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Frequent premature ventricular complexes and risk of atrial fibrillation, heart failure, stroke and mortality: a meta-analysis

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ABSTRACT

Background/aim Frequent premature ventricular complexes (PVCs) have historically been regarded as benign in structurally normal hearts, yet emerging evidence suggests substantial cardiovascular risk. This meta-analysis aimed to quantify associations between frequent PVCs and incident atrial fibrillation, heart failure, stroke and all-cause mortality in adults without established cardiovascular disease.

Methods PubMed/MEDLINE, Embase, CENTRAL, Web of Science and Scopus were searched through February 2025. Databases were searched from inception to February 2025. Eligible studies employed standardised PVC assessment methods with a minimum 12-month follow-up reporting adjusted effect estimates. Data were independently extracted and quality was assessed (Risk of Bias in Non-randomized Studies of Interventions) by two reviewers. Random-effects meta-analyses yielded pooled HRs with 95% CIs and prediction intervals (PI). Study-level meta-regression was used to evaluate dose–response relationships, and heterogeneity sources were explored via further meta-regression.

Outcomes 20 articles (17 studies; 26 783 590 participants) were analysed. Frequent PVCs were significantly associated with increased risks of atrial fibrillation (HR 1.69, 95% CI 1.39 to 2.05; PI 0.91–3.12), heart failure (HR 1.73, 95% CI 1.50 to 2.00; PI 1.18–2.54), stroke (HR 1.28, 95% CI 1.10 to 1.50; PI 0.90–1.82) and all-cause mortality (HR 1.31, 95% CI 1.10 to 1.56; PI 0.79–2.18). Heterogeneity was substantially reduced in sensitivity analyses restricted to Holter-quantified PVCs. Meta-regression identified a 5.4% increased atrial fibrillation risk per 1% increment in PVC burden.

Conclusion Frequent PVCs confer significantly increased cardiovascular risks in populations largely without overt structural heart disease, though baseline cardiac assessment varied across studies. Patients with frequent PVCs (≥500/day) may benefit from periodic echocardiography and rhythm monitoring to detect early structural or arrhythmic progression. Randomised trials are needed to determine if PVC burden-guided interventions can reduce cardiovascular risk.

PROSPERO registration number CRD420251006111.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Frequent premature ventricular complexes are linked to cardiomyopathy and have been reported to precede atrial fibrillation, heart failure, stroke and death, but the risk magnitude, dose–response by burden and measurement effects have remained uncertain.

WHAT THIS STUDY ADDS

⇒ This meta-analysis (>26 million adults) indicates frequent premature ventricular complexes confer ~69% higher atrial fibrillation risk, ~73% higher heart failure risk, ~28% higher stroke risk and ~31% higher mortality, with atrial fibrillation risk rising ~5% per 1% burden and more consistent estimates when quantified by 24-hour Holter monitoring.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results support periodic echocardiography and rhythm surveillance for frequent premature ventricular complexes (≥500/day or ≥1%), encourage extended monitoring to standardise burden assessment and prioritise randomised trials of burden-guided interventions to test event reduction.

INTRODUCTION

Premature ventricular complexes (PVCs) are among the most frequently detected ventricular arrhythmias in clinical settings, characterised by premature depolarisation originating from the ventricular myocardium. The prevalence of PVCs ranges from 1% to 4% in the general population and increases with advancing age, male sex, hypertension and other cardiovascular risk factors.[1 2] Historically considered benign in persons with structurally normal hearts, new evidence indicates that frequent PVCs could indicate considerable cardiovascular consequences beyond their clinical manifestations of palpitations, chest discomfort and syncope.[3]

A high PVC burden, which is usually defined as at least 1% of total beats or 100–500 PVCs per day, has been shown to cause PVC-induced cardiomyopathy.[4] Recent evidence indicates that frequent PVCs may correlate with a wider array of adverse outcomes, including the onset of atrial fibrillation (AF), heart failure (HF) that is not linked to overt cardiomyopathy and cerebrovascular events, even in individuals free of pre-existing structural heart disease. AF is linked to impaired quality of life, increased mortality and elevated thromboembolic risk.[5] HF contributes to cardiovascular morbidity

and mortality, while stroke remains a leading cause of death and long-term disability.[6 7]

Previous studies have examined the correlation between frequent PVCs and premature atrial contractions (PACs) and heightened risks of negative cardiovascular events. High PVC counts are a sign of new AF and HF, especially when they are mixed with high PAC numbers or when they are multiform.[8] Frequent PACs are indicative of developing AF and detrimental cardiovascular events.[9] Patients with AF who have a high PVC load (≥10%) are more likely to have an ischaemic stroke or be admitted to the hospital for HF.[10] High PAC counts in patients with frequent PVCs are associated with increased mortality, AF, stroke and HF events.[11] PVC burden independently predicts all-cause and cardiovascular mortality in patients with persistent AF.[12] Of note, a meta-analysis confirms that frequent PACs are associated with increased risks of stroke and death.[13] PVCs are also independently associated with incident HF.[14 15]

Despite these observations, the evidence remains fragmented due to heterogeneous methodologies, variable PVC quantification, inconsistent outcome definitions and limited adjustment for confounders. These findings highlight the independent predictive significance of frequent PVCs and PACs for detrimental cardiovascular outcomes, including AF, stroke, HF and mortality. Consequently, a comprehensive meta-analysis is required to accurately quantify these associations and furnish substantial evidence to inform clinical decision-making. This systematic review and meta-analysis aims to comprehensively combine the existing information concerning the prognostic influence of frequent PVCs on the onset of AF, HF and cerebrovascular incidents in persons free of pre-existing cardiovascular illness. Employing a rigorous PICOTT (Population, Intervention/Exposure, Comparison, Outcomes, Time, Type of study) framework, studies using standardised PVC assessment methods (eg, 12-lead electrocardiography, ambulatory Holter monitoring) with a minimum of 12-month follow-up and appropriate confounder adjustment will be integrated. The primary outcomes include acute AF, HF and stroke, and the secondary endpoint is all-cause mortality. The goal of this meta-analysis is to improve how we classify the risks for patients with frequent PVCs and to help with future research and treatment plans for managing arrhythmias.

METHODS

Protocol and registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; Registration No CRD420251006111).

Eligibility criteria

Studies were considered eligible if they: (1) enrolled adult participants (≥18 years) without documented AF, HF, cerebrovascular disease or significant structural heart disease at baseline as defined by individual study protocols. Ascertainment methods for excluding significant structural heart disease varied considerably across studies, ranging from administrative diagnostic code-based exclusion and clinical history review to systematic echocardiographic assessment or, rarely, cardiac MRI; (2) quantitatively assessed PVC burden using standardised methods (eg, 12-lead ECG, Holter monitoring, extended recording); (3) defined frequent PVCs as either ≥1% of total beats, ≥100–500 PVCs/24 hours, or alternative validated quantification methods; (4) included a comparison group with absence of PVCs or low PVC burden (below threshold defined as 'frequent'); (5) reported at least one primary outcome (incident AF, HF or stroke) or secondary outcome (all-cause mortality, cardiovascular mortality, systemic thromboembolism, ventricular arrhythmias, composite cardiovascular endpoints); (6) provided adjusted effect measures (HRs, ORs or relative risks) with corresponding CIs; (7) had a minimum follow-up duration of 12 months; and (8) employed randomised controlled trial, prospective cohort, retrospective cohort, nested case–control or registry study designs with appropriate adjustment methodology.

Exclusion criteria comprised: (1) case reports, editorials, reviews or letters without original data; (2) studies in paediatric populations; (3) studies without quantitative assessment of PVC burden; (4) studies with follow-up duration <12 months; (5) studies exclusively including patients with pre-existing AF, HF or cerebrovascular disease; (6) studies without appropriate control or comparison groups; (7) studies without adjusted effect estimates; and (8) duplicate reports of the same cohort without additional information.

For synthesis purposes, studies were grouped according to outcome reported (AF, HF, stroke), PVC burden threshold used to define 'frequent PVCs' and methodological characteristics.

Information sources

Electronic databases (PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, Scopus and Google Scholar) were searched from their inception to the most recent update, encompassing studies published from 2000 to 2025. The search combined concept blocks for PVCs (eg, 'premature ventricular complex*', 'ventricular ectop*', 'PVC*'), cardiovascular outcomes (eg, 'atrial fibrillation', 'heart failure', 'stroke', 'mortality') and study designs (eg, 'cohort', 'prospective', 'retrospective') using Boolean operators (AND/OR). The search was last conducted in February 2025. No language limits were applied apart from excluding articles without accessible English versions. Reference lists were also screened manually for additional studies. Detailed search strategies for reproducibility are documented in online supplemental table S1.

Data collection process

After duplicate records were removed, two independent reviewers screened titles and abstracts for relevance. Potentially eligible articles underwent full-text review to confirm adherence to inclusion criteria. Data were extracted into a standardised spreadsheet, capturing article design, patient demographics, methods of PVC assessment, methods used to define and ascertain absence of significant structural heart disease at baseline (including documentation of echocardiographic screening protocols, cardiac magnetic resonance utilisation, reliance on administrative codes or clinical assessment methodologies), follow-up duration and reported outcomes. Primary outcomes included incident AF, HF and stroke, while secondary outcomes comprised all-cause mortality, cardiovascular mortality, systemic thromboembolism, ventricular arrhythmias and composite cardiovascular endpoints. For each outcome, the most adjusted effect measure was extracted, with preference given to data from the longest follow-up period. Additional clinical covariates extracted included cardiovascular risk factors beyond standard parameters (eg, renal function indices, smoking status, body mass index, lipid profiles) and baseline cardiac parameters. Articles were categorised according to imaging-based versus

non-imaging-based exclusion criteria for planned sensitivity analyses. Discrepancies between reviewers were resolved by discussion or referral to a third reviewer, and efforts were made to contact article authors for clarification of missing or ambiguous data.

Study risk of bias assessment

Methodological quality and risk of bias were independently assessed by two investigators using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[17] The ROBINS-I tool evaluates bias in domains including confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement and selective reporting. Articles were categorised as having low, moderate or serious risk of bias. Discrepancies in quality assessments were resolved through discussion or consultation with a third reviewer. Risk of bias assessments were not employed as exclusion criteria but were incorporated into sensitivity analyses and certainty assessments. ROBINS-I classifications (low, moderate, serious) were prespecified; 'serious' was defined as high risk in ≥2 domains or critical in any domain. Sensitivity analyses excluded serious-risk articles and pooled by ROBINS-I strata. Evidence certainty was graded with GRADE (Grading of Recommendations Assessment, Development and Evaluation),[18] with downgrades for risk of bias (serious ROBINS-I predominance), inconsistency (I^2>50% or prediction interval (PI) spanning 1.0), indirectness (heterogeneous exposure/outcome definitions), imprecision (wide CI/PI relative to clinical relevance or total events <300) and publication bias (Egger p<0.10 or trim-and-fill imputations).

Statistical analysis

All statistical analyses were performed using R software V.4.2.3 with the 'meta' and 'metafor' packages,[19] and STATA V.17 (College Station, Texas, USA) was employed for meta-regression, sensitivity analyses and forest plot creation. Effect measures for dichotomous outcomes (incident AF, HF, stroke and mortality) were expressed as HRs, relative risks or ORs with 95% CIs, with HRs prioritised when multiple measures were available. For time-to-event outcomes, ORs were excluded from primary meta-analyses to maintain consistency of effect measures. For continuous outcomes, mean differences or standardised mean differences with corresponding 95% CIs were extracted. When studies provided outcomes across PVC burden categories, comparisons between the highest and lowest categories were prioritised, with additional data obtained for dose–response assessments. Effect estimates were log transformed prior to pooling.

Random-effects meta-analyses were conducted using the restricted maximum likelihood estimator for between-study variance (τ^2). Pooled HRs and their 95% CIs were calculated using Wald-type CIs. Additionally, 95% PIs were calculated to estimate the range where the true effect size in a new, similar study would be expected to lie, facilitating interpretation of results in the context of high heterogeneity. Heterogeneity was assessed by the χ^2 test and the I^2 statistic, with 95% CIs for I^2 also reported.

Dose–response analyses were conducted using meta-regression to evaluate the relationship between PVC burden and clinical outcomes across studies. As individual studies reported single PVC burden thresholds rather than multiple quantitative categories, meta-regression coefficients were calculated to represent the relative risk increase per percentage point increment in PVC burden across the spectrum of reported thresholds. Threshold effect analyses were performed to identify optimal PVC burden cut-points for risk stratification where data permitted.

Subgroup and sensitivity analyses were undertaken to explore potential effect modifiers (mean age, hypertension prevalence, coronary artery disease prevalence, PVC burden) and assess robustness. Robustness was examined with leave-one-out influence analyses; Holter-only subsets (24-hour quantitative burden); and subsets excluding articles at 'serious' ROBINS-I risk. Small-study effects were assessed using Egger's test and trim-and-fill where k≥10. Publication bias was examined using funnel plots and Egger's test for outcomes with at least 10 articles.[20]

RESULTS

Study selection

A systematic search across electronic databases identified 6244 records: PubMed (n=464), Scopus (n=2512), Web of Science (n=1121), Embase (n=2107) and Cochrane Central (n=40). After removing 1109 duplicate records and 53 non-English records, 5082 records underwent title and abstract screening. An additional 74 records were identified through citation searching. After excluding 4955 records based on title and abstract screening, 127 reports were sought for full-text retrieval, with no reports unavailable. Full-text assessment of 127 reports resulted in the exclusion of 110 articles due to the absence of desired outcomes (n=45), inappropriate study design (n=52) and insufficient statistical data (n=13). An additional 74 records were identified via other sources, all of which were retrieved and assessed, with 71 excluded based on the same criteria (desired outcomes not reported, n=25; inappropriate study design, n=34; insufficient statistical data, n=12). Ultimately, 20 articles were included in the final review. The PRISMA flow diagram detailing the study selection process is presented in figure 1.

Study characteristics

The systematic review included 20 articles published between 2006 and 2025, comprising 12 prospective cohort, seven retrospective cohort and one retrospective case–control articles.[8 10 14 15 21–36] Sample sizes exhibited substantial heterogeneity, ranging from 312 to 16 757 903 participants, with a median of 8047 participants. The cumulative study population totalled 26 573 015 individuals across 17 studies (parent datasets), representing diverse healthcare systems and geographical regions. The mean age of participants ranged from 46.1 to 72.2 years, with 12 articles reporting male predominance. Comorbidity prevalence demonstrated considerable variability; hypertension (16.8–86.0%) and diabetes mellitus (4.0–26.0) were the most frequently documented conditions.

PVC assessment methodologies encompassed 24-hour ambulatory Holter monitoring (n=11), standard 12-lead electrocardiography (n=7) and administrative diagnosis codes (n=2). Definitions of clinically significant PVC burden exhibited heterogeneity, with thresholds ranging from ≥1 PVC on a standard ECG to quantitative criteria of ≥20% of total heartbeats. Follow-up duration varied between 32.4 and 294 months (median 120 months), with rigorous ascertainment of cardiovascular outcomes through validated adjudication procedures. All articles established the absence of pre-existing cardiovascular disease at baseline through comprehensive medical record review, echocardiographic assessment or administrative data verification. The 20 articles yielded 40 effect estimates across four primary outcome domains: AF, HF, stroke and all-cause mortality. Eight articles reported multiple primary outcomes,

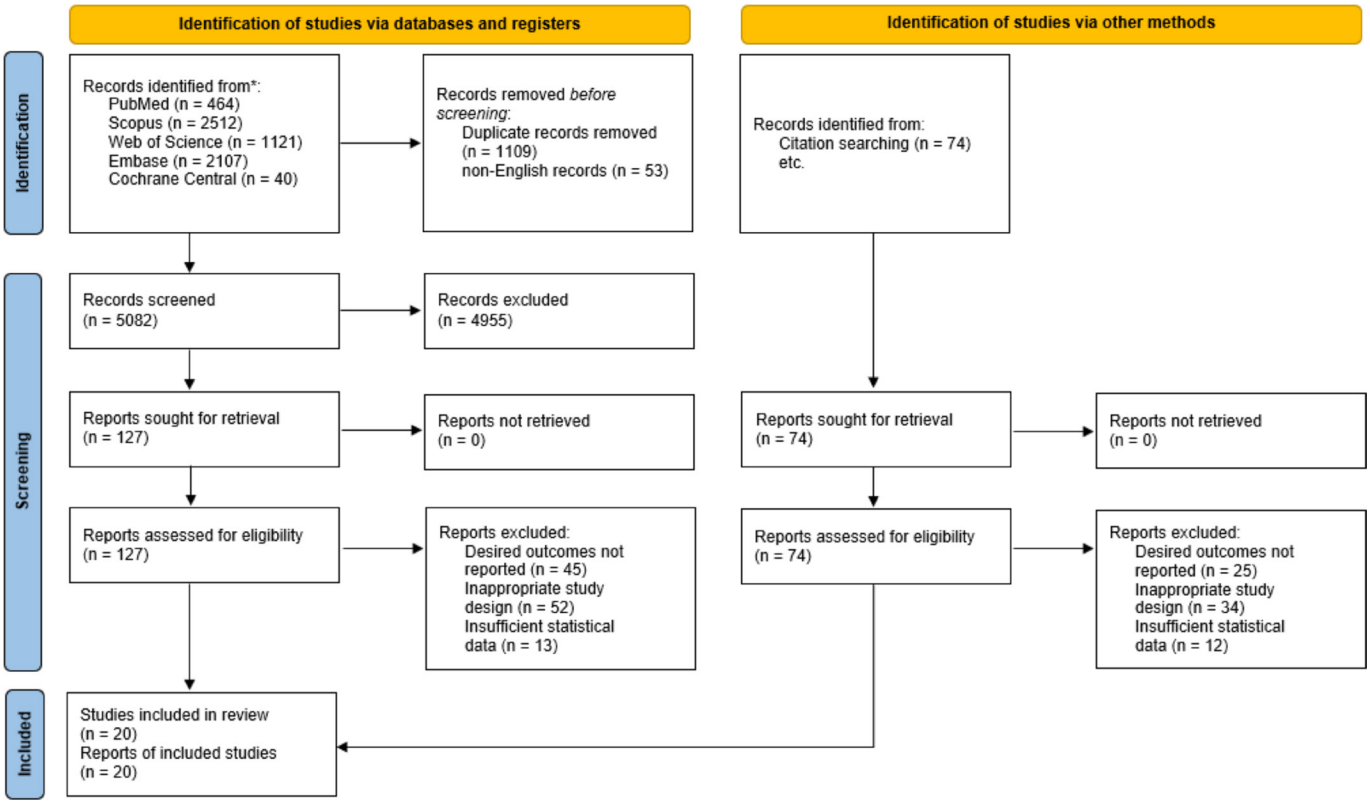

Figure 1 PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

enabling robust assessment of outcome-specific associations. Baseline characteristics of included articles are detailed in table 1.

Risk of bias in studies

Methodological quality was evaluated using the ROBINS-I tool, including bias in confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement and reported result selection.

Overall, risk-of-bias scores were generally low to moderate. Although exposure classification and outcome assessment were typically rigorous, numerous methodological limitations were apparent. Residual confounding emerged as a major concern as a result of incomplete adjustment for crucial factors such as detailed echocardiographic data, heart structural measurements and other clinically significant confounders. Furthermore, potential selection bias was frequently mentioned, especially due to the use of specialised populations, retrospective enrolment or administrative databases, which may limit generalisability. Additionally, the absence of prespecified analytical protocols and comprehensive reporting strategies in several evaluations raises concerns regarding selective reporting. Figure 2 illustrates the domain-specific ROBINS-I assessment for individual articles.

Results of syntheses

The meta-analyses examining associations between frequent PVCs and cardiovascular outcomes incorporated data from 25 articles encompassing 26 783 590 participants. Figure 3 presents a composite four-panel forest plot displaying individual study estimates and pooled HRs with corresponding 95% CIs and PIs for all primary outcomes.

AF risk

Eight articles reporting HRs with 9 672 658 participants were included in the meta-analysis examining the association between frequent PVCs and incident AF. The random-effects model demonstrated that frequent PVCs were significantly associated with increased AF risk (HR 1.69, 95% CI 1.39 to 2.05, $p<0.0001$). Substantial statistical heterogeneity was observed ($I^2=90.0\%$, $p<0.0001$), indicating considerable variability in effect estimates across articles. The 95% PI ranged from 0.91 to 3.12.

HF risk

11 articles with 16 875 119 participants examined the association between frequent PVCs and incident HF. The random-effects meta-analysis revealed a significant association between frequent PVCs and HF development (HR 1.73, 95% CI 1.50 to 2.00, $p<0.0001$). Moderate to substantial heterogeneity was detected ($I^2=63.2\%$, $p=0.002$). The 95% PI ranged from 1.18 to 2.54.

Stroke risk

Nine articles with 9 653 607 participants investigating the association between frequent PVCs and incident stroke were pooled. The meta-analysis demonstrated a significant association between frequent PVCs and stroke risk (HR 1.28, 95% CI 1.10 to 1.50, $p=0.0015$). Moderate heterogeneity was observed ($I^2=44.1\%$, $p=0.08$). The 95% PI ranged from 0.90 to 1.82.

All-cause mortality

Nine articles with 9 828 169 participants reported on the association between frequent PVCs and all-cause mortality.

Table 1 Baseline characteristics and methodologies of included studies

Study (author, year, cohort)	n	Age (years)*	Male (%)	PVC assessment†	PVC definition‡	Follow-up (years)*	SHD assessment§	Outcomes¶
Agarwal *et al*, 2015 (REGARDS)[21]	24 460	64.5±9.3	44.9	12L-ECG	≥1 PVC	6.0	Clin Hx/codes	S
Agarwal *et al*, 2017 (CalHCUP)[14]	16.7 million	50.3	42.4	ICD code	ICD-9: 427.69	5.0	ICD code	HF
Ahmad *et al*, 2023 (NHANES-III)[22]	8047	56.5±0.4	47.0	12L-ECG	Any PVC	22.0	Clin Hx/codes	S
Dukes *et al*, 2015 (CHS)[23]	1139	70.5	42.3	Holter (24 hours)	Any PVC	13.7	Echo	HF, M
Johnson *et al*, 2021 (ARIC)[24]	14 479	54±6	45.0	12L-ECG	Any PVC	24.5	Clin Hx/codes	S
Kim *et al*, 2021 (K-NHIS, HF/M)[25]	9.7 million	46.4	55.4	ICD code	Dx record	9.0	ICD code	HF, M
Kim *et al*, 2021 (K-NHIS, AF/S)[25]	9.5 million	46.1	55.7	ICD code	Dx record	9.0	ICD code	AF, S
Kim *et al*, 2024 (SMC)[10]	4834	62.3	68.0	Holter (24 hours)	≥10% burden	4.4	Mixed (SHD incl)	HF, S, M
Lee *et al*, 2023 (NCKU)[27]	16 030	57.3	45.2	Holter (24 hours)	≥1000/day	2.7	Echo (SHD incl)	AF, S
Limpitikul *et al*, 2022 (CHS)[28]	871	72.2±5.1	59.0	Holter (24 hours)	≥10 PVCs	11.0	Echo	HF
Lin *et al*, 2015 (TVGH, AF/S)[29]	3351	58.4	57.0	Holter (24 hours)	<720/day	10.0	Records (No syst Echo)	AF, S
Lin *et al*, 2017 (TVGH, HF/M)[15]	5778	62.7	61.2	Holter (24 hours)	>12/day	10.0	Records (Ltd Echo)	HF, M
Maneheim *et al*, 2022 (MDCS)[8]	375	64.5±5.9	45.1	Holter (24 hours)	Top quartile	17.0	Clin Hx/codes	AF, HF, S, M
Nguyen *et al*, 2017 (ARIC)[30]	15 792	45–64	45.8	12L-ECG	≥1 PVC	22.0	Clin Hx/codes	AF, HF, M
Nguyen *et al*, 2017 (CHS)[30]	5577	≥65	42.2	12L-ECG	≥1 PVC	12.0	Echo	AF, HF, M
Ogiso *et al*, 2025 (Shinken)[31]	6332	55.8	55.5	Holter (24 hours)	Burden cat	3.0	Echo, CMR (indic)	HF, S, M
Orini *et al*, 2023 (UKB)**[32]	54 000/29 000	58/64	46.0	ECG (15 s)	≥1 PVC	11.5/3.5	CAD excl (UKB1)	AF (1), HF (1, 2)
Parreira *et al*, 2021 (CHSet)[33]	312	69	60.0	Holter (24 hours)	>1% burden	8.3	Echo, CMR (indic)	HF, M
Perez *et al*, 2009 (PAVA)[34]	42 751	56.1±15	89.7	12L-ECG	Any PVC	5.3	Clin Hx/codes	AF

Records denote medical records with No syst Echo or Ltd Echo.
*Mean±SD, median (IQR) or range as reported.
†12L-ECG = 12-lead electrocardiogram; Holter (24h) = 24-hour Holter; ICD Code = International Classification of Diseases code; ECG (15s) = 15-second rhythm strip.
‡ Burden Cat. = Categorical burden (<1000, 1000-9999, ≥10000/day); Dx Record = Diagnosis record.
§ Clin Hx/Codes = clinical history/diagnostic codes; Echo = echocardiography; CMR (indic.) = cardiac MRI when indicated; CAD excl. = CAD excluded; Mixed (SHD incl.) = included SHD patients, adjusted.
¶AF = atrial fibrillation; HF = heart failure; S = stroke; M = all-cause mortality.
**Two UK Biobank cohorts (UKB1, UKB2); data for UKB1/UKB2. AF in UKB1; HF in both.
AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; Burden cat, categorical burden (<1000, 1000–9999, ≥10 000/day); CAD excl, coronary artery disease excluded; CalHCUP, California Healthcare Cost and Utilization Project; CHS, Cardiovascular Health Study; CHSet, Centro Hospitalar Setúbal; Clin Hx, clinical history/diagnostic; CMR (indic), cardiac MRI when indicated; Dx, diagnosis; ECG (15 s), 15 s rhythm strip; Echo, echocardiography; HF, heart failure; ICD, International Classification of Diseases; K-NHIS, Korean National Health Insurance Service; 12L-ECG, 12-lead ECG; Ltd Echo, limited echocardiography; M, all-cause mortality; MDCS, Malmö Diet and Cancer Study; Mixed (SHD incl), included patients with structural heart disease, adjusted; NCKU, National Cheng Kung University; NHANES, National Health and Nutrition Examination Survey; No syst Echo, no systematic echocardiography; PAVA, Palo Alto Veterans Affairs; PVC, premature ventricular complex; REGARDS, Reasons for Geographic and Racial Differences in Stroke; S, stroke; SHD, structural heart disease; SMC, Samsung Medical Center; TVGH, Taipei Veterans General Hospital; UKB, UK Biobank.

The meta-analysis revealed a significant association between frequent PVCs and increased mortality risk (HR 1.31, 95% CI 1.10 to 1.56, p=0.003). Substantial heterogeneity was present (I^2=81.2%, p<0.0001). The 95% PI ranged from 0.79 to 2.18.

Dose–response analyses

A dose–response analysis divided studies into four categories based on PVC burden: low (n=4), moderate (n=4), high (n=4) and any PVC detected (n=13), with some studies contributing to multiple strata through stratified analyses. Quantitative assessments typically used 24-hour Holter monitoring, while brief ECG recordings and administrative codes provided binary classifications.

Meta-regression analysis of the dose–response relationship revealed a significant association for AF (coefficient=0.053, p=0.02), indicating a 5.4% increase in relative risk per percentage point increment in PVC burden, accounting for 38.5% of the between-study heterogeneity, as illustrated in figure 4. A positive trend for HF (coefficient=0.018, p=0.14) corresponded to a 1.9% increased relative risk per percentage point increase in PVC burden, explaining 9.1% of heterogeneity, whereas a borderline significant relationship for stroke (coefficient=0.03, p=0.06) indicated an approximate 3.1% increase, with PVC burden accounting for 100% of the variance. Differences between categories were statistically significant for HF (p<0.0001) and AF (p=0.008), but not for stroke (p=0.24).

Threshold effect analyses identified an optimal PVC burden threshold of 2.1% of total beats for AF, with individuals above this threshold demonstrating a 2.01-fold higher risk (p=0.001) compared with those below. No statistically significant thresholds were identified for HF, stroke or mortality outcomes, suggesting potentially linear relationships across the burden spectrum for these endpoints.

Holter monitoring sensitivity analyses

Sensitivity analyses restricted to studies using 24-hour Holter monitoring for PVC quantification were conducted to address methodological heterogeneity. Holter-based analyses demonstrated significant associations for AF (three articles; HR 1.53, 95% CI 1.26 to 1.86, p<0.0001; I^2=0.0%; PI: 1.00–2.35), HF (six articles; HR 1.68, 95% CI 1.28 to 2.20, p=0.0002; I^2=35.6%; PI: 0.91–3.12) and all-cause mortality (six articles; HR 1.41, 95% CI 1.28 to 1.55, p<0.0001; I^2=0.0%; PI: 1.25–1.60). Stroke analysis (three articles) yielded non-significant results (HR 1.47, 95% CI 0.87 to 2.50, p=0.15; I^2=62.6%; PI: 0.21–10.33). Notably, heterogeneity was eliminated for AF and mortality outcomes (I^2=0.0%) and substantially reduced for HF when analyses were restricted to Holter-based assessments.

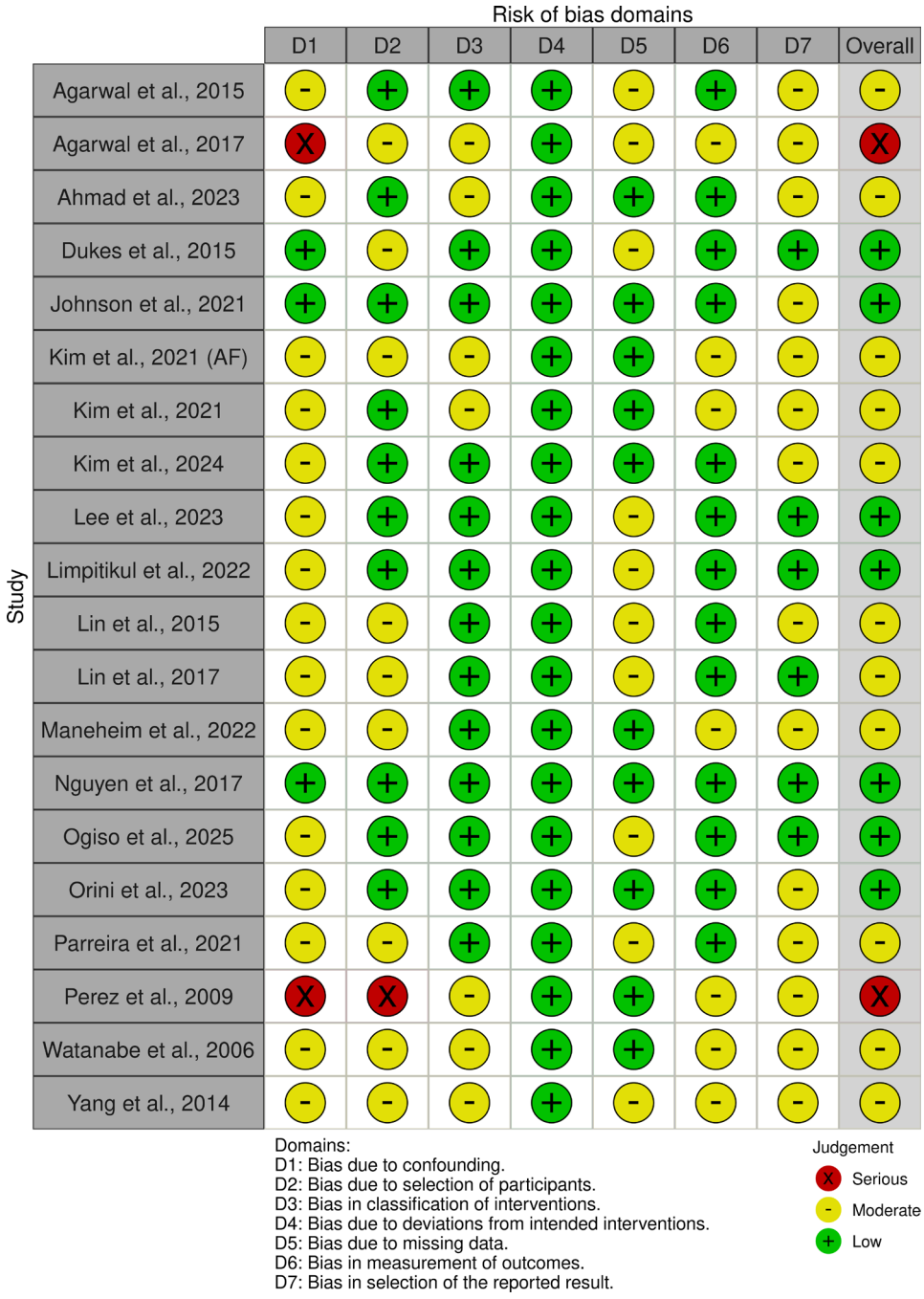

Figure 2 Domain-specific ROBINS-I assessment for included articles. AF, atrial fibrillation; ROBINS-I, Risk of Bias in Non-randomized Studies of Interventions.

Additional analyses

Meta-regression analyses were conducted to clarify sources of heterogeneity and identify clinical predictors. Mean age was identified as a significant moderator for AF (β=−0.039, p=0.001), with stronger associations identified in younger populations. Prevalence of hypertension demonstrated an inverse relationship with effect size (β=−0.021, p=0.03); these variables together explained approximately 94% of the between-study variance. For HF, the prevalence of coronary artery disease demonstrated a significant inverse relationship with effect size (β=−0.011, p=0.01), explaining 98.4% of the observed heterogeneity. No significant moderators were identified for stroke outcomes, while mean age was positively associated with all-cause mortality (β=0.02, p=0.01), with each decade increase representing a 20% greater relative risk, explaining 73.0% of the between-study variance. Combined meta-regression bubble plots for each analysis are included in online supplemental figure 1.

Sequential leave-one-out sensitivity analyses confirmed the robustness of the findings. The pooled HRs for AF ranged from 1.48 (95% CI 1.34 to 1.64) to 1.77 (95% CI 1.44 to 2.17), with the Kim *et al*[25] article exerting the greatest influence. HF and stroke demonstrated similar stability, whereas all-cause mortality demonstrated greater sensitivity, with exclusion of the Kim *et al*[25] article yielding a stronger association (HR 1.41, 95% CI 1.23 to 1.61). Additional sensitivity analyses excluding articles with high risk of bias on the ROBINS-I assessment provided similar results.

Figure 3 Association of frequent premature ventricular complexes with cardiovascular outcomes. (a) atrial fibrillation risk; (b) heart failure risk; (c) stroke risk; (d) all-cause mortality. ARIC, Atherosclerosis Risk In Communities; CalHCUP, California Healthcare Cost and Utilization Project; CHS, Cardiovascular Health Study; CHSet, Centro Hospitalar Setúbal; KNHI, Korean National Health Insurance Service; MDCS, Malmö Diet and Cancer Study; NCKU, National Cheng Kung University; NHANES-III, National Health and Nutrition Examination Survey III; PAVA, Palo Alto Veterans Affairs; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SMC, Samsung Medical Center; TVGH, Taipei Veterans General Hospital; UKB, UK Biobank.

Reporting biases

Publication bias was assessed using funnel plots and statistical tests. For AF, visual inspection indicated symmetry, with Egger's regression (p=0.06) and Begg's test (p=0.81) suggesting minimal bias. Similar symmetry was observed for HF, stroke and all-cause mortality, with Egger's p values of 0.24, 0.75 and 0.18, respectively. The trim-and-fill method identified two potentially missing articles for AF, yielding an adjusted pooled HR of 1.84 (95% CI 1.53 to 2.21). Evidence of potential bias was observed for HF (one article imputed) and stroke (four articles imputed), though adjusted estimates remained statistically significant. Combined funnel plots for each analysis are presented in online supplemental figure 2.

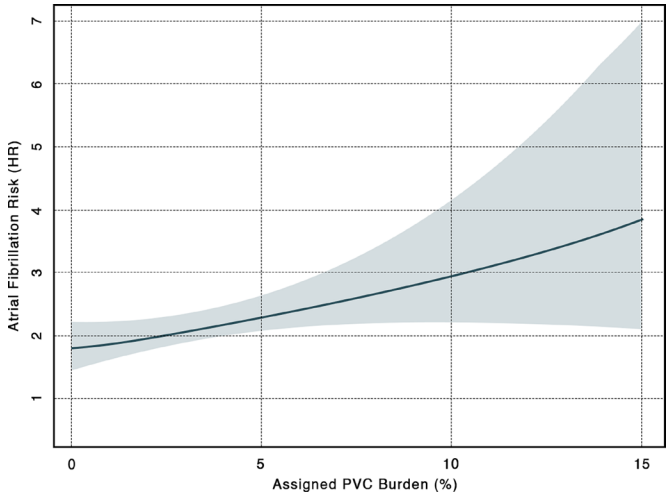

Figure 4 Dose–response relationship between premature ventricular complex (PVC) burden and risk of atrial fibrillation.

Certainty of evidence

According to the GRADE evaluation, the overall quality of evidence is low, due primarily to the observational design of the included articles, which limits confidence in the effect estimates.[18] Even though many articles used standardised methods to assess PVC burden and performed adjusted analyses, residual confounding, potential selection bias and variability in exposure measurement and definitions all contribute to significant heterogeneity and imprecision. Indirectness concerns arise from differences in study populations and methodological approaches, emphasising the need for well-designed prospective research to improve certainty in prognostic findings.

DISCUSSION

Across population-based studies largely free of overt structural heart disease at baseline, frequent PVCs were consistently associated with higher risks of AF, HF, stroke and mortality. Associations became more homogeneous when burden was quantified with ambulatory (Holter) monitoring, indicating exposure ascertainment as a principal source of variability.[37]

Contemporary cardiac magnetic resonance series identify concealed myocardial abnormalities in approximately 15% of individuals labelled idiopathic on conventional assessment, suggesting that unrecognised substrate contributes to observed risks and highlighting limitations of baseline phenotyping in

prior studies.[38 39] Selective advanced imaging appears reasonable in higher risk phenotypes.[40]

For AF, a study-level dose–response pattern was evident and heterogeneity diminished in Holter-restricted analyses, supporting a burden-dependent relationship.[37] The HF signal aligns with a reversible, burden-related cardiomyopathy, as ventricular function commonly improves after effective suppression of PVCs.[4 41–43] Mortality findings likewise converged under standardised ambulatory quantification, reinforcing the prognostic relevance of precise burden assessment.[37]

The stroke association was modest and incompletely explained by documented AF. Alternatively, non-AF pathways remain plausible but indirect; cerebrovascular risk should be appraised carefully without implying anticoagulation in the absence of AF.[44 45] Coexistent atrial ectopy may amplify risk and merits integrated ectopic profiling during stratification.[13 46]

Guidelines converge on considering intervention at burdens around 10–15%, and periodic imaging or rhythm surveillance is reasonable in higher burden or high-risk morphologic patterns.[47–49] Evidence gaps persist regarding outcome modification with burden-guided therapy; ongoing randomised comparisons of ablation and antiarrhythmic strategies should clarify treatment effects and inform threshold selection.[50]

Several limitations merit attention. Baseline structural heart disease ascertainment ranged from administrative codes to systematic echocardiography, with cardiac magnetic resonance seldom used; this variability introduces uncertainty about the true prevalence of concealed myocardial disease. Exposure measurement also varied, with heterogeneity in PVC identification (single ECG vs 24-hour Holter) and burden thresholds, although sensitivity analyses consistently favoured extended monitoring. Differences in confounder adjustment leave potential for residual confounding, the observational designs preclude causal inference and the predominance of older male participants limits generalisability.

Despite these constraints, PVC burden quantification remains useful for risk assessment. Baseline echocardiography and extended rhythm monitoring are reasonable for burdens ≥500 PVCs/day or >1% of beats, with lower thresholds for non-outflow-tract origin, multifocal PVCs or concomitant atrial ectopy. Advanced imaging, particularly cardiac magnetic resonance, is appropriate in high-risk phenotypes, and periodic surveillance may allow earlier detection of structural or arrhythmic progression and timely intervention.

CONCLUSIONS

Frequent PVCs confer increased risks of AF, HF, stroke and mortality in populations without overt structural heart disease at baseline. Associations are most consistent when burden is quantified with ambulatory monitoring and appear burden dependent. Focused echocardiography, extended rhythm monitoring and selective advanced imaging are reasonable in higher burden or high-risk phenotypes, while definitive trial evidence on risk reduction is awaited. Ongoing randomised studies should determine whether targeting PVC burden alters clinical outcomes and guide efficient monitoring and management strategies.

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