

Even mild mitral regurgitation is associated with incident atrial fibrillation in the general population

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Aims

Mitral regurgitation (MR) can be difficult to quantify. We sought to investigate whether the MR jet area to left atrial (LA) area ratio (MR/LA ratio) method for quantifying MRs can be used to predict incident atrial fibrillation (AF) in the general population.

Methods and results

The study included 4466 participants from the 5th Copenhagen City Heart Study, a prospective general population study, who underwent transthoracic echocardiography. MR jet area was measured and indexed to LA area. The endpoint was incident AF. MR was quantified in 4042 participants (mean age: 57 years, 43% men). Of these, 198 (4.9%) developed AF during a median follow-up period of 5.3 years (interquartile range: 4.4–6.1 years). MR was present in 1938 participants (48%) including 1593 (39%) trace/mild MRs (MR/LA ratio $\leq 20\%$ and $\leq 4 \text{ cm}^2$). In unadjusted analysis, MR/LA ratio was associated with incident AF [HR: 1.06 (1.00–1.13), $P = 0.042$ per 5% increase] but not after adjusting for CHARGE-AF score. However, the association was modified by age (P for interaction = 0.034), such that MR/LA ratio was associated with AF only in participants ≤ 73 years. In these participants, MR/LA ratio ‘was’ independently associated with AF after adjusting for CHARGE-AF score [HR: 1.14 (1.06–1.24), $P = 0.001$, per 5% increase]. This finding persisted when restricting the analysis to participants without moderate or severe MR and normal LA size [HR: 1.35 (1.09–1.68), $P = 0.005$, per 5% increase].

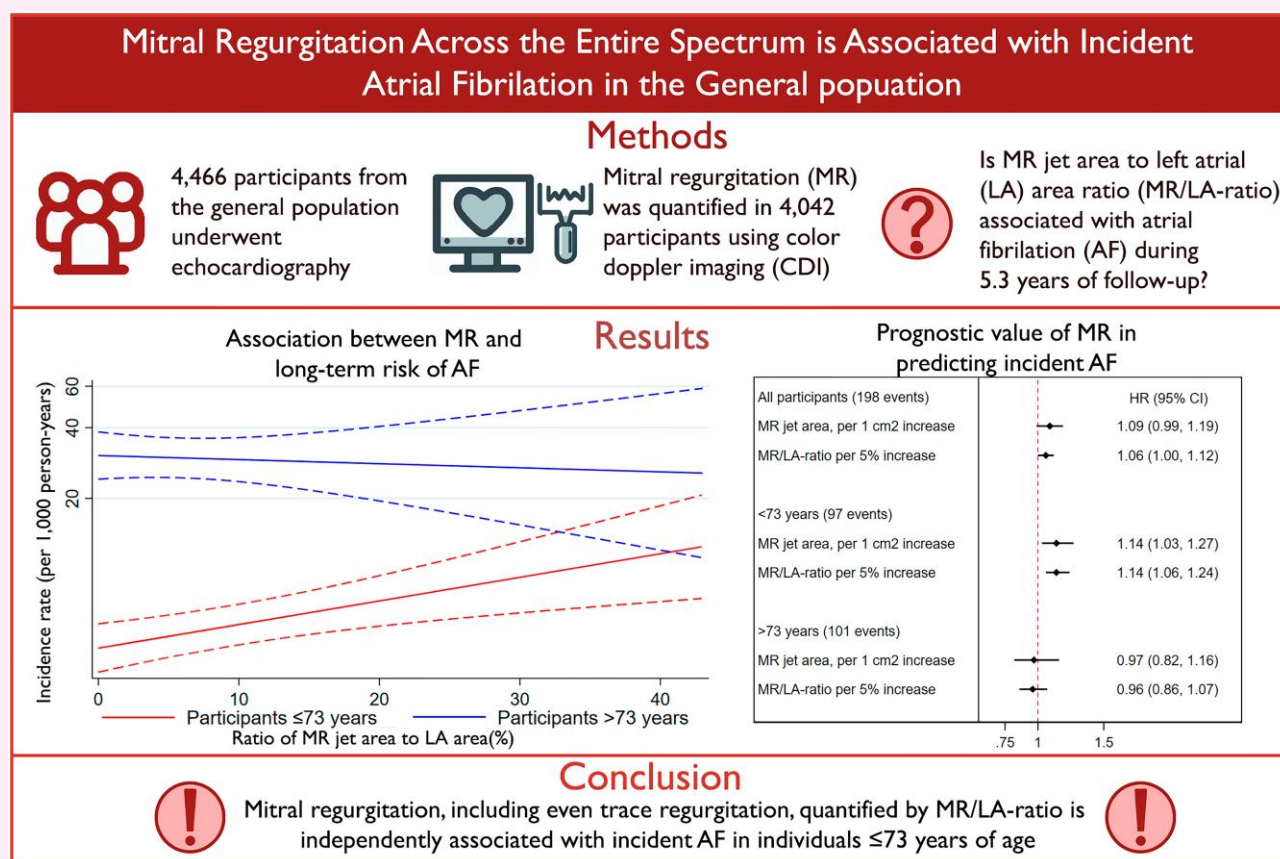
Conclusion

MR, including even trace regurgitations quantified by MR/LA ratio, is independently associated with incident AF in individuals ≤ 73 years of age.

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Graphical Abstract



Keywords

Copenhagen City Heart Study • Mitral regurgitation • General population • Prospective cohort study

Introduction

Mitral regurgitation (MR) is the most common valvular heart disease, with a prevalence in the adult population of 20% for mild to severe MR and 70% for trace MR.¹ Severe MR is associated with significant adverse cardiovascular outcomes, including atrial fibrillation (AF), heart failure, and cardiovascular death,² whereas trace MRs are generally considered benign.³ Larger studies have previously been conducted retrospectively in clinical patients and frequently used all-cause mortality as a primary endpoint, including showing an increased risk of death with mild MRs.^{3–5} However, differentiating trace from mild MRs remains difficult. Accordingly, the association between the degree of MR, on a wider spectrum, and cardiovascular outcomes has not been fully elucidated. Therefore, there is a gap in the literature as to the clinical implication of MR in the general population, in which trace and mild MRs predominate. Since even minor MRs may progress to cause LA remodelling, they may pose an increased risk of AF, which is important to recognize for the timely detection of AF and initiation of management.

Currently, guidelines recommend quantifying MRs by the vena contracta width and proximal isovelocity surface area (PISA) methods.⁶ However, trace and mild MRs are often not quantifiable by these methods and the assessment of trace and mild MRs often relies on a qualitative judgment. The jet area method derived from colour Doppler imaging (CDI) is, however, not constrained by these limitations, and thus remains a viable tool to quantitatively measure trace MRs across all severities.

Therefore, we sought to investigate (i) whether MR jet area is associated with incident AF in the general population; and (ii) whether even mild and trace MRs are associated with incident AF.

Methods

Study population

Participants were included as part of the 5th Copenhagen City Heart Study (CCHS5), a community-based prospective longitudinal cohort study on cardiovascular disease and risk factors in the Danish general population. A total of 4466 participants between the ages 20 and 99 were recruited in the Copenhagen area between 2011 and 2015. Participants underwent a systematic health examination as detailed below in addition to an echocardiographic examination. Informed consent was obtained for all patients. CCHS5 was performed in accordance with the Second Helsinki Declaration with approval from the regional ethics committee.

Participants were excluded if they had no available echocardiographic images ($n = 48$), a history of AF ($n = 204$), or unavailable 2D CDI in the apical four-chamber view ($n = 172$), which left 4042 participants for final analysis.

Health examination and baseline information

All participants underwent a physical examination. Data on blood pressure (BP), heart rate, weight, physical activity level, and smoking habits were collected during the initial health examination or by questionnaire. Data on comorbidities including hypertension, ischaemic heart disease, and diabetes

were collected using self-administered questionnaire and ICD-10 codes through the National Health Registry.

BP was measured with the London School of Hygiene sphygmomanometer. Plasma cholesterol, triglycerides, creatinine, haemoglobin, and glucose were collected on non-fasting venous blood samples. Obesity was defined as body mass index (BMI) ≥ 30 kg/m². Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Diabetes was defined as non-fasting plasma glucose concentration ≥ 11.1 mmol/L, use of antidiabetic medication, or self-reported disease. Family history of ischaemic heart disease was defined as having a biological parent with a myocardial infarction at any age.

Transthoracic echocardiography

All echocardiographic examinations were performed by experienced sonographers and clinicians using Vivid 9 ultrasound systems (GE Healthcare, Horten, Norway). To ensure image reproducibility, all echocardiographic examinations followed a strict protocol using standardized profiles for pulse repetition frequency, colour gain, and Nyquist limits of 60 cm/s. Echocardiograms were analysed offline using commercially available post-processing software, EchoPAC version 203 (GE Healthcare) for analysis of MRs and previous versions for conventional echocardiography. Analysis of MRs was performed by a single investigator who was blinded to clinical data and outcomes.

Conventional echocardiography

Left ventricular ejection fraction was measured with the Simpson's biplane method using semi-automated software in the apical four-chamber and two-chamber views. Interventricular septal thickness (IVSd), LV internal diameter (LVIDd), and LV posterior wall thickness (LVPWd) were measured on B-mode images in parasternal long-axis view and used to calculate the LV mass indexed to body surface area. Left atrial (LA) volume was measured with Simpson's biplane method and indexed to the surface area to obtain the LA volume index (LAVi). Global longitudinal strain (GLS) analysis was obtained with LV speckle tracking as previously described.⁷ E-wave, A-wave, and E/A ratio were obtained with pulsed-wave Doppler. Early

tissue wave velocity (e') of the septal and lateral mitral annulus were obtained through pulsed-wave tissue Doppler and indexed to E-wave to obtain E/e' .

Two-dimensional colour Doppler

As the magnitude of the MR jet area varies between the apical and parasternal views,⁸ the presence of MR was only assessed in the apical four-chamber view, as recommended by current guidelines,⁹ to ensure to ensure comparability. MR was traced in the frame where it was most prominent. LA area was measured on the same frame that the MR jet area was measured in, and the MR jet area was indexed to LA area (MR/LA ratio) (Figure 1).

Mild MR was defined as MR jet area ≤ 4 cm² and MR/LA ratio $\leq 20\%$, moderate MR as MR/LA ratio 20–40% or MR jet area ≥ 4 cm², and severe MR as MR/LA ratio $\geq 40\%$. These thresholds have previously been proposed by international guidelines.¹⁰ Abnormal LAVi was defined in accordance with recent guidelines as LAVi > 34 mL/m².¹¹ Secondary MR was defined as MR with ischaemic heart disease, heart failure, or left ventricle dilation at baseline, while primary MR was defined as any MR not fulfilling the criteria for secondary MR.

Follow-up and outcome

The outcome was incident AF as diagnosed by physicians during hospital contact. Outcome data were retrieved using ICD-10 codes retrieved from the Danish National Patient Registry. The process of diagnosing AF in the CCHS has been described in detail previously.¹² The positive predictive value in the diagnosis of AF in the Danish National Patient Registry is high [positive predictive value: 95%; 95% confidence interval (CI) 89–98%] and has previously been validated for research use.¹³ Follow-up was 100% complete. Participants were followed from time of examination until July 2018 or time of event.

Statistical analysis

STATA statistics/data analysis ME 17.0 (StataCorp, College Station, TX, USA) was used for all statistical analyses. Groupwise comparisons were

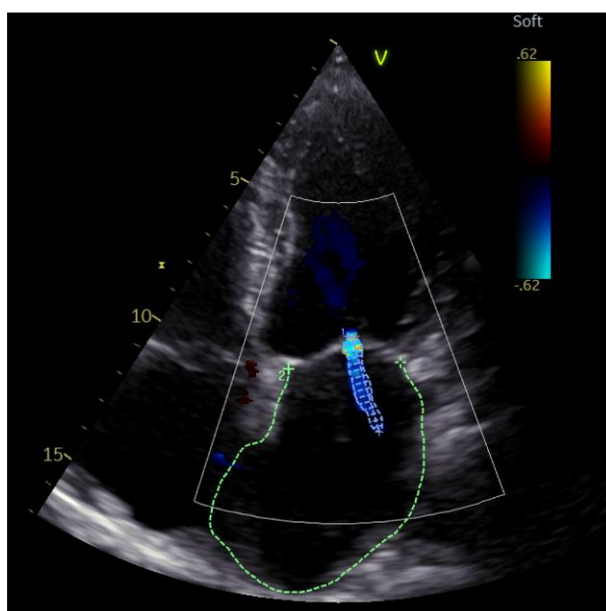


Figure 1 Two-dimensional colour Doppler analysis of the left atrium from the apical-four-chamber view. The frame where the holosystolic central mitral regurgitation is most prominent is found. The trace of the mitral regurgitation is represented by blue lines marked with a “1”, while the trace of the left atrium is represented by the green lines marked with a “2”.

made according to severity of MR (no MR, mild, moderate, or severe) and according to age strata (age cut-off: 73 years).

Continuous variables showing Gaussian distribution are shown as mean values $\pm$ standard deviation (SD) and compared with Student's *t*-test. Continuous variables showing non-Gaussian distribution are shown as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were compared using Pearson's χ^2 test and are reported as number and percentages. Variables divided into more than two groups are compared with a trend-test using linear regression. The association between MR/LA ratio and incident AF was assessed with univariable Cox proportional hazard regression. A multivariable Cox proportional hazard model, adjusting for the CHARGE-AF risk score, was applied to control for confounding variables. The CHARGE-AF risk score¹⁴ includes the following known predictors of incident AF in the general population:^{15–18} age, height, weight, systolic blood pressure, diastolic blood pressure, current smoker, antihypertensive medication, diabetes, congestive heart failure, and myocardial infarction. Additionally, a sensitivity analysis was performed where participants with moderate and severe MRs were excluded.

Potential effect modification was tested for age, sex, GLS, and LAVi.

Due to significant effect modification from age, the population was stratified according to age strata of 1-year intervals, with the most prominent age cut-off for effect modification found to be ≤ 73 years of age. Similarly, due to effect modification from LAVi, a sensitivity analysis was performed excluding participants with abnormal LA size.

The continuous association between MR/LA ratio and incident AF was visually depicted using restricted cubic spline curves constructed with Poisson regression. The number of knots that provided the lowest Akaike information criterion was chosen. Reproducibility was assessed by blinded investigators in 20 randomly selected participants. The results are reported as absolute mean differences with 95% limits of agreement and visually displayed with Bland–Altman plots.

Results

Patient characteristics

A total of 4042 participants were included in this study. Mean age was 57 ± 17 years and 43% were male. At baseline, MR was present in 1938 (48%) participants, including 1593 (39%) with trace/mild MR. Median mitral jet area was 0.0 (IQR 0.0–1.1) cm^2 in the total population and 1.2 (IQR 0.7–2.0) cm^2 among participants with MR. Median MR/LA ratio was 0.0% (IQR 0.0–9.4%) in the total population and 9.4% (IQR 5.7–15.9%) among participants with MR. A total of 1733 (42.9%) participants had primary MR while 205 (5.1%) had secondary MR.

Demographical, clinical, and echocardiographic characteristics are shown in Table 1 stratified by the presence of MR and MR severity. Differences in age, systolic and diastolic blood pressure, total cholesterol level, and LDL cholesterol level were observed with increasing MR severity. Of note, among echocardiographic parameters, only a difference in E/A ratio was observed.

When stratified by age, differences in nearly all clinical characteristics and echocardiographic measures were observed (see [Supplementary data online, Table S1](#)). When stratified by the presence of AF at follow-up in participants ≤ 73 years of age, differences in age, BMI, hypertension, family history of heart disease, hypercholesterolaemia as well as all echocardiographic parameters were observed (see [Supplementary data online, Table S2](#)). Baseline characteristics of participants excluded due to AF at baseline are shown in the Supplement (see [Supplementary data online, Table S3](#)).

Relationship between MR/LA ratio and incident AF

During a median follow-up period of 5.3 years (IQR 4.4–6.1 years), 198 participants (5%) developed AF. In univariable analysis, MR/LA ratio was

significantly associated with incident AF in the overall population [hazard ratio (HR) 1.06, 95% CI 1.00–1.13, $P = 0.042$, per 5% increase]. However, in multivariable analysis, after adjusting for CHARGE-AF score, the association between MR/LA ratio and AF was no longer significant (HR 1.06 95% CI 1.00–1.12, $P = 0.071$, per 5% increase). However, age was found to significantly modify the association between MR/LA ratio and incident AF (P for interaction = 0.034), such that MR/LA ratio was associated with AF in younger participants, but not in older. Of 3318 participants included in the group of participants ≤ 73 years of age, 97 (2.9%) developed AF during follow-up. In participants ≤ 73 years, MR/LA ratio was significantly associated with incident AF after adjusting for CHARGE-AF score (HR 1.14 95% CI 1.06–1.24, $P = 0.001$, per 5% increase), but not in participants older than 73 years (HR 0.97 95% CI 0.82–1.16, $P = 0.77$, per 5% increase) (Table 2). Figure 2 shows the incidence rate of AF by MR/LA ratio in participants ≤ 73 years and > 73 years of age. Effect modification was also tested and found significant for LAVi (P for interaction = 0.027) but not for gender (P for interaction = 0.11), GLS (P for interaction = 0.89), thyroid disease (P for interaction = 0.80), family history of ischaemic heart disease (P for interaction = 0.58), or MR mechanism (P for interaction = 0.56).

A sensitivity analysis restricting the analysis to participants without moderate or severe MR and with normal LAVi showed that MR/LA ratio was significantly associated with AF after adjusting for CHARGE-AF risk score in participants ≤ 73 years of age (HR 1.39 95% CI 1.09–1.68, $P = 0.005$, per 5% increase) but not in participants > 73 years of age (HR 0.92 95% CI 0.71–1.20, $P = 0.55$, per 5% increase).

Mitral jet area and incident AF

The unindexed MR jet area was also associated with incident AF in participants ≤ 73 years after adjusting for CHARGE-AF score (HR 1.14 95% CI 1.03–1.27, $P = 0.012$, per 1 cm^2 increase), and this finding persisted in the sensitivity analysis when restricting the population to only include participants without moderate or severe MR and normal LAVi (HR 1.39 95% CI 1.02–1.89, $P = 0.035$, per 1 cm^2 increase) but not in participants > 73 years of age (HR 1.06 95% CI 0.77–1.47, $P = 0.71$, per 1 cm^2 increase).

Reproducibility

Intraobserver variability for MR jet area was $-0.025 \pm 0.34 \text{ cm}^2$, and interobserver variability was $-0.68 \pm 0.75 \text{ cm}^2$. For MR/LA ratio, intraobserver variability was $-0.59 \pm 2.76\%$ and interobserver variability was $-6.8 \pm 7.8\%$. [Supplementary data online, Figure S1](#) in supplement shows Bland–Altman plot for inter- and intraobserver variability.

Discussion

In this prospective study of a large general population sample who underwent a full echocardiographic examination and long-term follow-up for clinical outcomes, we demonstrated the following: (i) presence of MR, as assessed by the MR/LA ratio and MR jet area, is independently associated with incident AF in young participants, but not in older participants, and (ii) this relationship in the young group persisted even in participants without significant MR.

Moderate and severe MRs have previously been linked to an increased risk of cardiovascular mortality,² and clinical guidelines recommend monitoring MRs continuously due to risk of progression and timely need for surgery.¹⁹

Pathophysiology of MR and AF

Several mechanisms linking MR to AF have been proposed. The current understanding for the mechanism of AF development is a complex

Table 1 Baseline demographic, clinical, and echocardiographic characteristics by mitral regurgitation

	All	No MR	Any MR	P-value	Trace/mild MR	Moderate MR	Severe MR	P-value for trend
Participants, n	4042	2104	1938		1593	290	55	
Demographic characteristics								
Age (years)	56.6 (17.4)	56.1 (17.5)	57.2 (17.3)	0.06	56.9 (17.3)	59.0 (17.2)	54.3 (17.1)	0.047
Male, n (%)	1741 (43.1%)	890 (42.3%)	851 (43.9%)	0.30	694 (43.6%)	129 (44.5%)	28 (50.9%)	0.18
Clinical characteristics								
BMI (kg/m ²)	25.8 (4.5)	25.7 (4.5)	25.9 (4.5)	0.28	25.9 (4.6)	26.0 (4.3)	26.1 (4.5)	0.21
Activity status in leisure time, n (%)				0.10				0.15
Inactive	295 (7.3%)	147 (7.0%)	148 (7.5%)		122 (7.7%)	23 (7.9%)	3 (5.5%)	
Low	1487 (36.8%)	777 (36.9%)	710 (36.6%)		569 (35.7%)	117 (40.3%)	24 (43.6%)	
Moderate	1725 (42.6%)	914 (43.4%)	811 (41.8%)		678 (42.6%)	110 (37.9%)	23 (41.8%)	
High	305 (7.6%)	165 (7.8%)	140 (7.2%)		117 (7.3%)	19 (6.6%)	4 (7.3%)	
Current smoker, n (%)	719 (18.7%)	386 (19.1%)	333 (18.2%)	0.47	268 (17.7%)	53 (20.2%)	12 (22.2%)	0.89
Heart failure, n (%)	53 (1.3%)	30 (1.4%)	23 (1.2%)	0.50	18 (1.1%)	5 (1.7%)	0 (0.0%)	0.59
Hypertension, n (%)	2069 (51.2%)	1055 (50.1%)	1014 (52.3%)	0.17	831 (52.2%)	159 (54.8%)	24 (43.6%)	0.27
Systolic blood pressure (mmHg)	137.9 (20.8)	137.0 (20.6)	139.0 (20.9)	0.003	138.6 (21.0)	141.4 (20.9)	135.4 (19.5)	0.03
Diastolic blood pressure (mmHg)	78.7 (10.7)	78.3 (10.7)	79.1 (10.7)	0.013	79.0 (10.6)	79.7 (11.0)	79.0 (11.5)	0.01
Diabetes, n (%)	195 (4.8%)	103 (4.9%)	92 (4.7%)	0.83	76 (4.8%)	13 (4.5%)	3 (5.5%)	0.84
Family history of IHD	505 (15.2%)	255 (14.9%)	250 (15.6%)	0.54	206 (15.5%)	39 (17.3%)	5 (10.2%)	0.52
Thyroid disease, n (%)	67 (1.7%)	36 (1.7%)	31 (1.6%)	0.78	27 (1.7%)	4 (1.4%)	0 (0.0%)	0.50
Hypercholesterolaemia, n (%)	2549 (62.8%)	1319 (62.7%)	1221 (63.0%)	0.84	981 (61.6%)	205 (70.7%)	35 (63.6%)	0.20
Total cholesterol (mmol/L)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	0.24	5.4 (1.1)	5.6 (1.2)	5.5 (1.3)	0.04
LDL cholesterol (mmol/L)	3.1 (1.0)	3.1 (1.0)	3.1 (1.0)	0.21	3.1 (1.0)	3.2 (1.0)	3.2 (1.2)	0.02
HDL cholesterol (mmol/L)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	0.35	1.6 (0.5)	1.6 (0.5)	1.5 (0.5)	0.10
Creatinine (μmol/L)	76.7 (13.9)	76.4 (13.7)	76.9 (14.1)	0.22	76.8 (13.7)	77.5 (16.5)	77.7 (13.4)	0.13
Haemoglobin (mmol/L)	8.8 (0.7)	8.7 (0.7)	8.8 (0.7)	0.23	8.8 (0.7)	8.8 (0.7)	8.9 (0.8)	0.06
Echocardiographic characteristics								
Mitral jet area (cm ²), median (IQR)	0.0 (0.0–1.1)	0.0 (0.0–0.0)	1.2 (0.7–2.0)	<0.001	1.0 (0.6–1.5)	3.3 (2.5–4.4)	6.1 (3.7–7.8)	<0.001
MR/LA ratio (%), median (IQR)	0.0 (0.0–9.4)	0.0 (0.0–0.0)	9.7 (5.9–15.9)	<0.001	8.2 (5.2–12.0)	25.5 (22.1–30.0)	46.5 (42.9–53.8)	<0.001
LV mass index (g/m ²), median (IQR)	82.8 (70.9–96.7)	82.5 (70.8–96.3)	83.0 (71.0–97.3)	0.45	83.0 (71.1–96.8)	84.7 (72.8–99.5)	81.2 (68.1–92.1)	0.56
LVEF (%)	56 (6)	57 (7)	56 (6)	0.13	56 (6)	56 (7)	56 (7)	0.13
E/e', median (IQR)	7.1 (5.7–9.1)	7.0 (5.7–8.9)	7.2 (5.7–9.2)	0.64	7.2 (5.7–9.2)	7.2 (5.7–9.1)	6.7 (5.1–8.2)	0.28
E/A, median (IQR)	1.09 (0.85–1.47)	1.10 (0.87–1.49)	1.07 (0.85–1.46)	0.08	1.07 (0.85–1.47)	1.03 (0.82–1.35)	1.20 (0.87–1.52)	0.047
LA volume index (mL/m ²)	24.0 (8.0)	23.8 (7.7)	24.2 (8.3)	0.11	23.8 (7.7)	24.2 (8.2)	24.6 (8.6)	0.08
GLS (%)	19.4 (2.5)	19.5 (2.4)	19.3 (2.5)	0.09	19.3 (2.5)	19.5 (2.2)	19.5 (2.4)	0.34

Variables shown as mean (SD) unless stated otherwise.

BMI, body mass index; IHD, ischaemic heart disease; MR/LA ratio, MR jet area to LA area ratio; LV, left ventricle; LVEF, left ventricle ejection fraction; GLS, global longitudinal strain.

Table 2 Univariable and multivariable analyses evaluating the prognostic value of MR jet area and MR/LA ratio in predicting AF stratified by age

	Univariable analysis		Multivariable analysis		Only in participants without moderate or severe MR and normal LA size	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All participants (198 events)						
MR jet area, per 1 cm ² increase	1.08 (0.99–1.17)	0.08	1.09 (0.99–0.19)	0.08	1.22 (0.98–1.51)	0.08
MR/LA ratio per 5% increase	1.06 (1.00–1.13)	0.042	1.06 (1.00–1.12)	0.07	1.14 (0.97–1.34)	0.11
CHARGE-AF score, per 1 point increase	2.40 (2.13–2.71)	<0.001				
Participants ≤ 73 years (97 events)						
MR jet area, per 1 cm ² increase	1.13 (1.03–1.25)	0.012	1.14 (1.03–1.27)	0.012	1.39 (1.02–1.89)	0.035
MR/LA ratio per 5% increase	1.12 (1.05–1.20)	0.001	1.14 (1.06–1.24)	0.001	1.35 (1.09–1.68)	0.005
CHARGE-AF score, per 1 point increase	2.72 (3.20–3.37)	<0.001				
Participants > 73 years (101 events)						
MR jet area, per 1 cm ² increase	1.02 (0.87–1.18)	0.83	0.97 (0.82–1.16)	0.77	1.06 (0.77–1.47)	0.71
MR/LA ratio per 5% increase	0.98 (0.88–1.10)	0.77	0.96 (0.86–1.07)	0.48	0.92 (0.71–1.20)	0.55
CHARGE-AF score, per 1 point increase	2.36 (1.82–3.06)	<0.001				

Multivariable model adjusted for CHARGE-AF score that includes the following parameters: age, height, weight, systolic blood pressure, diastolic blood pressure, current smoker, antihypertensive medication, diabetes, congestive heart failure, and myocardial infarction. Sensitivity analysis: multivariable analysis restricted to participants with MR/LA ratio ≤ 20%, MJ jet area ≤ 4 cm², and left atrial volume index ≤ 34 cm³/m². MR, mitral regurgitation; LA, left atrium; HR, hazard ratio; CI, confidence interval.

interaction between triggering and maintaining arrhythmic substrate.²⁰ MR is hypothesized to be a contributing factor of both.^{21,22} MR induced volume overload during sinus rhythm has been hypothesized to increase rapid firing from the pulmonary veins mediated by stretch sensitive ion channels triggering AF.²¹ Likewise, MR induced volume overload causes LA dilation and remodelling, which through a complex series of transduction pathways results in abnormal increases in reactive oxygen species, catecholamines and inflammatory cytokines that cause adverse cardiomyocyte apoptosis, collagen loss and fibrosis that serves to maintain and promote AF.^{22–25} Interestingly, in the present study, we did not find an increase in MR severity to be associated with an increase in LAVi. LA dilation is a function of both MR severity and chronicity of MR induced volume overload. While we do not have data on MR chronicity, a low MR chronicity could explain the absence of LA dilation among these participants.

Association between MR and AF

Several previous studies have investigated the association between MR and clinical outcomes. Antoine et al.³ retrospectively studied clinical reports of 3914 patients with degenerative MR from a single laboratory over 10 years and found an increased mortality risk for moderate and severe MRs, but not mild MR. Samad et al.⁴ retrospectively reviewed 93 007 clinical reports of echocardiograms from a single laboratory, and after a median follow-up of 5.4 years (IQR 2.6–9.2 years) found an increased risk of all-cause mortality regardless of severity including mild MR. Notably, both studies included trace MR in the same category as no MR. Gammie et al.²⁶ have previously described significant heterogeneity in MR severity categorization in the published literature, including trace MR often being placed in the same category as no MR or together with mild MR. Accordingly, the clinical implications of trace MRs remain unclarified. Our study, which included predominantly mild MR, found that increasing MR severity posed a linear

increased risk of AF. Consequently, increasing MR size throughout the entire spectrum of MR severity seems to be of clinical importance, but few other studies have looked at trace MR or graded MR on a continuous scale using MR jet area and associated this with outcome. Notably, Matsushita et al.²⁷ examined 2106 echocardiograms from a single community of black participants in a prospective cohort study, and after a median follow-up time of 22.5 years (IQR 15.6–23.5 years) found trace MR to not increase mortality compared with no MR, whereas mild MR increased mortality.

Previous studies have investigated the association between MR and AF. In the previously mentioned study, Matsushita et al.²⁷ found mild MR to increase the risk of AF compared with no/trivial MR. Likewise, Padfield et al.⁵ in a registry-based study of 755 Canadian participants with paroxysmal AF found moderate and severe MRs to be a risk factor for progression to persistent AF. Notably, outcomes for mild or trace MR were not included. Our study is the first to find MR, regardless of severity, to increase risk of AF, including for trace/mild MR. This may possibly be due to our larger sample size, or MR being treated as a continuous variable as compared with a categorical variable in all previous studies.

We found age to modify the risk of AF in the general population, with MR only being significantly associated with AF in participants younger than ≤73 years of age. This is possibly due to the MR having longer time to progress in severity and induce adverse remodelling in the atrium, while a small MR in elderly patients has likely been present for an extended period without being likely to progress in severity to a point that increased the risk of adverse outcomes.

Clinical application

For technical reasons, the MR/LA ratio and MR jet area methods are currently not recommended for MR severity grading, but our study demonstrates that MR/LA ratio and MR jet area provide prognostic value in terms of diagnosis of incident AF in non-elderly adults, with any degree

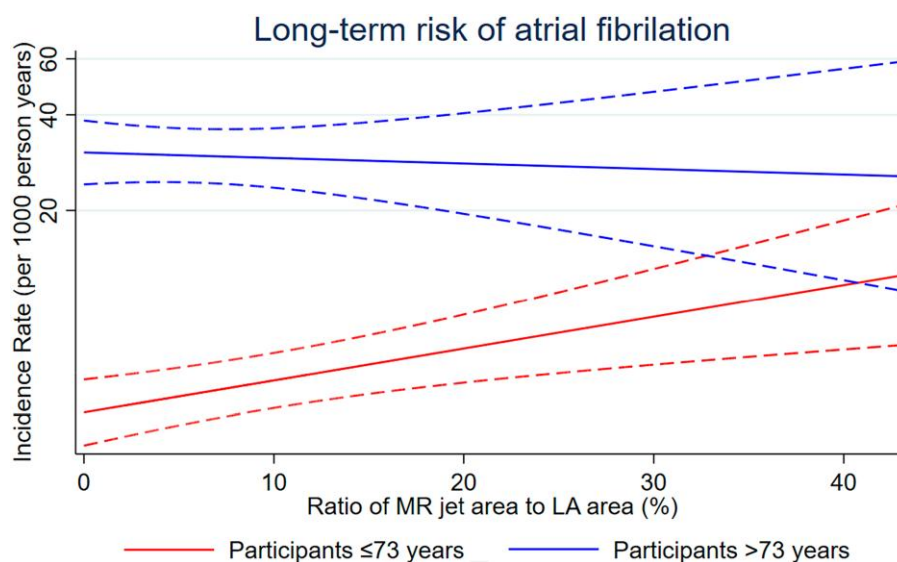


Figure 2 Mitral regurgitation to left atrial area ratio (MR/LA ratio) and long-term risk of atrial fibrillation. The figure displays the unadjusted association between MR/LA ratio and the incidence rate of incident atrial fibrillation per 1000 person-years in the general population among participants ≤ 73 and >73 years (with 95% confidence intervals).

of MR. Diagnosis of AF remains costly and time consuming.²⁸ Our results show that MR/LA ratio and MR jet area may be useful for risk stratification of non-elderly adults in the general population. As the images required for quantifying MR by this method are already integrated within the routine echocardiographic examination, their use for risk stratification would be easy to implement and could potentially aid in identifying patients in need of rhythm monitoring for AF detection.

Limitations

This study had several limitations. We did not have data on some relevant confounding factors such as obstructive sleep apnoea,²⁹ thus some residual confounding may remain. Since AF was not screened for systematically but instead was obtained through the national registries using ICD-10 codes, participants with asymptomatic or subclinical AF may have been missed and categorized as having no AF. In addition, patients diagnosed with AF in private practice who did not have any hospital contacts would not be identified. The MR jet area method is affected by loading conditions. However, we sought to account for this by including BP in our multivariable analysis. In addition, the method may overestimate in the setting of the hypertensive patients and eccentric MR as the jet may be directed out of the imaging plane. We did not have colour Doppler images in the apical two-chamber and three-chamber views for all patients. While standardized profiles were used for all echocardiographic exams, the authors cannot exclude that settings for some exams could have been changed by accident. Unfortunately, images to calculate PISA were not obtained in the present study, which made it impossible to assess true MR severity, but given that PISA is primarily used to distinguish between moderate and severe MRs, and our study containing primarily trace/mild MR, it is unlikely that addition of PISA measurements would have changed the results of our study.

Conclusion

In the general population, presence and increasing severity of MR as assessed by MR/LA ratio and MR jet area provide independent prognostic

information regarding the risk of AF in younger participants, but not in elderly. Importantly, the association between MR and AF was continuous, indicating that even MRs of mild severity confer an increased risk of AF.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Due to the confidential nature of the data, it is not possible to share, publicly as per Danish regulations. All requests to access the data should be directed at the Danish Data Protection Agency (Videnscenter for Dataanmeldelser).

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