59	32.3 (8.0)	602 (18)	Age, sex, ethnicity, study center
Tedrow[70]	2010	Women's Health Study	Prospective cohort	34,309 (100)	55	16,765 overweight or obese	834 (2.4)	Age, ethnicity, hypertension, hypercholesterolemia, diabetes, alcohol consumption, smoking, physical activity, inflammatory markers
Wang[71]	2004	Framingham Heart and Offspring Studies	Prospective cohort	5,282 (55)	57	2,991 overweight or obese	526 (10.0)	Age, systolic blood pressure, antihypertensive therapy, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, smoking, cardiac murmur, left atrial size
Wilhelmsen[72]	2001	Multifactor Primary Prevention Study	Prospective cohort	7,495 (0)	47-55	4,759 overweight or obese	754 (10.1)	Age, family history of cardiovascular disease, chest pain, dyspnea, smoking, coffee consumption, alcohol, height, weight, weight change, heart rate, hypertension treatment, systolic blood pressure
Zhang[52]	2009	China Multi-center Collaborative study of Cardiovascular Epidemiology	Cross-sectional	18,615 (55.7)	56	25.1 (3.9) AF, 24.1 (3.3) no AF	194 (1.0)	Age, electrocardiographic left ventricular hypertrophy, regular use of cigarettes and alcohol, history of myocardial infarction and history of doctor-diagnosed diabetes

AF = atrial fibrillation, SD = standard deviation, AGES = Age, Gene/Environment Susceptibility-Reykjavik Study, CHS = Cardiovascular Health Study, GHS = Gutenberg Health Study.

Table 5: Associations of epicardial fat volume with AF, by sub-groups

	Any AF vs Sinus Rhythm			Paroxysmal AF vs Sinus Rhythm			Persistent AF vs Sinus Rhythm			Post-Ablation AF		
	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P
Imaging modality												
MRI	13.28 (2.22-79.53)	N/A	0.58	3.77 (1.37-10.38)	N/A	0.43	3.64 2.72-7.91)	75.3%	0.28	1.39 (0.52-3.05)	N/A	0.32
CT	2.30 (1.67-3.16)	79.9%		1.91 (1.28-2.87)	72.0%		10.36 (3.89-27.59)	N/A		2.20 (1.44-3.34)	67.2%	
Fat type												
Epicardial	2.46 (1.60-3.79)	82.6%	0.041	2.09 (1.42-3.06)	41.2%	0.02	4.80 (2.35-9.79)	76.1%	0.12	1.19 (0.52-2.70)	52.4%	0.28
Pericardial	1.50 (1.20-1.87)	N/A		1.09 (0.84-1.42)	N/A		2.61 (1.87-3.65)	N/A		1.39 (0.52-3.69)	N/A	
Not specified	4.16 (2.29-7.55)	0.0%		3.23 (1.62-6.43)	15.8%		11.57 (5.33-25.10)	0.0%		3.21 (1.67-6.18)	70.5%	
Fat Location												
Total	2.34 (1.66-3.28)	80.0%	0.39	2.09 (1.32-3.26)	75.4%	0.95	5.08 (2.81-9.18)	78.1%	0.75	2.10 (1.03-4.29)	72.2%	0.89
Peri-atrial	N/A	N/A		N/A	N/A		N/A	N/A		N/A	N/A	
Peri-venticular	3.33 (1.87-5.94)	N/A		2.03 (1.01-4.06)	N/A		6.00 (2.91-12.40)	N/A		N/A	N/A	
Not specified	N/A	N/A		N/A	N/A		N/A	N/A		2.26 (1.20-4.23)	57.6%	
Covariate adjustment												
Adjusted	1.76 (1.25-2.47)	69.5%	0.20	1.48 (1.39-3.05)	20.9%	0.30	2.03 (1.22-3.37)	N/A	0.039	1.54 (1.29-1.83)	0.0%	0.45
Unadjusted	3.72 (1.79-7.70)	86.3%		2.28 (1.35-3.86)	N/A		6.29 (3.50-11.33)	73.8%		3.57 (1.31-9.74)	68.4%	
Study region												
North America	1.47 (1.16-1.85)	0.0%	0.030	1.48 (1.02-2.15)	N/A	0.11	2.03 (1.22-3.37)	N/A	0.003	1.46 (1.06-2.02)	N/A	0.053
Europe	1.45 (1.20-1.74)	0.0%		1.09 (0.94-1.42)	N/A		2.61 (1.87-3.65)	N/A		N/A	N/A	
Asia	4.30 (2.69-6.87)	57.1%		2.47 (1.97-3.81)	0.0%		7.43 (5.07-10.91)	0.0%		2.40 (1.41-3.05)	66.1%	
Study type												
Cohort	3.73 (0.45-30.58)	94.7%	0.006	N/A	N/A	0.003	N/A	N/A	0.001	2.08 (1.42-3.05)	62.8%	N/A
Cross-sectional	1.48 (1.26-1.74)	0.0%		1.24 (0.92-1.66)	42.3%		2.42 (1.83-3.20)	0.0%		N/A	N/A	
Case-control	3.25 (2.36-4.47)	13.3%		2.74 (1.97-3.81)	0.0%		7.43 (5.07-10.91)	0.0%		N/A	N/A	
Prospective design												
Prospective	3.73 (0.45-30.58)	94.7%	0.85	N/A	N/A	N/A	N/A	N/A	N/A	2.08 (1.42-3.05)	62.8%	N/A
Retrospective	2.26 (1.65-3.10)	73.1%		2.05 (1.38-3.05)	71.4%		5.16 (3.05-8.72)	76.0%		N/A	N/A	

P Values are tests for interaction. OR = odds ratio, CI = confidence interval.

Table 6: Sensitivity analyses for associations of epicardial fat with AF

	OR (95% CI)	I^2
Any AF vs Sinus Rhythm		
Primary analysis	2.43 (1.75-3.38)	79.9%
Secondary analysis including other studies	2.86 (2.04-4.00)	88.9%
Paroxysmal AF vs Sinus Rhythm		
Primary analysis	2.05 (1.38-3.05)	71.4%
Secondary analysis including other studies	2.39 (1.62-3.53)	86.8%
Persistent AF vs Sinus Rhythm		
Primary analysis	5.16 (3.05-8.72)	76.0%
Secondary analysis including other studies	7.58 (4.02-14.32)	90.0%
Persistent AF vs Paroxysmal AF		
Primary analysis	2.19 (1.76-2.69)	27.7%
Secondary analysis including other studies	3.24 (2.24-4.68)	83.8%
Post-Ablation AF		
Primary analysis	2.08 (1.42-3.05)	62.8%
Secondary analysis including other studies	2.67 (1.72-4.15)	78.3%
Post-Operative AF		
Primary analysis	2.25 (1.24-4.09)	61.1%
Secondary analysis including other studies	3.69 (1.42-9.57)	85.6%

Secondary analyses included other studies which used echocardiography or non-volumetric methods to quantify epicardial fat. P Values are tests for interaction. OR = odds ratio, CI = confidence interval.

FIGURE LEGENDS

Figure 1: Profile of included studies

Results of electronic database search leading to study selection.

Figure 2: Associations of epicardial fat with atrial fibrillation

Associations of epicardial fat (EFat) with A) any atrial fibrillation (AF), B) AF severity, C) AF subtypes and D) post-procedural AF . The point estimates (center of each square), weight of study (proportional area of square) and confidence intervals (CI) for the estimate of each study (horizontal line) are shown. The overall summary estimates are also shown (diamond).

Figure 3: Associations of abdominal adiposity with atrial fibrillation

Associations of waist circumference (WC) and waist-to-hip ratio (WHR) with atrial fibrillation (AF). Symbols and conventions used are as for the Central Illustration.

Figure 4: Association of overall adiposity with atrial fibrillation

Association between body mass index (BMI) and atrial fibrillation (AF). Symbols and conventions as per Central Illustration. AGES = Age, Gene/Environment Susceptibility-Reykjavik Study, CHS = Cardiovascular Health Study, GHS = Gutenberg Health Study.

Figure 1

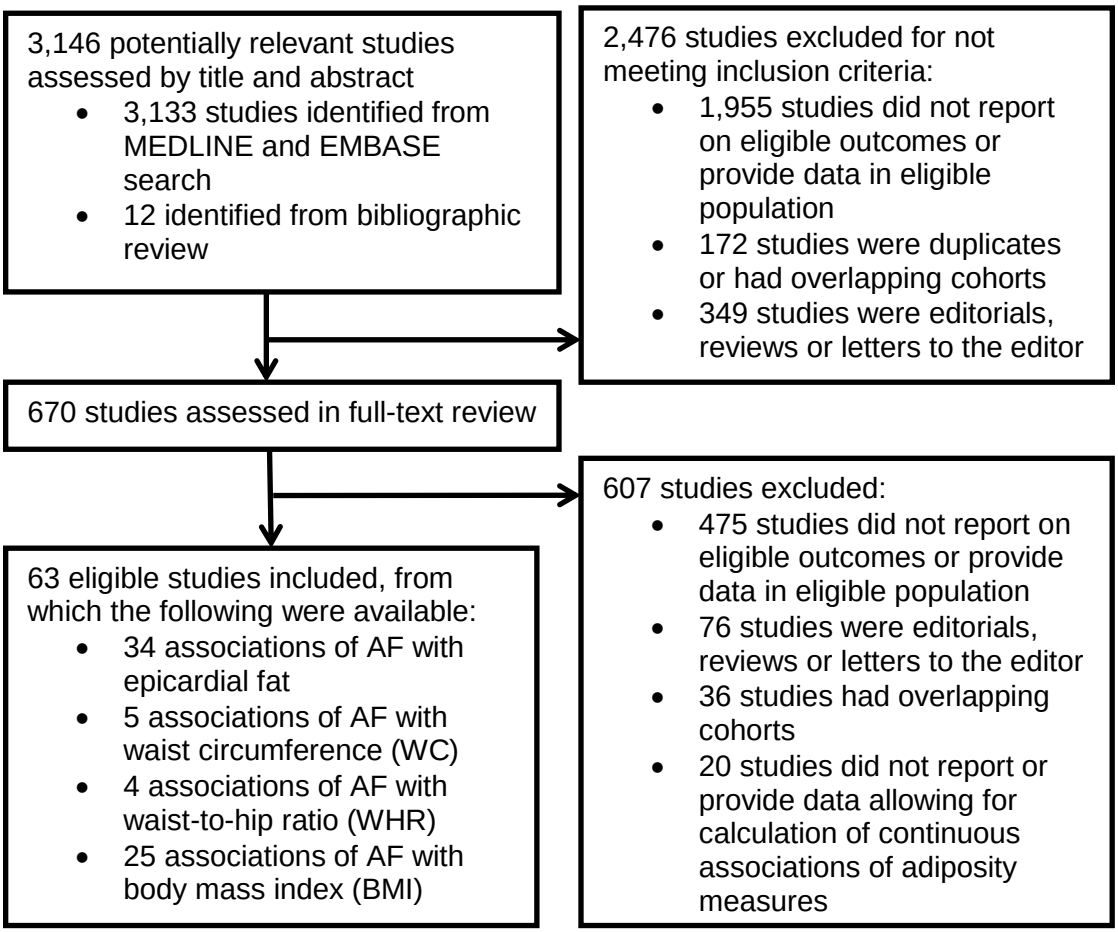

3,146 potentially relevant studies assessed by title and abstract
3,133 studies identified from MEDLINE and EMBASE search
12 identified from bibliographic review
2,476 studies excluded for not meeting inclusion criteria:
1,955 studies did not report on eligible outcomes or provide data in eligible population
172 studies were duplicates or had overlapping cohorts
349 studies were editorials, reviews or letters to the editor
670 studies assessed in full-text review
607 studies excluded:
475 studies did not report on eligible outcomes or provide data in eligible population
76 studies were editorials, reviews or letters to the editor
36 studies had overlapping cohorts
20 studies did not report or provide data allowing for calculation of continuous associations of adiposity measures
63 eligible studies included, from which the following were available:
34 associations of AF with epicardial fat
5 associations of AF with waist circumference (WC)
4 associations of AF with waist-to-hip ratio (WHR)
25 associations of AF with body mass index (BMI)

Figure 2

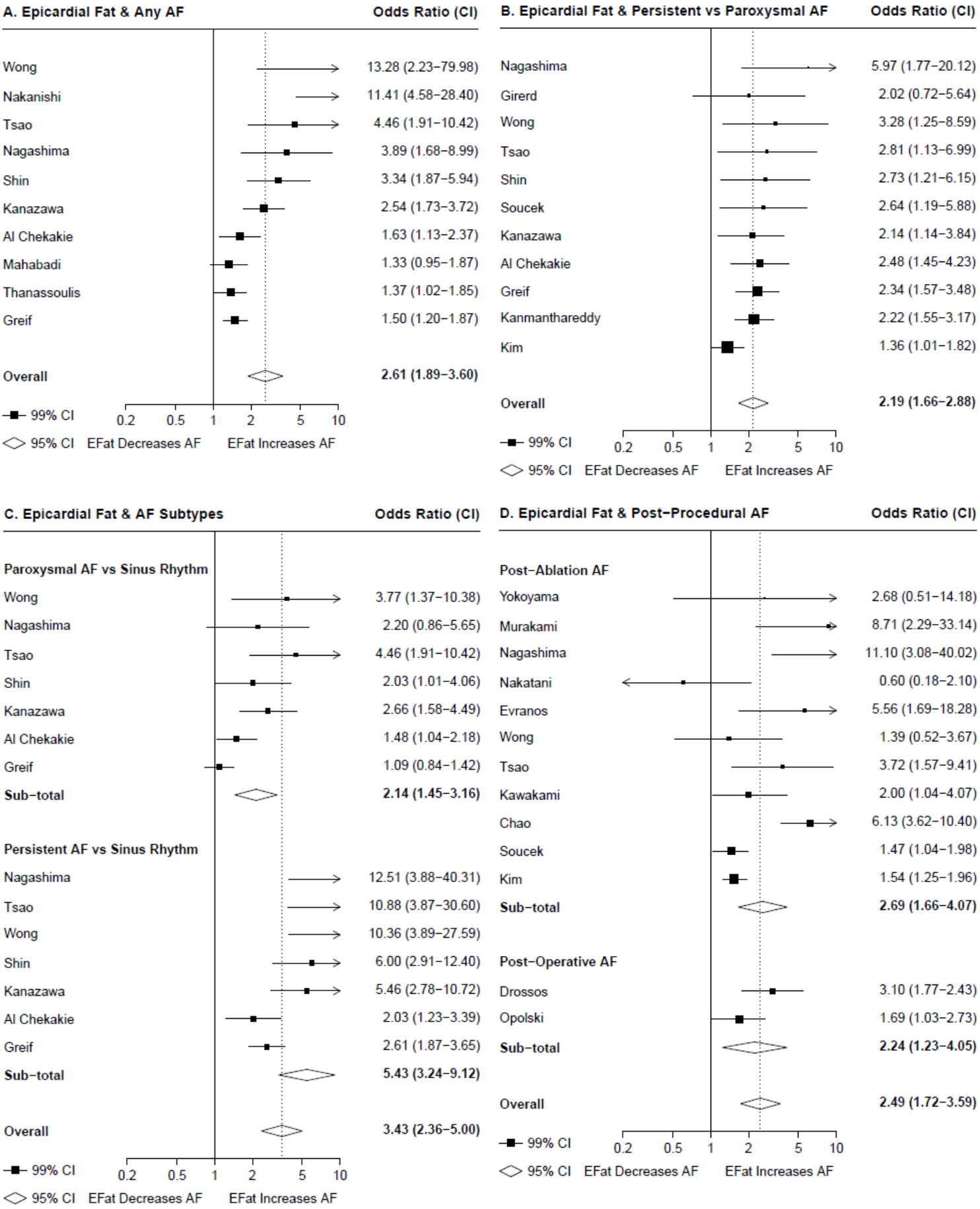

A. Epicardial Fat & Any AF
Odds Ratio (CI)
Wong 13.28 (2.23–79.98)
Nakanishi 11.41 (4.58–28.40)
Tsao 4.46 (1.91–10.42)
Nagashima 3.89 (1.68–8.99)
Shin 3.34 (1.87–5.94)
Kanazawa 2.54 (1.73–3.72)
Al Chekakie 1.63 (1.13–2.37)
Mahabadi 1.33 (0.95–1.87)
Thanassoulis 1.37 (1.02–1.85)
Greif 1.50 (1.20–1.87)
Overall 2.61 (1.89–3.60)
99% CI
95% CI
0.2 0.5 1 2 5 10
EFat Decreases AF
EFat Increases AF
B. Epicardial Fat & Persistent vs Paroxysmal AF
Odds Ratio (CI)
Nagashima 5.97 (1.77–20.12)
Girerd 2.02 (0.72–5.64)
Wong 3.28 (1.25–8.59)
Tsao 2.81 (1.13–6.99)
Shin 2.73 (1.21–6.15)
Soucek 2.64 (1.19–5.88)
Kanazawa 2.14 (1.14–3.84)
Al Chekakie 2.48 (1.45–4.23)
Greif 2.34 (1.57–3.48)
Kanmanthareddy 2.22 (1.55–3.17)
Kim 1.36 (1.01–1.82)
Overall 2.19 (1.66–2.88)
99% CI
95% CI
0.2 0.5 1 2 5 10
EFat Decreases AF
EFat Increases AF
C. Epicardial Fat & AF Subtypes
Odds Ratio (CI)
Paroxysmal AF vs Sinus Rhythm
Wong 3.77 (1.37–10.38)
Nagashima 2.20 (0.86–5.65)
Tsao 4.46 (1.91–10.42)
Shin 2.03 (1.01–4.06)
Kanazawa 2.66 (1.58–4.49)
Al Chekakie 1.48 (1.04–2.18)
Greif 1.09 (0.84–1.42)
Sub–total 2.14 (1.45–3.16)
Persistent AF vs Sinus Rhythm
Nagashima 12.51 (3.88–40.31)
Tsao 10.88 (3.87–30.60)
Wong 10.36 (3.89–27.59)
Shin 6.00 (2.91–12.40)
Kanazawa 5.46 (2.78–10.72)
Al Chekakie 2.03 (1.23–3.39)
Greif 2.61 (1.87–3.65)
Sub–total 5.43 (3.24–9.12)
Overall 3.43 (2.36–5.00)
99% CI
95% CI
0.2 0.5 1 2 5 10
EFat Decreases AF
EFat Increases AF
D. Epicardial Fat & Post–Procedural AF
Odds Ratio (CI)
Post–Ablation AF
Yokoyama 2.68 (0.51–14.18)
Murakami 8.71 (2.29–33.14)
Nagashima 11.10 (3.08–40.02)
Nakatani 0.60 (0.18–2.10)
Evranos 5.56 (1.69–18.28)
Wong 1.39 (0.52–3.67)
Tsao 3.72 (1.57–9.41)
Kawakami 2.00 (1.04–4.07)
Chao 6.13 (3.62–10.40)
Soucek 1.47 (1.04–1.98)
Kim 1.54 (1.25–1.96)
Sub–total 2.69 (1.66–4.07)
Post–Operative AF
Drossos 3.10 (1.77–2.43)
Opolski 1.69 (1.03–2.73)
Sub–total 2.24 (1.23–4.05)
Overall 2.49 (1.72–3.59)
99% CI
95% CI
0.2 0.5 1 2 5 10
EFat Decreases AF
EFat Increases AF

Figure 3

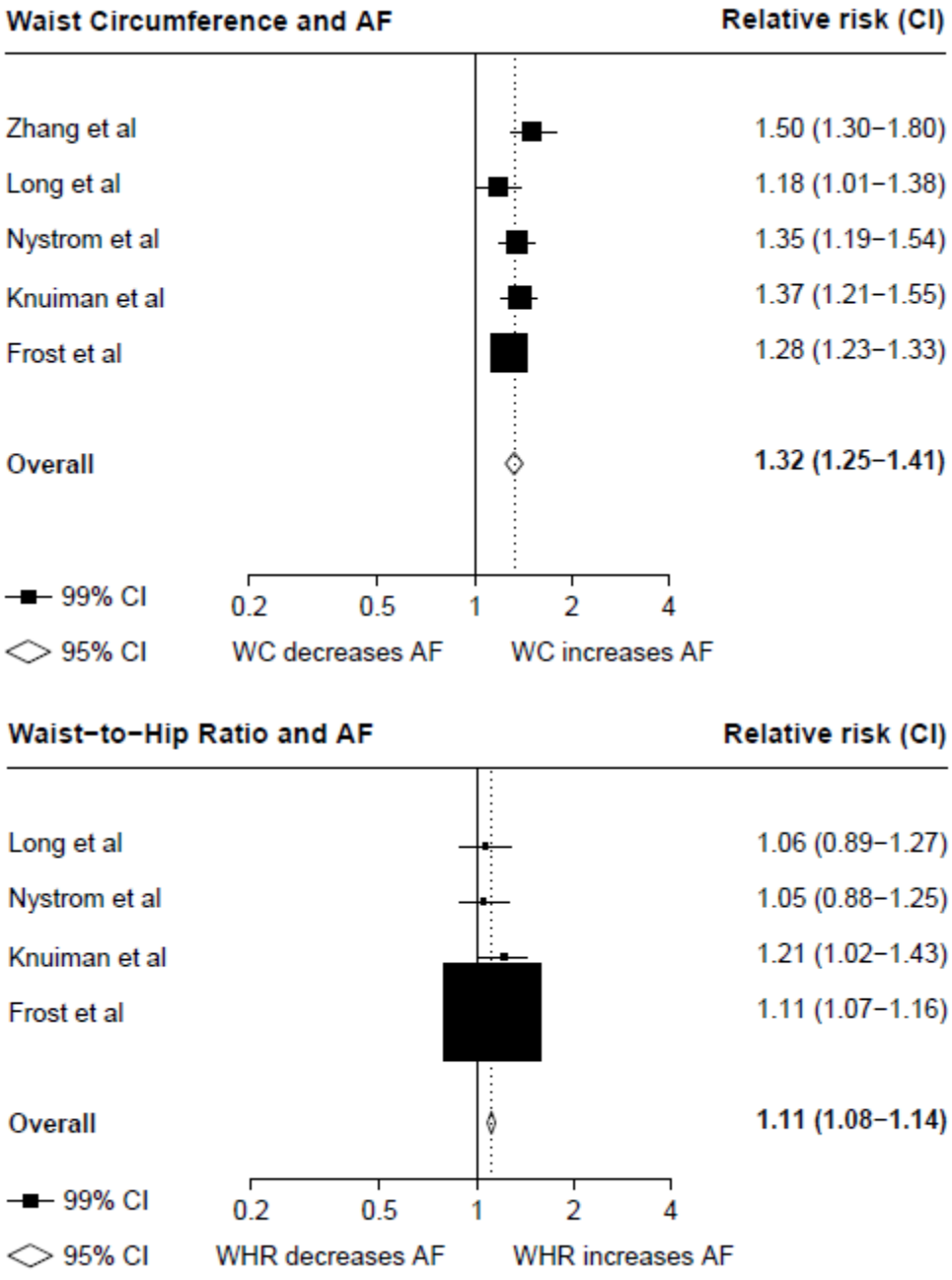
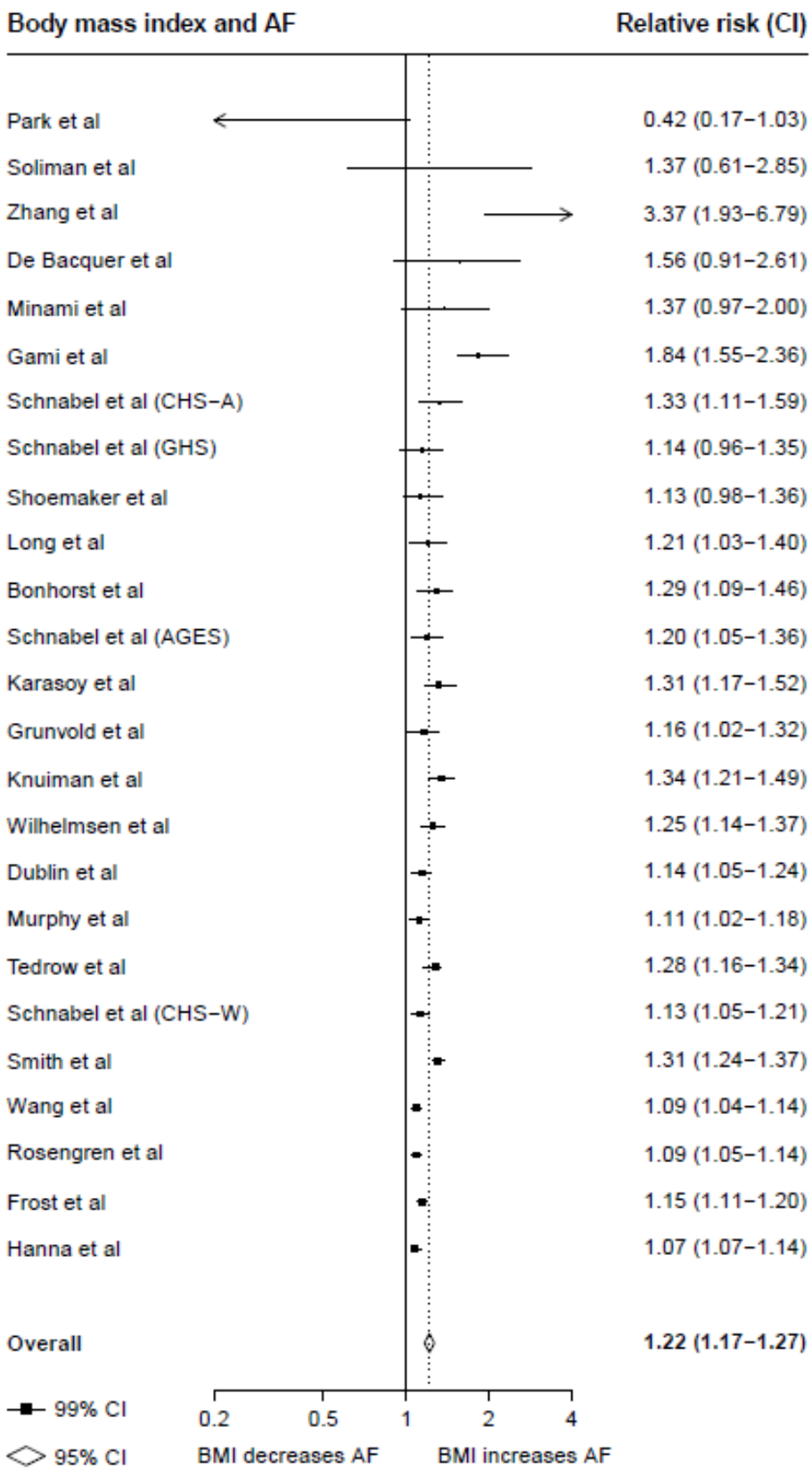

Waist Circumference and AF
Relative risk (CI)
Zhang et al
1.50 (1.30–1.80)
Long et al
1.18 (1.01–1.38)
Nystrom et al
1.35 (1.19–1.54)
Knuiman et al
1.37 (1.21–1.55)
Frost et al
1.28 (1.23–1.33)
Overall
1.32 (1.25–1.41)
99% CI
95% CI
0.2
0.5
1
2
4
WC decreases AF
WC increases AF
Waist–to–Hip Ratio and AF
Relative risk (CI)
Long et al
1.06 (0.89–1.27)
Nystrom et al
1.05 (0.88–1.25)
Knuiman et al
1.21 (1.02–1.43)
Frost et al
1.11 (1.07–1.16)
Overall
1.11 (1.08–1.14)
99% CI
95% CI
0.2
0.5
1
2
4
WHR decreases AF
WHR increases AF

Figure 4


Body mass index and AF
Relative risk (CI)
Park et al
0.42 (0.17–1.03)
Soliman et al
1.37 (0.61–2.85)
Zhang et al
3.37 (1.93–6.79)
De Bacquer et al
1.56 (0.91–2.61)
Minami et al
1.37 (0.97–2.00)
Gami et al
1.84 (1.55–2.36)
Schnabel et al (CHS–A)
1.33 (1.11–1.59)
Schnabel et al (GHS)
1.14 (0.96–1.35)
Shoemaker et al
1.13 (0.98–1.36)
Long et al
1.21 (1.03–1.40)
Bonhorst et al
1.29 (1.09–1.46)
Schnabel et al (AGES)
1.20 (1.05–1.36)
Karasoy et al
1.31 (1.17–1.52)
Grunvold et al
1.16 (1.02–1.32)
Knuiman et al
1.34 (1.21–1.49)
Wilhelmsen et al
1.25 (1.14–1.37)
Dublin et al
1.14 (1.05–1.24)
Murphy et al
1.11 (1.02–1.18)
Tedrow et al
1.28 (1.16–1.34)
Schnabel et al (CHS–W)
1.13 (1.05–1.21)
Smith et al
1.31 (1.24–1.37)
Wang et al
1.09 (1.04–1.14)
Rosengren et al
1.09 (1.05–1.14)
Frost et al
1.15 (1.11–1.20)
Hanna et al
1.07 (1.07–1.14)
Overall
1.22 (1.17–1.27)
99% CI
95% CI
0.2
0.5
1
2
4
BMI decreases AF
BMI increases AF