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REVIEW

Prognostic implications of left ventricular strain by speckle-tracking echocardiography in the general population: a meta-analysis

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Lamia Al Saikhan[1]
Chloe Park[2,3]
Rebecca Hardy[3]
Alun Hughes[2,3]

[1]Department of Cardiac Technology, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam 34212, Kingdom of Saudi Arabia; [2]Institute of Cardiovascular Science, School of Life and Medical Sciences, University College London, London, UK; [3]MRC Unit for Lifelong Health and Ageing, University College London, London, UK

Purpose: Left ventricular (LV) mechanics by speckle-tracking echocardiography (STE) is prognostic in patients with cardiovascular diseases, but evidence related to community-dwelling individuals is uncertain. We therefore performed a systematic review and meta-analysis of STE as a predictor of adverse outcomes in the general population.

Methods: PRISMA guidelines were followed and MEDLINE and EMBASE were searched to identify eligible studies. Primary outcome was all-cause mortality and secondary outcomes were composite cardiac and cardiovascular end-point. Random effects meta-analysis was performed, and a modified Newcastle-Ottawa Assessment Scale was used for quality assessment.

Results: Eight papers matched the predefined criteria (total number of individuals studied=11,744). All publications assessed global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography (2D-STE), one assessed circumferential, radial and transverse strains, and one assessed GLS-derived post-systolic shortening. None assessed LV rotational measures in association with outcomes. Two studies reported associations between GLS and all-cause mortality and composite cardiovascular end-point. Six papers reported an association between GLS and composite cardiac end-point, three of which were from the same study. Four papers were suitable for meta-analysis. GLS predicted all-cause mortality (pooled minimally adjusted HR per unit strain (%)=1.07 [95% CI 1.03–1.11], p=0.001), and composite cardiovascular (pooled maximally adjusted HR=1.18 [1.09–1.28], p<0.0001) and cardiac (HR=1.08 [1.02–1.14], p=0.006) end-points. GLS also predicted coronary heart disease (HR=1.15 [1.03–1.29], p=0.017) and heart failure (HR=1.07 [1.02–1.13], p=0.012). The quality of all studies was good.

Conclusions: This study provides some evidence that STE may have utility as a measure of cardiac function and risk in the general population. 2D-STE-based GLS predicts total mortality, major adverse cardiac and cardiovascular end-points in community-dwelling individuals in a limited number of studies. Despite this, this systematic review also highlights important knowledge gaps in the current literature and further evidence is needed regarding the prognostic value of LV mechanics in unselected older populations.

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Keywords: community-dwelling individuals, mortality, cardiovascular disease, left ventricular strain

Correspondence: Lamia Al Saikhan
Institute of Cardiovascular Science, University College London, Gower Street, London WC1E 6BT, UK
Tel +44 207 679 9437
Email lkalsaikhan@iau.edu.sa

Introduction

Left ventricular systolic dysfunction (LVSD), measured as a reduction in left ventricular (LV) ejection fraction (LVEF), is prognostic of adverse outcomes, including all-cause mortality and heart failure (HF) in the general population.[1]

Nevertheless, LVEF has well-recognized limitations and LVSD may occur when LVEF is normal.[2]

Speckle-tracking echocardiography (STE) is a comparatively new tool that quantifies myocardial mechanics,[3] and may detect LVSD when LVEF is still preserved.[2] Alterations in STE-derived LV strain are associated with risk factors for cardiovascular disease (CVD), including diabetes mellitus (DM),[4] hypertension[5] and obesity,[6] and lower global longitudinal strain (GLS) predicts unfavorable outcomes in aortic stenosis, HF and hypertrophic cardiomyopathy.[7–10]

While systematic reviews and meta-analyses of STE-based LV strain as a predictor of adverse outcomes have previously been conducted based on studies of patients with established[11,12] or established plus suspected CVD,[13] a systemic review has not been performed for community-dwelling individuals, who were not selected on the basis of disease or clinical status. This is important, since selecting samples based on disease status can distort associations between risk factors and outcomes – termed index event bias (collider bias).[14] Also, community-dwelling individuals are at lower risk of CVD compared with selected diseased populations, and the utility of STE in this setting is uncertain but potentially of value.

We therefore conducted a systematic review and meta-analysis to examine whether STE is associated with risk of total and cardiovascular mortality and morbidity independent of conventional risk factors in community-dwelling individuals (ie, in the general population).

Materials and methods

This systematic review and meta-analysis was conducted according to a previously published protocol[15] and conforms to the PRISMA guidance.[16] The protocol was registered with the PROSPERO database (CRD42018090302).

Eligibility criteria

All longitudinal studies (including placebo arms of population-based clinical trials) that assessed the prospective association of any STE-derived parameter with at least one of the pre-specified outcomes in community-dwelling individuals (>18 years), who were not selected on the basis of disease or clinical status were eligible. Studies were included if they were reported in English, published in peer-reviewed journals and adhered to appropriate ethical standards. Abstracts, reviews, conference proceedings or letters to the editor were excluded.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes were 1) a composite cardiac end-point, including any combination of cardiovascular mortality, coronary heart disease (CHD) events (myocardial infarction, unstable angina, angina/ischemia requiring emergent hospitalization or revascularization), HF hospitalization, new-onset atrial fibrillation (AF), life-threatening arrhythmia, recorded automatic implantable cardioverter defibrillator shocks, or 2) composite cardiovascular end-points, including a composite cardiac end-point and stroke, transient-ischemic attacks or peripheral arterial disease with arterial revascularization procedure. Any individual secondary end-points included in composite cardiac or cardiovascular end-points were considered as tertiary outcomes.

Search strategy

Literature was searched in MEDLINE and EMBASE via OvidSP interface. Search strategies are shown in the Supplementary materials and data to be extracted were predefined.[15] The last search was carried out on February 28, 2018. Additional papers could be identified by searching the reference lists of relevant articles and their citation metrics using Web of Science Core Collection.

Study selection and data extraction

Search results from each database were combined and duplicates were removed before screening. Initial title and abstract screening were performed and full texts of selected articles were retrieved and double screened for eligibility using a predefined eligibility form,[15] and data extracted using a predefined form.[15] Screening and extraction was performed by two researchers working independently (L.A. and C.P.). Discrepancies were reviewed and resolved through consensus.

Quality assessment

A modified version of the Newcastle-Ottawa Quality Assessment Scale of cohort studies[17] was used to assess the quality of included papers.[15] The total quality score was reported as the average of the two researchers' scores ranging from 0 (lowest quality score) to 7 (highest quality score). Papers were included irrespective of the quality assessment score.

Statistical methods

All analyses were performed using Stata 15.1 (StataCorp LLC, USA). We used random effects meta-analysis to pool

effect estimates and calculated the 95% CIs of the relevant HRs based on the expectation of heterogeneity between different studies. All HRs were rescaled to per unit strain (%). Results were presented graphically as forest plots and heterogeneity was assessed using Higgins Thompson I^2 test and Cochran's Q test.[15]

We planned to carry out a meta-analysis on a minimally adjusted model (ie, age, sex and ethnicity [if relevant]) and a maximally adjusted model, including cardiovascular risk factors and conventional echocardiographic measures. Meta-analyses were only possible for GLS. Endocardial strain was used for primary analyses, but we performed sensitivity analysis by repeating analyses replacing endocardial with midwall or epicardial strains when available.

We planned to assess potential sources of heterogeneity,[15] but were unable to perform any subgroup analysis or meta-regression due to the limited number of identified studies per analysis. Similarly, it proved impossible to compare different software for STE analysis due to lack of relevant data.

Results

Search results and study selection

A PRISMA diagram is shown in Figure 1. A total of 7040 records were identified. After removing duplicates, 6222 records of 6235 were excluded by title and abstract. Thirteen full text articles were assessed for eligibility. Five did not meet the inclusion criteria (n=1: ineligible outcome;[18] n=4: same cohort, deemed not population representative due to selection criteria[19–22]), the other eight papers from five studies were eligible (n=2 from Cardiovascular Abnormalities and Brain Lesion study,[23,24] n=3 from Copenhagen City Heart Study[25–27], and n=1 from

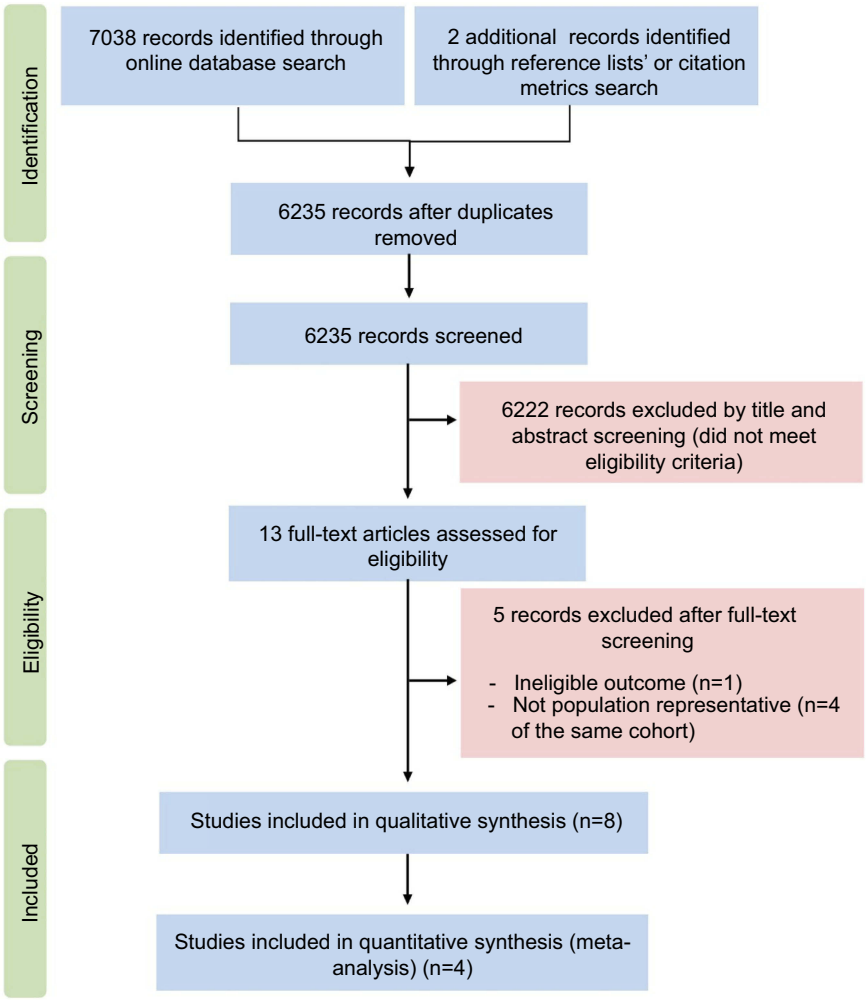

Figure 1 PRISMA flow diagram illustrates different stages of this systematic review.

Framingham Offspring Study and Framingham Omni Study,[28] Flemish Study on Environment, Genes and Health Outcomes [FLEMENGHO],[29] and Atherosclerosis Risk in Communities [30]).

Characteristics of included papers

Characteristics of included papers are shown in Table 1 (additional information regarding the studies is included in Table S1). Most (4/8) were based on US samples (two papers from the same study).[23,24,28,30] The remainder included one paper from Belgium[29] and three papers (from the same study) from Denmark.[25–27] The total number of participants was 11,744, participants in the five studies reported in the eight identified papers ranged between 675 and 6118. Follow-up ranged between 608 days (469–761) (median; IQR)[30] and 12.5 years (9.4–12.8).[27] One study recruited participants free of CVD at baseline,[28] while others included participants with known CVD.

Exposures and outcomes of included papers

Exposures and outcomes from included papers are shown in Table 2. All used two-dimensional speckle-tracking echocardiography (2D-STE). Two used Philips QLAB 8.1, two used TomTec CPA and four used EchoPac. All studies (n=8) assessed GLS. One study also assessed circumferential, radial and transverse strains[28] and another assessed GLS-derived post-systolic shortening measures.[26] None assessed LV rotational measures in association with the chosen outcomes. All papers except one[27] provided data on exposure reliability (intra-observer,[29,30] inter-observer[24] reproducibility or both[23,25,26,28]).

GLS and all-cause mortality

Two studies found associations between 2D-STE-derived measures and all-cause mortality Table (3).[26,28] GLS was reported in both studies; however, only one[28] provided both minimally and maximally adjusted estimates. Consequently, meta-analysis was only performed on the two minimally adjusted estimates; pooled HR=1.07 (1.03–1.11), p=0.001 (Figure 2A).

GLS and composite cardiovascular end-point

Two studies reported associations between GLS and a composite cardiovascular end-point, but neither provided a minimally adjusted estimate (Table 3).[23,29] Random effect meta-analysis indicated that lower 2D-STE-based GLS was associated with higher risk of a composite cardiovascular end-point; pooled maximally adjusted HR=1.18 (1.09–1.28), p<0.0001 (Figure 2C). Substituting mid-wall or epicardial-wall strains for endocardial strain did not alter this finding (Figure S1).

GLS and composite cardiac end-point

Among six papers which assessed different 2D-STE-derived measures,[25–30] only GLS or a GLS-derived measure (post-systolic index) was associated with a composite cardiac end-point (Table 3). Three of these papers were from the same study population;[25–27] one study was not suitable for quantitative synthesis because the estimates provided combined GLS and LVEF, and were available only for a selected high-risk subset of the population (stage A and B HF);[30] therefore, data from three papers[25,28,29] were used for meta-analysis. Low GLS predicted higher HR of a composite cardiac end-point; pooled maximally adjusted HR=1.08 (1.02–1.14), p=0.006 (Figure 2B). A sensitivity analysis showed that replacing the endocardial with mid- or epicardial-wall strains[29] had minimal effect (Figure S3). Analysis of minimally adjusted estimates is shown in Figure S2.

GLS and tertiary outcomes

Four papers provided data on GLS in association with tertiary outcomes,[24,25,28,29] one of which assessed circumferential, radial and transverse strains[28] (Table 4). Three papers reported CHD,[25,28,29] two HF,[25,28] one AF[24] and one cardiovascular death.[25] GLS was associated with CHD, AF and HF, whereas circumferential strain was only associated with HF although this was assessed in only one study (Table 4). Meta-analysis showed that GLS was a predictor of CHD and HF (CHD maximally adjusted HR=1.15 [1.03–1.29], p=0.017; HF HR=1.07 [1.01–1.13], p=0.012; Figure 3). Meta-analysis based on minimally adjusted estimates is shown in Figure S4, and further sensitivity analysis was performed for CHD replacing the endocardial with mid- or epicardial-wall strains and results were hardly altered (Figure S5). Additional information from studies that reported Kaplan–Meier data related to various outcomes is shown in Table S1.

Publication bias and study quality

Assessment of publication bias was not possible due to the small number of identified studies. The quality of the

Table 1 Brief characteristics of included studies

Reference	Study name	Study design	Region	n	Age (years)	Female (%)	Ethnicity	F/U	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking status (%)	Known CVD (%)
*Russo et al (2014)[23]	Cardiovascular Abnormalities and Brain Lesion (CABL) study	Longitudinal (cohort) study	Manhattan, USA	708	71±9	431 (61)	66.8% Hispanics, 17.1% blacks, 14.1% whites, and 2% of other race-ethnicities.	4.8±1.5 years (0.06, 7.38)	548 (77.4)	197 (27.8)	Hypercholesterolemia: 462 (65.2)	Smoking history: 374 (53)	CAD: 36 (5.08) AF: 41 (5.79
Cheng et al (2015)[28]	The Framingham Offspring Study and the Framingham Omni Study		Framingham, Massachusetts, USA	2831	66±9	1613 (57)	259 (9) non-white ethnicity	6.0±1.2 years	1679 (59)	365 (13)	N/A	Current smoker: 236 (8)	0
*Russo et al (2015)[24]	CABL study		Manhattan, USA	675	71±9	408 (60)	N/A	63.6±18.7 months	521 (77)	187 (27.7)	Hypercholesterolemia: 443 (65.6)	N/A	CAD: 39 (5.7) Hx HF: 19 (2.8)
Kuznetsova et al (2016)[29]	Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO)		Northern Belgium	791	50.8±15.5	410 (51.8)	White Europeans	Median (5^{th}–95^{th} percentile): 7.9 years (3.7–9.6)	326 (41.2)	34 (4.3)	N/A	Current smokers: 167 (21.1)	43 (5.4)
†Biering-Sorensen et al (2017)[25]	Copenhagen City Heart Study		Copenhagen, Denmark	1296	57.0±16.2	747 (57.6)	Almost all white	Median (IQR): 11.0 years (9.9–11.2)	489 (37.8)	122 (9.4)	N/A	Never: 428 (33.3) Previous: 426 (33.2) Current: 430 (33.5)	Previous IHD: 64 (4.9)
†Brainin et al (2018)[26]	Copenhagen City Heart Study		Copenhagen, Denmark	1296	56.9±16.2	747 (57.6)	Almost all white	Median (IQR): 11.0 years (9.9–11.2)	489 (37.7)	122 (9.4)	186 (14.3)	Never: 380 (29.3) Previous: 394 (30.4) Current: 401 (30.9)	Previous IHD: 64 (4.9)

(*Continued*)

Table 1 (Continued).

Reference	Study name	Study design	Region	n	Age (years)	Female (%)	Ethnicity	F/U	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking status (%)	Known CVD (%)
†Modin et al (2018)[27]	Copenhagen City Heart Study		Copenhagen, Denmark	1294	57.0±16.2	744 (57.5)	N/A	Median (IQR): 12.5 years (9.4–12.8)	489 (38.3)	123 (9.5)	N/A	406 (33.4)	IHD: 63 (4.9) Ischemic stroke: 25 (1.9)
Shah et al (2017)[30]	Atherosclerosis Risk in Communities (ARIC)		USA	6118	Median (IQR): 75.3 (71.7, 79.7)	3548 (58)	22% black	Median (IQR): 608 days (469–761)	5078 (83)	2325 (38)	N/A	Ever: 3793 (62) Current smoker: 367 (6)	CAD: 1040 (17) MI: 489 (8) PAD: 367 (6) Stroke: 245 (4) AF: 428 (7)

Notes: *Studies are from the same cohort (CABL study). †Studies are from the same cohort (Copenhagen City Heart Study).

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; F/U, follow up; HTN, hypertension; HF, heart failure; Hx, history of; IHD, ischemic heart disease; MI, myocardial infarction; N/A, not reported; PAD, peripheral arterial disease.

Table 2 Exposure and outcome characteristics of the included papers

	Exposure characteristics				Outcome characteristics			
References	• **Hardware** • **Software** • **Procedure**	• **Measured parameter** • **Images obtained from** • **Number of segments involved**	**Number of sonographers perform the analysis**	**Provided data on exposure reliability**	**Primary outcome (All- cause mortality)**	**Secondary outcomes**		**Tertiary outcomes**
						Composite CV end point	**Composite cardiac end point**	
Russo et al (2014)[23]	• E 33, Philips • Philips QLAB 8.1 • 2D-STE	• Longitudinal strain • Apical 4- and 2-chamber views • 12 segments	• N/A	Intra-observer reproducibility: ICC 0.82 (95% CI; 0.60–0.93, <0.01), mean difference (0.07 ±2.3%), and COV (SD/mean) 8.4%. Inter-observer reproducibility: ICC 0.85, mean difference (0.08 ±2.4%) and COV 9.2%.		n=58 (included ischemic stroke [n=16], MI [n=10], and vascular death [n=32])		
Cheng et al (2015)[28]	• Hewlett-Packard 5500, Philips • Cardiac Performance Analysis [CPA] v1.1; TomTec Imaging Systems • 2D-STE	1. Longitudinal strain • Apical 4- and 2-chamber views • N/A 2. Circumferential strain • Mid-ventricular parasternal short-axis • N/A 3. Radial strain • Mid-ventricular parasternal short axis • N/A 4. Transvers strain • Apical 4- and 2-chamber views • N/A	• 1 sonographer per specific view	Intra-observer reproducibility: Average COV: <6% for global longitudinal and circumferential strain. <9% for global transvers and radial strain. Inter-observer reproducibility: Average COV: ≤4% for global longitudinal and circumferential strain. <8% for global transvers and radial strain.	n=199 14= CHD, 8= cerebrovascular disease, and 13= other CVD causes. 164 death not attributable to a CVD cause.		New-onset CHD: n=69 (comprising fatal or nonfatal MI, coronary insufficiency, and angina pectoris)	New-onset CHD: n=69 (comprising fatal or nonfatal MI, coronary insufficiency, and angina pectoris) HF: n=71

(*Continued*)

Table 2 (Continued).

References	Exposure characteristics				Outcome characteristics			
	• Hardware • Software • Procedure	• Measured parameter • Images obtained from • Number of segments involved	Number of sonographers perform the analysis	Provided data on exposure reliability	Primary outcome (All- cause mortality)	Secondary outcomes		Tertiary outcomes
						Composite CV end point	Composite cardiac end point	
Russo et al (2015)[24]	• iE 33, Philips • Philips QLAB 8.1 • 2D-STE	• Longitudinal strain • Apical 4- and 2-chamber views • 12 segments	• N/A	Inter-observer reproducibility: ICC 0.85, mean difference (0.08 ±2.4%), and COV 0.09.				AF: n=32
Kuznetsova et al (2016)[29]	• Vivid7 Pro, GE • EchoPac, BT113, GE • 2D-STE	• Longitudinal strain • Apical 4-chamber view • N/A	• 1	Intra-observer reproducibility: Absolute bias 0.47±0.55% and absolute limit of agreement ranged from 0.62% to 1.55% (reproducibility =1.1%). Relative bias −2.51±3.02% and the limits of agreement ranged from 8.44% to 3.41% (reproducibility=6.1%).		n=96 (comprised cardiac endpoints, stroke, transient ischemic attack, aortic aneurysm, arterial embolism, and revascularization of peripheral arteries)	n=68 (Included coronary events, fatal and nonfatal HF, pulmonary heart disease, new-onset AF, and life-threatening arrhythmias)	Coronary events: n=34 [included fatal and nonfatal MI, coronary revascularization, and new-onset angina (stable or unstable)]
Biering-Sorensen et al (2017)[25]	• Vivid 5, GE • EchoPac, 2008, GE • 2D-STE	• Longitudinal strain • Apical 4-, 3- and 2-chamber views when possible • N/A	• 1	Intra-observer reproducibility: Mean difference ±1.96 SD (0.1 ±1.6%). Inter-observer reproducibility: Mean difference ±1.96 SD (−0.08 ±2.0%).			n=149 (comprising AMI [n=43], HF [n=78], and CV death [n=74])	AMI: n=43 (3.3%) HF: n=78 (6.0%) CV death: n=74 (5.7%)

(*Continued*)

Table 2 (Continued).

	Exposure characteristics				Outcome characteristics			
References	• **Hardware** • **Software** • **Procedure**	• **Measured parameter** • **Images obtained from** • **Number of segments involved**	**Number of sonographers perform the analysis**	**Provided data on exposure reliability**	**Primary outcome (All- cause mortality)**	**Secondary outcomes**		**Tertiary outcomes**
						Composite CV end point	**Composite cardiac end point**	
Brainin et al (2018)[26]	• Vivid 5, GE • EchoPac, 2008, GE • 2D-STE	• Longitudinal strain • Post-systolic index, post-systolic strain, peak post-systolic time and, post-systolic shortening • Apical 4-, 3- and 2-chamber views when possible • 18 (6 per view)	• 1	Intra-observer reproducibility: PSS: mean difference ±1.96 SD (0.2±0.95) PSI: mean difference ±1.96 SD (0.25±0.74) Inter-observer reproducibility: PSS: mean difference ±1.96 SD (−0.04±0.73) PSI: mean difference ±1.96 SD (0.06±0.56)	n=236 (18.1%)		n=149 (11.5%) (composite of HF [n=78], MI [n=43], and CV death [n=74])	
Modin et al (2018)[27]	• Vivid 5, GE • EchoPac, 2008, GE • 2D-STE	• Longitudinal strain • Apical 4-, 3- and 2-chamber views when possible • GLS was calculated as the average of strain values from available views	• N/A	No			n=222 (17.2%) (Composite outcome of either IHD or HF) n=145 (65%) in hypertensive participants and n=77 (35%) in non-hypertensive individuals	

(*Continued*)

Table 2 (Continued).

	Exposure characteristics				Outcome characteristics			
References	• **Hardware** • **Software** • **Procedure**	• **Measured parameter** • **Images obtained from** • **Number of segments involved**	**Number of sonographers perform the analysis**	**Provided data on exposure reliability**	**Primary outcome (All- cause mortality)**	**Secondary outcomes**		**Tertiary outcomes**
						Composite CV end point	**Composite cardiac end point**	
Shah et al (2017)[30]	• iE 33, Philips • TomTec CPA package • 2D-STE	• Longitudinal strain • Apical 4- and 2-chamber views • 6 in each view	• Multiple (4)	Intra-observer reproducibility: Mean difference±SD (0.2±1.4% for LS in apical 4 chamber view; and 0.8±1.2% in apical 2-chamber view) and COV 7.7% for LS in apical 4-chamber view and 6.4% in apical 2-chamber view.			n=194 (composite of deaths [n=145] and HF [n=113])	

Abbreviations: AF, atrial fibrillation; CV, cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease; COV, coefficient of variation; GLS, global longitudinal strain; HF, heart failure; ICC, intra-class correlation coefficient; IHD, ischemic heart disease; MI, myocardial infarction; PSI, post-systolic index; PSS, post-systolic shortening; 2D-STE, two-dimensional speckle-tracking echocardiography.

Table 3 Results of studies assessed the association between two-dimensional speckle-tracking echocardiographic-derived measures and all-cause mortality, composite cardiovascular and cardiac end-points

Citation	Exposure	Primary outcome		Secondary outcomes				Unit
		All- cause mortality		Composite CV end point		Composite cardiac end point		
		HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	
Russo et al (2014)[23]	Global longitudinal strain (GLS)	• N/A	• N/A		n = 58	• N/A	• N/A	Per unit decrease
				1.24 (1.12, 1.37), <0.001 1.15 (1.03, 1.28), 0.012	None Age, sex, SBP, DBP, HTN, anti-hypertensive medications, DM, LVMi, relative wall thickness, LAVi, diastolic dysfunction, and AF (Model 1)			
				1.15 (1.03, 1.28), 0.012	Model 1+ LVEF			
Cheng et al, (2015)[28]	Global average longitudinal strain		n = 199	• N/A	• N/A		n = 69	Per 1 SD change (SD=3.3%)
		1.31 (1.14, 1.52), 0.0002	Age, sex and ethnicity (Model 1)			1.37 (1.06, 1.76), 0.01	Model 1	
		1.24 (1.05, 1.46), 0.01	Age, sex, ethnicity, BMI, SBP, DBP, anti-hypertensive treatment, total/HDL cholesterol, DM, smoking status, and HR (Model 2)			1.36 (1.03, 1.79), 0.03	Model 2	
		1.21 (1.02, 1.44), 0.03	age, sex, ethnicity, BMI, SBP, DBP, anti-hypertensive treatment, total/ HDL cholesterol, DM, smoking status, LV mass, LV fractional shortening, and HR (Model 3)			1.29 (0.96, 1.74), 0.09	Model 3	

(*Continued*)

Table 3 (Continued).

Citation	Exposure	Primary outcome		Secondary outcomes				Unit
		All- cause mortality		Composite CV end point		Composite cardiac end point		
		HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	
	Global average circumferential strain	1.3 (1.12, 1.52), 0.0007 1.21 (1.04, 1.42), 0.02 1.11 (0.92, 1.34), 0.27	Model 1 Model 2 Model 3			1.1 (0.85, 1.42), 0.48 1.14 (0.87, 1.48), 0.34 1.11 (0.81, 1.51), 0.53	Model 1 Model 2 Model 3	Per 1 SD change (SD=5.8%)
	Global average radial strain	0.73 (0.61, 0.87), 0.0003 0.76 (0.64, 0.91), 0.002 0.82 (0.68, 0.98), 0.03	Model 1 Model 2 Model 3			0.87 (0.67, 1.13), 0.3 0.9 (0.68, 1.17), 0.43 0.95 (0.72, 1.26), 0.72	Model 1 Model 2 Model 3	Per 1 SD change (SD=16.8%)
	Global average transvers strain	0.93 (0.81, 1.07), 0.32 0.99 (0.85, 1.14), 0.85 1 (0.85, 1.17), 0.97	Model 1 Model 2 Model 3			1.02 (0.80, 1.29), 0.89 1.02 (0.81, 1.29), 0.87 1.04 (0.81, 1.34), 0.75	Model 1 Model 2 Model 3	Per 1 SD change (SD=7.1%)
Kuznetsova et al (2016)[29]	GLS				• n =96		n = 68	
	• Mid-wall	• N/A	• N/A	1.75 (1.39, 2.20), <0.0001	Clinical model = Family clusters, sex, age, BMI, SBP, serum cholesterol, smoking, antihypertensive treatment, DM, and a history of cardiac disease.	1.54 (1.21, 1.96), 0.0005	Clinical model	Per 1 SD decrease (SD= 2.5%)
				1.75 (1.36, 2.20), <0.0001	Clinical model + LVMi	1.54 (1.21, 2.0), 0.0005	Clinical model + LVMi	
				1.61 (1.27, 2.08), <0.0001	Clinical model + TDI e′	1.45 (1.13, 1.85), 0.0045	Clinical model + TDI e′	
				1.61 (1.27, 2.08), <0.0001	Clinical model + LVMI + TDI e′	1.45 (1.13, 1.89), 0.0041	Clinical model + LVMI + TDI e′	

(*Continued*)

Table 3 (Continued).

Citation	Exposure	Primary outcome		Secondary outcomes				Unit
		All- cause mortality		Composite CV end point		Composite cardiac end point		
		HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	
	• Endocardial	• N/A	• N/A	1.74 (1.35, 2.19), <0.0001	Clinical model	1.54 (1.22, 1.95), 0.0005	Clinical model	Per 1 SD decrease (SD= 2.9%)
				1.7 (1.35, 2.14), <0.0001	Clinical model + LVMi	1.54 (1.22, 1.95), 0.0005	Clinical model + LVMi	
				1.62 (1.25, 2.05), <0.0001	Clinical model + TDI e′	1.43 (1.12, 1.87), 0.0043	Clinical model + TDI e′	
				1.62 (1.25, 2.05), 0.0001	Clinical model + LVMI + TDI e′	1.46 (1.12, 1.87), 0.0041	Clinical model + LVMI + TDI e′	
	• Epicardial	• N/A	• N/A	1.66 (1.33, 2.10), <0.0001	Clinical model	1.49 (1.18, 1.90), 0.001	Clinical model	Per 1 SD decrease (SD= 2.2%)
				1.66 (1.31, 2.10), <0.0001	Clinical model + LVMi	1.49 (1.18, 1.90), 0.001	Clinical model + LVMi	
				1.55 (1.23, 1.97), 0.0002	Clinical model + TDI e′	1.41 (1.10, 1.81), 0.0067	Clinical model + TDI e′	
				1.55 (1.23, 1.97), 0.0002	Clinical model + LVMI + TDI e′	1.41 (1.11, 1.81), 0.0062	Clinical model + LVMI + TDI e′	
Biering-Sorensen et al (2017)[25]	GLS	• N/A	• N/A	• N/A	• N/A		• n = 149	
						1.12 (1.08, 1.17), <0.001	None	Per unit (1%) decrease
						1.08 (1.04, 1.13), <0.001	Age and sex	
						1.07 (1.01, 1.11), 0.013	Clinical model = Age, sex, HR, HTN, DM, previous ischemic heart disease, SBP, and pro-BNP (>150 pmol/L)	
						1.05 (1.0, 1.11), 0.045	Clinical model + LVEF(<50%), LVMi, LV dimension, deceleration time, LA dimension, and E/e′	

(*Continued*)

Table 3 (Continued).

Citation	Exposure	Primary outcome		Secondary outcomes				Unit
		All- cause mortality		Composite CV end point		Composite cardiac end point		
		HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	
Brainin et al (2018)[26]			• n = 236	• N/A	• N/A		• n = 149	
	GLS	1.05 (1.02, 1.09), 0.004	None			1.12 (1.08, 1.17), <0.001	None	Per unit (1%) decrease
	Post systolic index	1.33 (1.21, 1.47), <0.001 1.14 (1.0, 1.30), 0.044	None Age, sex, HTN, HR, LVMi, LVEF, GLS, pro-B-type natriuretic peptide, previous ischemic heart disease, SBP, LAVi, e', estimated glomerular filtration rate, and E/A			1.36 (1.20, 1.54), <0.001 1.22 (1.04, 1.43), 0.014	None Age, sex, HTN, HR, LVMi, LVEF, GLS, pro-B-type natriuretic peptide, previous ischemic heart disease, SBP, LAVi, e', estimated glomerular filtration rate, and E/A	Per 1% increase
Modin et al (2018)[27]	GLS	• N/A	• N/A	• N/A	• N/A		• n = 222	
						1.67 (1.41, 1.99), <0.001 1.37 (1.14, 1.65), 0.001 1.23 (0.99, 1.52), 0.06	None Clinical model = Age, sex, SBP, smoking status, DM and total cholesterol and HTN Clinical model + GLS, LVMi, LAVi, LVIDd/height, HR, E/e', a', prevalent IHD, and abnormal ECG.	Per 5% decrease

(*Continued*)

Table 3 (Continued).

Citation	Exposure	Primary outcome		Secondary outcomes				Unit
		All- cause mortality		Composite CV end point		Composite cardiac end point		
		HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	HRs, 95% CI, P	n (events) Adjustments,	
Shah et al (2017)[30]	GLS	• N/A	• N/A	• N/A	• N/A	Results were not used for meta-analysis as GLS and LVEF were combined into a composite measure and used as a surrogate of LV systolic dysfunction		

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; GLS, global longitudinal strain; HTN, hypertension; HRs, hazard rations; HR, heart rate; IHD, ischemic heart disease; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVIDd, left ventricular internal dimension in diastole; SBP, systolic blood pressure; SD, standard deviation; TDI, tissue Doppler Imaging.

studies was good. Seven scored a maximum 7[23–26,28–30] and one scored 6[27] (Table S2). The degree of heterogeneity indicated by I-square was small in most of the meta-analyses and was only large in two analyses.

Discussion

This systematic review and meta-analysis summarizes current evidence about the prognostic value of STE-derived measures in the general population. 2D-STE-derived GLS was the most studied measure and it predicted total mortality, major adverse cardiac and cardiovascular end-points in community-dwelling individuals in a limited number of studies that included a total of 11,744 participants. Although information on potential confounders was limited and inconsistent, there was some evidence that this was independent of conventional cardiovascular risk factors and other echocardiographic measures. There was insufficient evidence in relation to other myocardial deformation indices or 3D-STE-derived indices to draw conclusions with respect to outcomes. Therefore, this systematic review also highlights important knowledge gaps in the current literature regarding the possible utility of myocardial deformation indices in unselected older populations, and further evidence is still required, particularly regarding 3D-STE.

Risk assessment and management of patients with CVD are guided by the measurement of LV global systolic function.[2] LVEF is considered the cornerstone in assessing LV systolic function,[1] but LV strain imaging is attracting interest as an additional tool to improve risk assessment and guide management in diseased populations.[2,12] Nevertheless, the evidence on the utility of STE as a measure of cardiac function and risk in community-dwelling individuals has been limited. We provide a synthesis of current evidence that provides some support for GLS as a useful risk measure but also highlights the need for more information regarding the utility of STE for risk assessment and diagnosis. Based on limited numbers of identified studies, GLS was a prognostic marker of cardiovascular mortality and morbidity independent of conventional risk factors. This is important because risk factors which potentially lead to CVDs such as aging, hypertension and DM are common characteristics of longitudinal population-based samples of elderly[23–30] and are known to be associated with alterations in GLS even when LVEF is still normal.[4,5,31,32]

According to the disease progression, the layers of the myocardium as well as the various other contributors to cardiac mechanics can be affected differently.[33] Disease affecting the subendocardial layer such as ischemia,

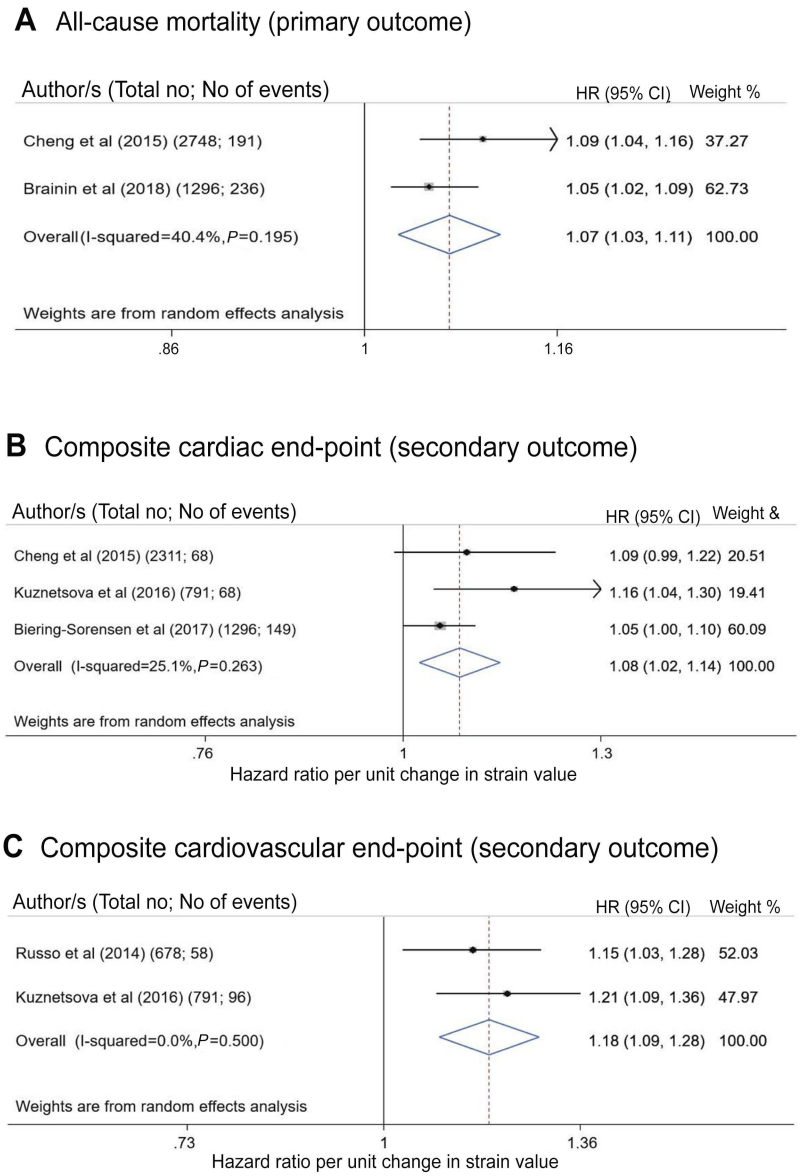

Figure 2 GLS as a predictor of all-cause mortality (**A**), composite cardiac end-point (**B**) and cardiovascular end-point (**C**). All-cause mortality HR estimates are from minimally adjusted (Cheng et al) and unadjusted (Brainin et al) models. Composite cardiovascular and cardiac end-points are based on maximally adjusted models (listed in the Supplementary materials). For Kuznetsova et al, endocardial-wall strain is shown. Hazard ratios are per unit change in strain value. The heterogeneity assessment including the I^2 statistics and *p*-value of Q test is shown.

hypertension or DM tends to impair longitudinal mechanics, while circumferential and twist mechanics remain preserved or even enhanced to preserve the overall LV systolic performance and LVEF.[33,34] With more involvement of the mid-myocardial and subepicardial layers, both circumferential and twist mechanics will deteriorate leading to a reduction in LVEF.[3,33] In unselected population without overt cardiac diseases, Russo et al characterized the relationship between multidirectional myocardial mechanics with radial thickening and LVEF.[35] Radial strain was more influenced by circumferential strain than longitudinal strain explaining why radial thickening, and hence LVEF, is less sensitive than longitudinal function in detecting subclinical LVSD.[35] This may contribute to the added prognostic value of GLS over LVEF especially when LVEF is still normal or mildly impaired.[12]

STE-based LV strain imaging allows comprehensive quantification of complex myocardial mechanics. While STE is increasingly used in clinical practice, it suffers from inherent technical limitations.[31] High-quality images and adequate frame rates are crucial for accurate tracking. For 2D-STE, multiple views are required which is time-consuming to

Table 4 Results of studies assessed the association between two-dimensional speckle-tracking echocardiographic-derived measures and tertiary outcomes

References	Tertiary outcomes (n)	Exposure	Results		Unit
			HRs, 95% CI, P	Adjustments	
Cheng et al (2015)[28]	1. Coronary heart disease (69) (comprising fatal or non-fatal myocardial infarction, coronary insufficiency, and angina pectoris)	Global average longitudinal strain	1.37 (1.06, 1.76), 0.01 1.36 (1.03, 1.79), 0.03 1.29 (0.96, 1.74), 0.09	Age, sex and ethnicity (Model 1) Age, sex, ethnicity, BMI, SBP, DBP, anti-hypertensive treatment, total/HDL cholesterol, DM, smoking status, and HR (Model 2) age, sex, ethnicity, BMI, SBP, DBP, anti-hypertensive treatment, total/ HDL cholesterol, DM, smoking status, LV mass, LV fractional shortening, and HR (Model 3)	Per 1 SD change (SD=3.3%)
		Global average circumferential strain	1.1 (0.85, 1.42), 0.48 1.14 (0.87, 1.48), 0.34 1.11 (0.81, 1.51), 0.53	Model 1 Model 2 Model 3	Per 1 SD change (SD=5.8%)
		Global average radial strain	0.87 (0.67, 1.13), 0.3 0.9 (0.68, 1.17), 0.43 0.95 (0.72, 1.26), 0.72	Model 1 Model 2 Model 3	Per 1 SD change (SD=16.8%)
		Global average transvers strain	1.02 (0.80, 1.29), 0.89 1.02 (0.81, 1.29), 0.87 1.04 (0.81, 1.34), 0.75	Model 1 Model 2 Model 3	Per 1 SD change (SD=7.1%)
	2. Heart failure (71)	Global average longitudinal strain	1.45 (1.14, 1.84), 0.003 1.29 (0.99, 1.69), 0.06 1.14 (0.86, 1.50), 0.37	Model 1 Model 2 Model 3	Per 1 SD change (SD=3.3%)
		Global average circumferential strain	1.7 (1.29, 2.25), 0.0002 1.59 (1.18, 2.14), 0.002 1.41 (1.0, 2.0), 0.05	Model 1 Model 2 Model 3	Per 1 SD change (SD=5.8%)
		Global average radial strain	0.64 (0.46, 0.88), 0.007 0.82 (0.59, 1.13), 0.22 0.98 (0.72, 1.34), 0.92	Model 1 Model 2 Model 3	Per 1 SD change (SD=16.8%)
		Global average transvers strain	0.73 (0.57, 0.93), 0.01 0.79 (0.61, 1.02), 0.07 0.84 (0.65, 1.1), 0.21	Model 1 Model 2 Model 3	Per 1 SD change (SD=7.1%)

(*Continued*)

Table 4 (Continued).

References	Tertiary outcomes (n)	Exposure	Results		Unit
			HRs, 95% CI, P	Adjustments	
Russo et al, (2015)[24]	Atrial fibrillation (32)	Global average longitudinal strain	1.2 (1.08, 1.34), 0.001 1.22 (1.04, 1.43), 0.015	None Age, obesity, HTN, antihypertensive treatment, coronary artery disease, LVMi, relative wall thickness.	Per unit (1%) decrease Death as a Competing Risk
Kuznetsova et al (2016)[29]	Coronary heart disease (34) Comprising fatal and nonfatal myocardial infarction, coronary revascularization, and new-onset angina (stable or unstable).	Global longitudinal strain			
		• Mid-wall	2.45 (1.61, 3.66), <0.0001 2.53 (1.68, 3.82), <0.0001 2.32 (1.51, 3.55), <0.0001 2.4 (1.54, 3.71), <0.0001	Clinical model = Family clusters, sex, age, BMI, SBP, serum cholesterol, smoking, antihypertensive treatment, DM, and a history of cardiac disease. Clinical model + LVMi Clinical model + TDI e′ Clinical model + LVMI + TDI e′	Per 1 SD decrease (SD= 2.5%)
		• Endocardial	2.34 (1.58, 3.50), <0.0001 2.44 (1.62, 3.77), <0.0001 2.24 (1.46, 3.43), 0.0002 2.29 (1.50, 3.56), 0.0002	Clinical model Clinical model + LVMi Clinical model + TDI e′ Clinical model + LVMI + TDI e′	Per 1 SD decrease (SD= 2.9%)
		• Epicardial	2.3 (1.58, 3.38), <0.0001 2.4 (1.61, 3.56), <0.0001 2.2 (1.47, 3.30), <0.0001 2.26 (1.49, 3.38), <0.0001	Clinical model Clinical model + LVMi Clinical model + TDI e′ Clinical model + LVMI + TDI e′	Per 1 SD decrease (SD= 2.2%)

(*Continued*)

Table 4 (Continued).

References	Tertiary outcomes (n)	Exposure	Results		Unit
			HRs, 95% CI, P	Adjustments	
Biering-Sorensen et al (2017)[25]	1. Heart failure (78)	Global longitudinal strain	1.16 (1.09, 1.23), <0.001 1.12 (1.05, 1.18), <0.001 1.1 (1.03, 1.17), 0.003 1.09 (1.02, 1.17), 0.016	None Age and sex (Model 1) Age, sex, HR, HTN, DM, previous IHD, SBP, and pro-BNP (>150 pmol/L) (Model 2) Age, sex, HR, HTN, DM, previous IHD, SBP, pro-BNP (>150 pmol/L), LVEF(<50%), LVMi, LV dimension, deceleration time, LA dimension, and E/e′ (Model 3)	Per unit (1%) decrease
	2. Acute myocardial infarction (43)		1.16 (1.08, 1.26), <0.001 1.13 (1.04, 1.22), 0.003 1.1 (1.01, 1.19), 0.022 1.11 (1.01, 1.22), 0.024	None Model 1 Model 2 Model 3	Per unit (1%) decrease
	3. Cardiovascular death (74)		1.06 (1.0, 1.13), 0.059 1.02 (0.96, 1.08), 0.54 0.99 (0.93, 1.06), 0.85 0.98 (0.91, 1.06), 0.59	None Model 1 Model 2 Model 3	Per unit (1%) decrease

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; HRs, hazard rations; HR, heart rate; IHD, ischemic heart disease; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; SBP, systolic blood pressure; SD, standard deviation; TDI, tissue Doppler Imaging.

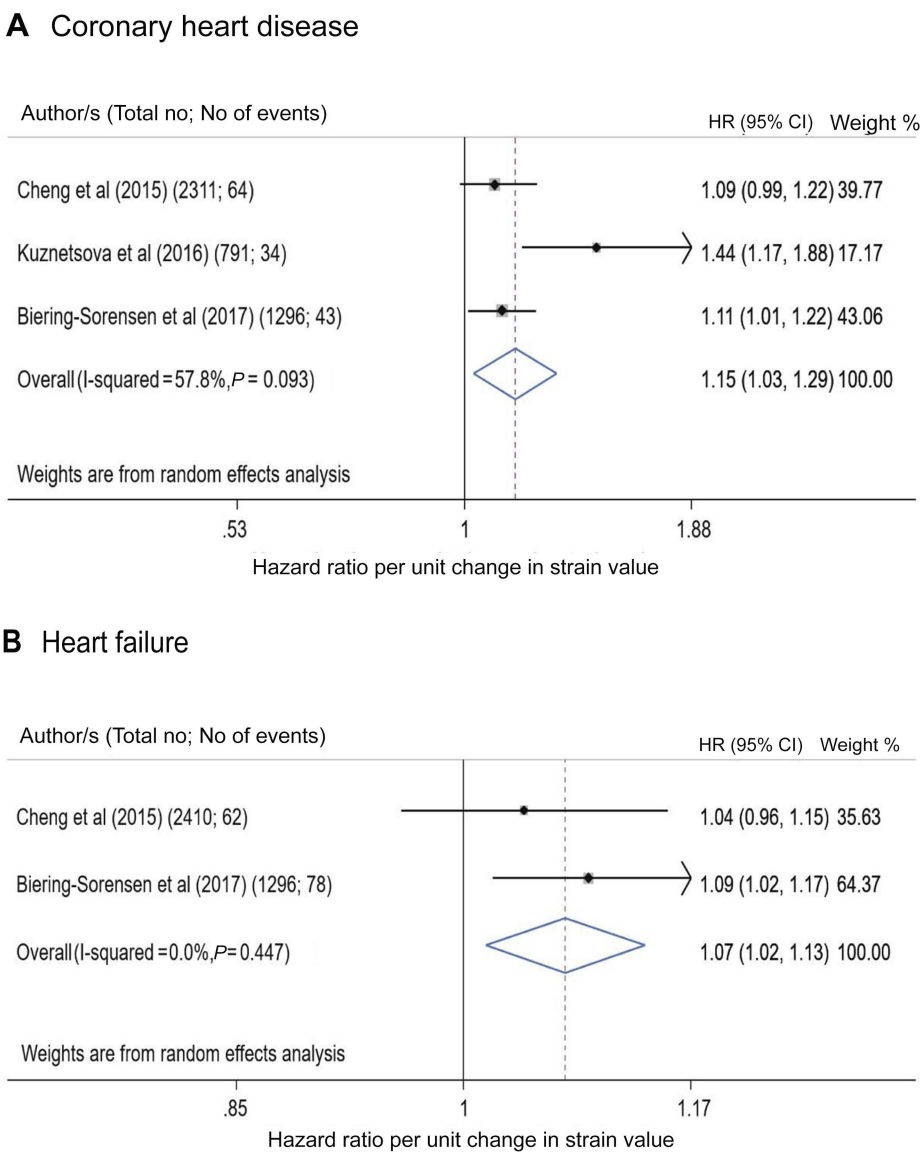

Figure 3 GLS as a predictor of coronary heart disease (**A**) and heart failure (**B**) on maximally adjusted models (listed in the Supplementary materials). For Kuznetsova et al, endocardial-strain is shown. Hazard ratios are per unit change in strain value. The heterogeneity assessment including the I^2 statistics and *p*-value of Q test is shown.

apply in large population-based studies. Indeed, among identified studies,[23–30] only one study measured circumferential, radial and transverse strains,[28] while none measured LV rotation.[26] This could be due to analysis time required or the limited feasibility and reproducibility of these measurements. Nevertheless, circumferential strain, both MRI-based[36] and 2D-STE based,[28] was an independent prognostic marker for incident HF over and beyond traditional risk factors and conventional measures in subjects free of CVDs of community-dwelling individuals. Further, Cheng et al have suggested that distinct components of LV mechanics (ie, GLS, circumferential strain, etc.) are differently associated with individual CVD outcomes,[28] but it was not possible to answer this question due to the limited number of studies. In the future, 3D imaging methods may overcome some of the limitations of 2D-STE and provide additional insight to the different relationship between individual components of LV mechanics and CVD outcomes.

Study limitations

A number of limitations of this study ought to be acknowledged. This systematic review was limited to English language publications, which may have introduced a selection bias. We identified only eight papers based on five

different studies; all identified studies used 2D-STE and no study examined additive the prognostic value of 3D-STE-derived LV deformation indices in a general population. Once multiple publications from the same study were accounted for, meta-analyses were based on either two or three studies limiting the precision of estimates of between-study variance which could result in an underestimate of the width of the confidence intervals. Further, meta-analysis should be performed when results of at least ten relevant studies are available. The small number of studies also precluded sub-group analysis and meta-regression to explore sources of heterogeneity between studies. We assumed a priori that there would be heterogeneity between the various observational studies and consequently used random effects modeling, although there was not strong evidence of heterogeneity in the identified studies. Since estimates from random effects models behave like the fixed effect estimate as heterogeneity decreases, it is not likely that this will have introduced substantial error. The small number of studies also prevented us from employing formal assessment of publication bias (e.g. funnel plots), but this bias cannot be excluded. Analyses employed different vendor-specific software and possibly different software versions; both are factors which may introduce systematic differences between studies. For this reason, GLS analysis including LV segmentation is different between studies included in this meta-analysis (e.g. endocardial analysis of GLS from 12 LV-segments,[28] transmural analysis of GLS from 18 LV-segments[25] or GLS from only 6 LV-segments[29]). However, since we examined associations with outcomes in relation to a continuous exposure (GLS) the impact of this source of heterogeneity is likely to be small, consistent with our sensitivity analysis.

Conclusion

This study synthesized current evidence regarding STE-derived measures as prognostic indicators of mortality and cardiovascular events in community-dwelling individuals. Despite limited number of studies in this meta-analysis, LV GLS by 2D-STE showed prognostic value in this population and may add to conventional cardiovascular risk factors and other echocardiographic measures. However, our findings also highlight the limitations of the existing evidence base and identify important knowledge gaps in the current literature regarding the possible utility of myocardial deformation indices and 3D-STE in unselected older populations – these are issues where further evidence is needed.

Abbreviation list

AF, atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; STE, speckle-tracking echocardiography.

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Disclosure

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