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SYSTEMATIC REVIEW AND META-ANALYSIS

Three-Dimensional Global Left Ventricular Myocardial Strain Reduced in All Directions in Subclinical Diabetic Cardiomyopathy: A Systematic Review and Meta-Analysis

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BACKGROUND: Three-dimensional (3D) speckle tracking echocardiography can identify subclinical diabetic cardiomyopathy without geometric assumption and loss of speckle from out-of-plane motions. There is, however, significant heterogeneity among the previous reports. We performed a systematic review and meta-analysis to compare 3D strain values between adults with asymptomatic, subclinical diabetes mellitus (ie, patients with diabetes mellitus without known clinical manifestations of cardiac disease) and healthy controls.

METHODS AND RESULTS: After systematic review of 5 databases, 12 valid studies (544 patients with diabetes mellitus and 489 controls) were eligible for meta-analysis. Pooled means and mean difference (MD) using a random-effects model for 3D global longitudinal, circumferential, radial, and area strain were calculated. Patients with diabetes mellitus had an overall 2.31 percentage points lower 3D global longitudinal strain than healthy subjects (16.6%, 95% CI, 15.7–17.6 versus 19.0; 95% CI, 18.2–19.7; MD, –2.31, 95% CI, –2.72 to –2.03). Similarly, 3D global circumferential strain (18.9%; 95% CI, 17.5–20.3 versus 20.5; 95% CI, 18.9–22.1; MD, –1.50; 95% CI, –2.09 to –0.91); 3D global radial strain (44.6%; 95% CI, 40.2–49.1 versus 48.2; 95% CI, 44.7–51.8; MD, –3.47; 95% CI, –4.98 to –1.97), and 3D global area strain (30.5%; 95% CI, 29.2–31.8 versus 32.4; 95% CI, 30.5–34.3; MD, –1.76; 95% CI, –2.74 to –0.78) were also lower in patients with diabetes mellitus. Significant heterogeneity was noted between studies for all strain directions (inconsistency factor [I^2], 37%–78%). Meta-regression in subgroup analysis of studies using the most popular vendor found higher prevalence of hypertension as a significant contributor to worse 3D global longitudinal strain. Higher hemoglobulin A_{1c} was the most significant contributor to worse 3D global circumferential strain in patients with diabetes mellitus.

CONCLUSIONS: Three-dimensional myocardial strain was reduced in all directions in asymptomatic diabetic patients. Hypertension and hemoglobin A_{1c} were associated with worse 3D global longitudinal strain and 3D global circumferential strain, respectively.

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Key Words: 3D speckle tracking echocardiography ■ diabetes mellitus ■ healthy controls ■ meta-analysis ■ myocardial strain ■ standardized mean difference ■ subclinical diabetic cardiomyopathy

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CLINICAL PERSPECTIVE

What Is New?

- Our systematic review and meta-analysis pools three-dimensional strain values among patients with subclinical diabetic cardiomyopathy.
- After performing our literature search, we identified 544 patients and 489 controls from 12 relevant articles.
- We found that three-dimensional strain reduced in every direction with three-dimensional global longitudinal strain being the most sensitive by 2.3% lower than the control group.

What Are the Clinical Implications?

- Three-dimensional strain, especially three-dimensional global longitudinal strain, can assist to identify patients with subclinical diabetic cardiomyopathy.
- These patients might benefit the most from early and aggressive glycemic control to prevent clinical manifestations of diabetic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

3D	3-dimensional
DCM	diabetic cardiomyopathy
GAS	global area strain
GCS	global circumferential strain
GLS	global longitudinal strain
GRS	global radial strain
MD	mean difference
STE	speckle tracking echocardiography

Diabetes mellitus is one of the most prevalent risk factors of heart failure.[1,2] Diabetic cardiomyopathy (DCM) occurs in patients with diabetes mellitus independent of coronary artery disease, hypertension, or valvular or congenital heart disease.[3] In its early stages, DCM includes a subclinical phase characterized by structural and functional abnormalities.[4] Currently, conventional echocardiography is not an effective method to detect subclinical cardiac dysfunction.[5] However, advanced echocardiography techniques such as speckle tracking echocardiography (STE) by assessment of cardiac mechanics has been shown to be sensitive in early identification of subclinical systolic dysfunction in patients with diabetes mellitus with normal left ventricular ejection fraction (LVEF) and even normal left ventricular (LV) diastolic function.[5–7] Three-dimensional STE (3D-STE) as a relatively new technology can more comprehensively and objectively assess cardiac systolic dysfunction without geometrical assumption, and has superior accuracy and reproducibility over 2-dimensional STE because of the ability to avoid the loss of speckles because of out-of-plane motions.[8,9]

Some studies have aimed to assess the effects of diabetes mellitus on cardiac function using 3D-STE.[10–21] Most of these studies reported worse myocardial deformation indexes in patients with diabetes mellitus compared with healthy controls. However, the data are not robust and somewhat heterogeneous among studies. For example, the measured 3D global longitudinal strain (GLS) of controls in some studies[14] is worse than measured 3D GLS of patients with diabetes mellitus in some other studies.[10,13,21] Furthermore, it is unclear which direction has the largest difference between patients with diabetes mellitus and controls, and whether there are any significant differences between vendors in measured strain values in these studies.

We hypothesized that patients with diabetes mellitus would have a statistically significant reduction in myocardial strain compared with healthy controls but that significant heterogeneity would exist between cohorts. To answer this, we conducted a systematic review on the LV strain values assessing by 3D-STE between asymptomatic adults with diabetes mellitus (ie, patients with diabetes mellitus without known clinical manifestations of cardiac disease) and healthy controls. Our aims were to (1) synthesize the information qualitatively, and then (2) to perform the quantitative analysis using meta-analysis to determine the pooled mean difference (MD) of these strain values in patients with diabetes mellitus and controls and to define possible sources of variation affecting the strain values by meta-regression analysis.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. The study was prospectively registered with the International Prospective Register of Systematic Reviews database (CRD42020197825).

Search Strategy

We performed this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[22] Under the guidance of a librarian at the University of Sydney, we searched 5 databases (MEDLINE, Embase, Scopus, Web of Science, and Cochrane central register of controlled trials) for the key terms “myocardial strain/function, dysfunction,” “speckle tracking echocardiography, deformation imaging/

analysis," and "diabetes mellitus." The search was limited to human articles published in English and completed on March 30, 2020. Search hedges created are listed in Data S1. The reference lists of relevant studies were manually searched for any possible additional appropriate study.

Study Selection

From these lists, studies were included if the articles reported strain values using 3D-STE in patients with asymptomatic diabetes mellitus and a control group. Two independent investigators reviewed (S.G. and A.G.) and chose studies if the articles met the following criteria: (1) studies reported LV strain values of adult patients with diabetes mellitus (type 1 or 2), (2) studies included a control group, and (3) patients were >18 years of mean age. The definition of each group and exclusion criteria vary with the studies and are shown in Table S1. If one study had multiple groups of patients, we selected the lower-risk group for our meta-analysis to avoid extreme cases.

Study Exclusion

Our exclusion criteria were reduced LVEF, presence of known coronary artery disease, or any structural heart disease. We also excluded studies in which strain was calculated using Doppler tissue imaging or cardiac magnetic resonance imaging, or there were no 3D-STE data reported. In addition, case reports, conference presentations, review articles, editorials, and expert opinions were excluded.

Data Collection

All demographic, ultrasound system and software, common clinical characteristics, and strain information was extracted from texts, tables, and graphs and summarized into a standardized extraction sheet. Authors of eligible studies were contacted by e-mail to obtain missing information.

Outcome of Interest

In this meta-analysis, our outcomes of the interest were 3D LV strain values: 3D GLS, 3D global circumferential strain (3D GCS), 3D global radial strain (3D GRS), and 3D global area strain (3D GAS) measured by 3D-STE in the group of adult patients with diabetes mellitus and the control group. Based on the European Association of Cardiovascular Imaging/American Society of Echocardiography/Industry taskforce recommendation[23] and to avoid confusion, we considered the absolute value of the number in each strain value.

Quality Assessment

Critical appraisal was performed using the Joanna Briggs Institute critical appraisal checklist[24] for cross-sectional studies, and the Newcastle-Ottawa Quality Assessment scale[25] for cohort studies.

Statistical Analysis

The pooled MD and 95% CI of 3D GLS, GCS, GRS, and GAS in the group of patients with diabetes mellitus and the control group were computed using the random-effects model weighted by inverse variance and are shown in the forest plot. We chose a random-effects model as our primary analysis because we assumed that the differences in 3D strain values between patients with diabetes mellitus and controls would vary significantly among studies. Although we assumed that the selected studies had enough in common that it made sense to synthesize the information, we could not assume that they were identical in the sense that the true effect size was exactly the same in all the studies. By choosing the random-effects model, we estimated the mean distribution of LV strain differences between the 2 groups across all studies, rather than presuming that there was a true, fixed MD in LV strain between patients with diabetes mellitus and controls. The heterogeneity between studies was assessed by the Cochran Q test and the inconsistency factor. Inconsistency factor values of 25%, 50%, and 75% corresponded to a low, moderate, and high degree of heterogeneity, respectively.

An influence analysis with leave-one-out analysis was performed to determine whether particular studies contributed significantly toward heterogeneity and pooled mean strain. A Baujat plot was used to represent this influence graphically in the specific setting of GLS, and a subsequent subgroup analysis was conducted to determine whether excluding these highly influential studies changed mean GLS significantly. Potential publication bias was assessed using funnel plots with and without the Duval and Tweedie trim and fill methodology and Egger's test.

Univariable meta-regression analysis was performed for variables that were reported in >50% of studies to assess possible study factors associated with heterogeneity. The beta coefficient and its 95% CIs were derived using the least mean squares fitting method. Statistical analysis was performed using R version 4.0.0 and RStudio version 1.4.1103 (The R Foundation for Statistical Computing, Vienna, Austria) with the "dmetar" and "meta" packages.[26] Two-tailed *P* values were used, and the threshold of statistical significance was 0.05 except for the Egger test, where 0.1 was applied.

RESULTS

Study Selection

Figure 1 shows the Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart of our study. Our search strategy revealed 791 results from 5 databases (MEDLINE [n=121], EMBASE [n=330], Scopus [n=40], Web of Science [n=290], and Cochrane central register of controlled trials [n=10]). Following the removal of 259 duplicates, the titles and abstracts of

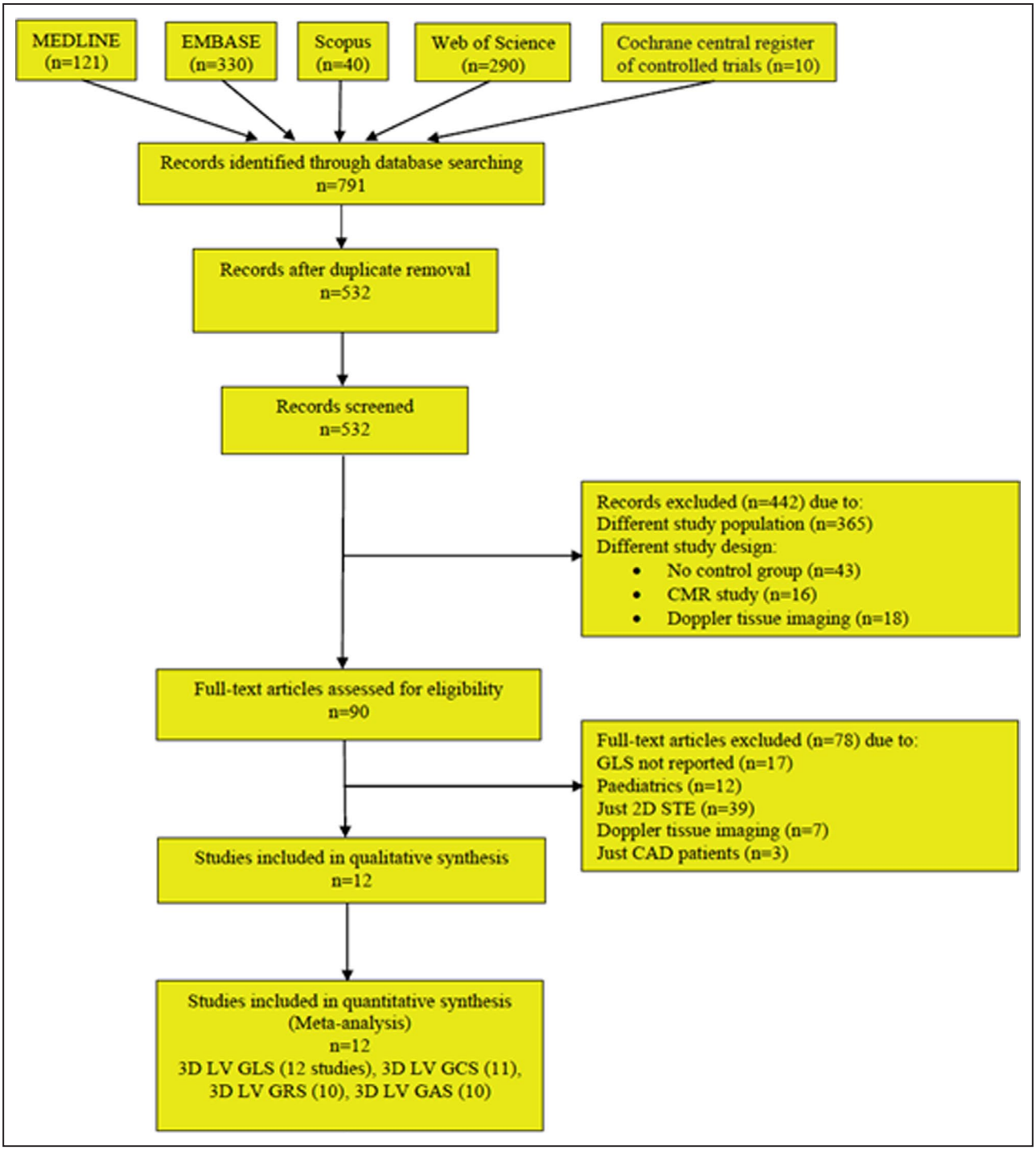

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart.
This flowchart illustrates the selection process for published reports on 3D LV strain values (3D LV GLS, 3D LV GCS, 3D LV GRS, and 3D LV GAS) measured by 3D-STE in the group with adult diabetes mellitus and the control group. After searching 5 databases, 12 full-text articles were identified from 791 search results. 2D indicates 2-dimensional; 3D, 3-dimensional; CAD, coronary artery disease; CMR, cardiac magnetic resonance; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LV, left ventricular; and STE, speckle tracking echocardiography.

Table 1. Summary of Clinical and Vendor Characteristics Among Included Studies

Study	Year	DM (n)	Control (n)	Study Type	Ultrasound System	Software	Vendor	Age, y, Mean±SD (DM)	Age, y, Mean±SD (Control)	Women, % (DM)	Women, % (Control)	BMI Mean±SD (DM)	BMI Mean±SD (Control)	Hypertension, % (DM)	Hypertension, % (Control)
Zhang[10]	2013	37*	63	CS	Vivid E9	EchoPAC	GE	60±10	58±10	43	52	24.4±3.6	23.9±3.7	54	44
Wang[11]	2015	46	40	CS	Vivid E9	EchoPAC	GE	63.1±9.8	65.5±5.9	47.8	47.5	25±2.1	23±3.4	0	0
Tadic[12]	2015	50	50	CS	Vivid 7	EchoPAC	GE	52±8	50±7	48	52	27±2.5	24±2.2	0	0
Wang[13]	2015	36†	40	CS	Vivid E9	EchoPAC	GE	64.4±7.9	66.8±8.4	50	50	22.77±1.3	22.48±2.4	0	0
Enomoto[14]	2016	77	35	CS	Aplio-Artida	3D Wall Motion Tracking	Toshiba	56±15	52±16	31.1	48.5	23.2±3.5	22.1±2.2	45	0
Wang[15]	2017	40‡	40	CS	Vivid E9	EchoPAC	GE	66±6.6	68±7.7	50	50	24.6±2.4	23.52±3.1	0	0
Luo[16]	2018	38	35	PC	IE33	TomTec	Philips	59.1±6.7	58.3±6.5	34.2	34.2	24.9±2.1	24.3±2.3	0	0
Ringle[17]	2018	66	26	PC	IE33	TomTec	Philips	37.6±9	35.1±7	71	69	24±3	23±3	0	0
Wang[18]	2018	40§	40	CS	Vivid E9	EchoPAC	GE	60.8±8.1	61.9±6.9	47.5	50	24.5±2.6	24.7±2.1	0	0
Wang[19]	2018	40‖	40	CS	Vivid E9	EchoPAC	GE	68.1±7.9	67.5±7.4	50	52.5	24.89±3	24.42±2.7	0	0
Wang-1[20]	2019	40¶	40	CS	Vivid E9	EchoPAC	GE	66.6±8.3	67±7.8	50	50	24.7±2.4	25±2.9	0	0
Wang[21]	2019	34#	40	CS	Vivid E9	EchoPAC	GE	65.38±7.05	64.32±7.9	50	50	24±2.2	24.5±2.6	0	0

BMI indicates body mass index; CS, cross sectional; DM, diabetes mellitus; and PC, prospective cohort.
*Uncontrolled DM.
†DM without obesity.
‡DM with normal pulse pressure.
§DM alone.
‖DM without hyperlipidemia.
¶DM alone.
#DM with left ventricular normal geometry.

Table 2. Summary of Diabetes Mellitus Cohorts Among Included Studies

Study	Year	DM, n	DM Type	DM Duration, y	Metformin, %	Sulfonylureas, %	Insulin, %	Fasting Plasma Glucose	Hemoglobin A_{1c}, %	DM Complications (%)			
										PVD	Retinopathy	Neuropathy	Nephropathy
Zhang[10]	2013	37*	2	7±3	19	10	61	0	6.10±0.53	10	19	6	0
Wang[11]	2015	46	2	12.7±5.2	52	39	7	6.6±0.4	…	…	…	…	…
Tadic[12]	2015	50	2	…	0	0	0	7.3±1.1	7.4±0.7	…	…	…	…
Wang[13]	2015	36†	2	12.7±5.2	56	42	8	7.4±0.5	7.0±0.48	…	…	…	…
Enomoto[14]	2016	77	2	…	51‡		53	9±2.7	10.6±2.5	0	35	62	83
Wang[15]	2017	40§	2	11±4	38	35	15	6.9±0.7	…	…	…	…	…
Luo[16]	2018	38	2	…	…	…	…	11.9±3.2	10.4±2.6	100‖			
Ringle[17]	2018	66	1	21±12	…	…	…	…	7.7±1.5	39‖			
Wang[18]	2018	40¶	2	9.0±4.8	40	43	13	6.9±0.7	7.0±0.6	…	…	…	…
Wang[19]	2018	40#	2	12.2±5.6	45	40	13	6.8±0.7	6.7±0.6	…	…	…	…
Wang[20]	2019	40**	2	10.0±4.2	50	18	9	6.5±0.6	…	…	…	…	…
Wang[21]	2019	34††	2	13.5±5.5	45	30	5	6.7±0.8	…	…	…	…	…

BMI indicates body mass index; DM, diabetes mellitus; and PVD, peripheral vascular disease.
*Uncontrolled DM.
†DM without obesity.
‡Oral medication not specified.
§DM with normal pulse pressure.
‖DM complications not differentiated
¶DM alone.
#DM without hyperlipidaemia.
**DM alone.
††DM with left ventricular normal geometry.

Table 3. Echocardiography Parameters Among the Diabetes Mellitus Group

Study	Year	Strain	IVSD, mm	PWD, mm	LV Mass, g/m^2	E/A	E/e′	LA Volume Indexed, mL/m^2	2D LVEF, %	3D LVEF, %
Zhang[10]	2013	L/C/R/A	11.3±1.4	10.3±1.1	93.9±15.1	0.9±0.3	15.2±6.3	…	62±5	…
Wang[11]	2015	L/C/R/A	8.5±1.2	8.6±1.3	…	0.81±0.21	8.4±2.4	21.8±1.9	64.8±7.9	57.9±6.9
Tadic[12]	2015	L/C/R/A	9.6±0.9	…	…	1.02±0.15	9.3±1.8	…	63±4	…
Wang[13]	2015	L/C/R/A	8.7±1.0	8.5±1.1		0.83±0.23	8.7±2.3	…	65.7±7.3	61.9±6.7
Enomoto[14]	2016	L/C/R/A	8.7±1.8	8.7±1.3	90.1±29.2	1.1±0.5	8.2±3.0	26.2±8.7	66.3±7.7	…
Wang[15]	2017	L/C/R/A	9.0±1.2	8.7±1.1	83.2±16.8	0.85±0.26	8.3±2.7	…	64.0±7.0	60.7±6.0
Luo[16]	2018	L/C	…	…	…	0.86±0.22			68.1±2.5	55.1±1.3
Ringle[17]	2018	L	…	…	60±14	1.6±5	6.8±2	28±7	60±8	57±4
Wang[18]	2018	L/C/R/A	8.83±1.3	8.61±1.2	81.8±16.5	0.86±0.22	7.7±2.7	…	61.6±7.1	64.3±15.3
Wang[19]	2018	L/C/R/A	8.8±1.1	8.7±1.1	82.6±14.0	0.84±0.24	8.8±2.3	…	64.0±7.6	59.9±7.0
Wang[20]	2019	L/C/R/A	8.4±0.9	8.2±0.8	77.0±11.2	0.83±0.20	8.7±2.7	…	65.3±7.2	60.3±6.9
Wang[21]	2019	L/C/R/A	8.8±1.0	8.5±1.1	81.5±12.6	0.82±0.24	8.9±2.7	…	64.5±7.3	60.3±5.7

2D indicates 2-dimensional; 3D, 3-dimensional; A, area; C, circumferential; IVSD, interventricular septal diameter; L, longitudinal; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PWD, posterior wall dimension; and R, radial.

532 articles were screened for eligibility. Four hundred forty-two studies were excluded because of the different study populations and different study designs (no control group, cardiac magnetic resonance study, Doppler tissue imaging). Ninety full-text articles were assessed for eligibility. An additional 78 studies were excluded for the following reasons: no GLS data, Doppler tissue imaging, only 2-dimensional STE results, pediatric patients, and patients with coronary artery disease. Finally, 12 valid studies (544 patients with diabetes mellitus and 489 controls) met the selection criteria and were included in this meta-analysis, where 12 were eligible for 3D GLS, 11 for GCS, 10 for GRS, 10 for GAS. The interinvestigator agreement for study selection was moderate, at 51%. Disparities in study selection were adjudicated by a third senior author. Articles included were published from 2013 to 2019. Most of these studies used age- and sex-matched healthy subjects for the control group. A summary of the included studies is shown in Tables 1 and 2. Echocardiographic characteristics from included studies are shown in Tables 3 and 4, and hemodynamic data are displayed in Table S2.

3D LV Strain Values in Diabetic Versus Control Cohort

Table 5 summarizes the main results of our meta-analysis. All 3D LV strain values (GLS, GCS, GRS, and GAS) were reduced in patients with diabetes mellitus compared with healthy subjects. Patients with diabetes mellitus had significantly lower 3D GLS than healthy subjects (16.6%; 95% CI, 15.7–17.6 versus 19; 95% CI, 18.2–19.7). MD analysis of GLS showed a large effect size between patients with diabetes mellitus and controls (MD, −2.31; 95% CI, −2.72, −2.03]). Forest plots of GLS MD in the group of patients with diabetes mellitus and the control group are shown in Figure 2.[10–21] 3D GCS, GRS, and GAS were also lower in patients with diabetes mellitus. However, GCS had a medium effect size, and GRS and GAS had a small effect size (Table 5, Figures S1 through S3).

Our initial meta-regression (Tables S3 and S4) found that a study that used 3D wall motion tracking (Toshiba, Canon Medical Systems, Otawara, Japan) software[14] reported significantly lower 3D GLS and GRS as well as higher 3D GCS and GAS compared with studies that used EchoPAC software (GE Healthcare, Chicago, IL) in both the group of patients with diabetes mellitus and the control group (β for 3D GLS of DM, −5.8; 95% CI, −7 to −4.6]; P<0.001; β for GCS of DM, 8.8; 95% CI, 6.7–10.9; P<0.001; β for 3D GRS of DM, −14.7; 95% CI, −18 to −11.6; P<0.001; and β for 3D GAS of DM, 8.4; 95% CI, 6.3–10.5; P<0.001). In addition, 2 studies that used TomTec software (Phillips Imaging Systems GMBH, Hamburg, Germany)[16,17] reported significantly

Table 4. Echocardiography Parameters Among the Control Group

Study	Year	Strain	IVSD, mm	PWD, mm	LV Mass, g/m^2	E/A	E/e′	LA Volume Indexed, mL/m^2	2D LVEF, %	3D LVEF, %
Zhang[10]	2013	L/C/R/A	10.5±1.9	9.2±1.1	86.6±13.0	1.1±0.5	11.2±2.9	…	63.0±4.6	…
Wang[11]	2015	L/C/R/A	8.3±0.7	8.2±0.8	…	0.88±0.30	8.4±1.3	21.7±2.1	65.1±5.1	59.4±6.5
Tadic[12]	2015	L/C/R/A	9±0.8	…	…	1.37±0.19	6.2±1.5	…	64±4	…
Wang[13]	2015	L/C/R/A	8.6±0.9	8.3±0.7	…	0.87±0.26	8.1±1.9	…	65.5±6.2	61.5±5.8
Enomoto[14]	2016	L/C/R/A	8.2±1.1	8.5±1.0	90.5±17.4	1.3±0.5	6.7±1.5	26.2±9.2	68.9±5.6	…
Wang[15]	2017	L/C/R/A	8.8±1.0	8.8±1.1	83.0±17.4	0.87±0.19	8.1±3.0	…	65.4±6.3	60.8±5.5
Luo[16]	2018	L/C	…	…	…	0.93±0.21	…	…	66.9±3.3	55.3±1.9
Ringle[17]	2018	L	…	…	58±9	1.6±4	5.6±1	28±6	61±3	59±4
Wang[18]	2018	L/C/R/A	8.6±1.0	8.3±0.9	81.4±17.8	0.85±0.20	7.1±2.15	…	62.5±5.1	57.8±6.0
Wang[19]	2018	L/C/R/A	8.3±1.1	8.3±1.2	83.7±13.6	0.92±0.36	9.0±2.3	…	65.4±6.3	61.5±7.3
Wang[20]	2019	L/C/R/A	8.7±0.8	8.1±1.0	78.1±14.1	0.86±0.24	8.1±1.9	…	64.1±5.7	60.1±6.5
Wang[21]	2019	L/C/R/A	8.5±1.1	8.3±1.2	80.8±14.7	0.84±0.29	8.4±3.1	…	65.6±7.9	60.7±6.0

2D indicates 2-dimensional; 3D, 3-dimensional; A, area; C, circumferential; IVSD, interventricular septal diameter; L, longitudinal; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; PWD, posterior wall dimension; and R, radial.

higher 3D GCS compared with studies that used EchoPAC software (GE Healthcare) software in both the group of patients with diabetes mellitus and the control group (β for 3D GCS of DM, 4; 95% CI, 2.3–5.7; P<0.001).

Publication Bias

We found significant publication bias by the funnel plot with and without trim and fill (Figures S4 through S7) and Egger's test (except for GLS of patients with diabetes mellitus, and GRS of patients with diabetes mellitus and controls). There was a high degree of heterogeneity (37%–78%) in all 3D LV strain values in the group of patients with diabetes mellitus and the control group (Tables 5 and 6). Good reproducibility was shown among all studies for all directions of strain. A summary of intra- and interobserver variability is displayed in Table S5.

Subgroup Analysis of Studies Used the Most Popular Vendor

We performed a subgroup analysis on 9 studies[10–13,15,18–21] that used the most popular STE software (EchoPAC, GE Healthcare). Table 6 shows the main results of our subgroup analysis. Most of the I^2 characteristics improved compared with the whole-group analyses, most substantially in 3D GAS in patients with diabetes mellitus from 68% to 49%, followed by 3D GLS from 78% to 69%. Forest plots of 3D GLS in the group of patients with diabetes mellitus and the control group as well as MD of our subgroup analysis are shown in Figure 3,[10–13,15,18–21] which was consistent with the main meta-analysis. The other results of subgroup analysis in each group and MD of each strain value were also consistent with our main meta-analysis (Figures S8 through S10). On the contrary, meta-regression results of subgroup analysis were not consistent between diabetes mellitus and control groups (Tables S6 and S7). They showed a higher prevalence of hypertension (β, −0.02; 95% CI, −0.04 to 0; P=0.04) as the significant contributor to worse 3D LV GLS in patients with diabetes mellitus. In addition, hemoglobin A_{1c} (β, −0.5; 95% CI, −0.9 to −0.1; P=0.007) had the largest β in 3D GCS in patients with diabetes mellitus.

Study Quality

The results of our critical appraisal of included studies are shown in Tables 7 and 8. The majority of cross-sectional studies included in our review described their measurement of outcome well, and appropriate statistical tests were used in all cases. However, there were consistent issues with the lack of detail around recruitment setting for included patients. There was also a lack of information regarding

Table 5. Main Results of Meta-Analysis (Mean Difference)

Strain Variable	Studies, n	DM, n	Pooled Mean in DM	Control, n	Pooled Mean in Control	Mean Difference, Fixed Effects	Mean Difference, Random Effects	I^2, %
3D LV GLS	12	544	16.6 [15.7 to 20.3]	489	19.0 [18.2 to 19.7]	–2.33 [–2.65 to –2.02]	–2.34 [–3.01 to –1.66]	78%
3D LV GCS	11	506	18.9 [17.5 to 20.3]	454	20.5 [18.9 to 22.1]	–1.45 [–1.83 to –1.07]	–1.50 [–2.09 to –0.91]	57%
3D LV GRS	10	440	44.6 [40.2 to 49.1]	428	48.2 [44.7 to 51.8]	–3.45 [–4.64 to –2.27]	–3.47 [–4.98 to –1.97]	37%
3D LV GAS	10	440	30.5 [29.2 to 31.8]	428	32.4 [30.5 to 34.3]	–1.66 [–2.20 to –1.11]	–1.76 [–2.74 to –0.78]	68%

95% confidence intervals shown in brackets. 3D indicates 3-dimensional; DM, diabetes mellitus; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; I^2, heterogeneity statistic; LV, left ventricular.

diabetes mellitus type, duration, and control in 6 of the included 10 cross-sectional studies. The 2 prospective cohort studies had similar concerns regarding the setting from which patients were recruited, and diabetes mellitus inclusion criteria were poorly defined.

Our influence analysis and Baujat plot showed that 2 studies, Wang (2015)[13] and Enomoto (2016),[14] contributed significantly toward heterogeneity and pooled mean effect on GLS (Figure 4). A leave-one-out analysis confirmed that omission of these 2 studies resulted in a lower difference in GLS (Enomoto [2016],[14] –2.15; Wang [2015],[13] –2.16) between patients with diabetes mellitus and control cohorts (Table S8). Our sensitivity analysis without these 2 studies (Figure 5[10–12,15–21]) showed a reduced MD in GLS of –1.88 (95% CI, –2.23 to –1.53) using fixed-effects model, and –1.91 (95% CI, –2.38 to –1.44) using a random-effects model, when compared with our original results illustrated in Figure 2. This sensitivity analysis had a lower level of heterogeneity (I^2=44%) compared with the original analysis (I^2=78%).

Given our findings that strain reductions occur in all directions, we evaluated whether LVEF was reduced in the group of patients with diabetes mellitus compared with controls. Reported 2-dimensional LVEF and 3D LVEF from the group of patients with diabetes mellitus and the control group are shown in Tables 3 and 4 . We found no statistically significant difference in LVEF between the group of patients with diabetes mellitus and the control group, where mean difference in 2-dimentional ejection fraction was –0.47% (95% CI, –1.16 to 0.22) and that of 3D ejection fraction was 0.41% (95% CI, –1.34 to 0.52).

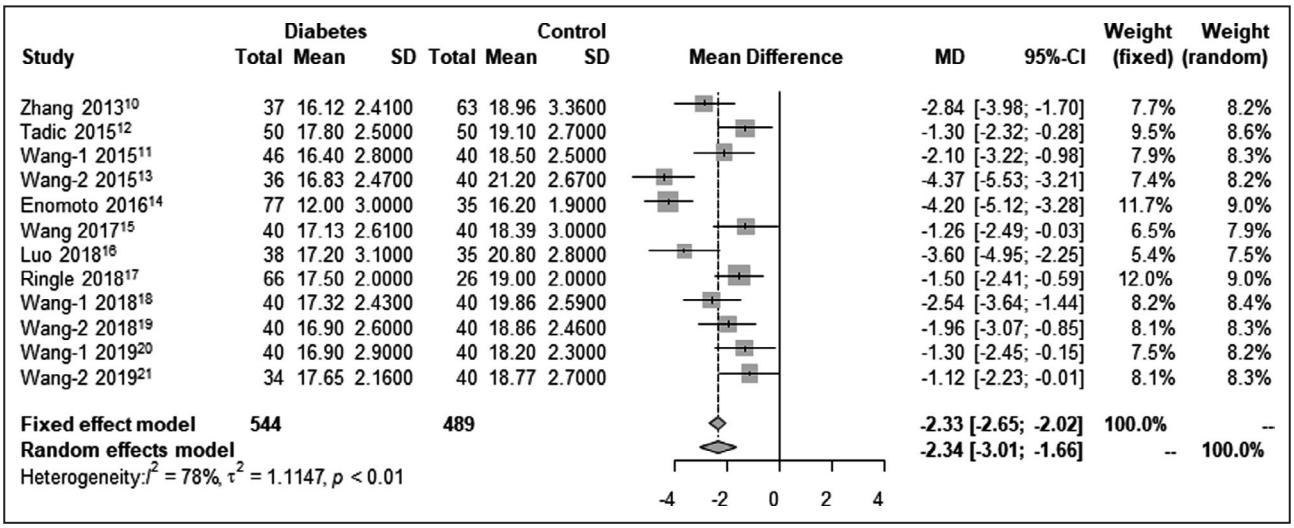

Figure 2. Forest plot of mean difference in 3D LV GLS in the group with diabetes mellitus and the control group in all included studies.

This forest plot showed an overall mean difference in 3D GLS of –2.34 (random effects) and –2.33 (fixed effects) toward the group with diabetes mellitus compared with the control group. Significant heterogeneity (I^2=78%) was noted between studies. 2D indicates 2-dimensional; 3D, 3-dimensional; CAD, coronary artery disease; GLS, global longitudinal strain; and MD, mean difference.

Table 6. Main Results of Meta-Analysis (Mean Difference) Using Most Popular Vendor

Strain Variable	Studies, n	DM, n	Pooled Mean in DM	Control, n	Pooled Mean in Control	Mean Difference, Fixed Effects	Mean Difference, Random Effects	I^2, %
3D LV GLS	9	363	17 [16.7 to 17.4]	393	19.1 [18.5 to 19.7]	−2.07 [−2.44 to −1.70]	−2.08 [−2.76 to −1.41]	69%
3D LV GCS	9	363	17.6 [17 to 18.1]	393	18.7 [18.2 to 19.2]	−1.26 [−1.65 to −0.86]	−1.24 [−1.72 to −0.75]	54%
3D LV GRS	9	363	46.7 [44.6 to 48.9]	393	50.1 [47.6 to 52.6]	−3.42 [−4.65 to −2.19]	−3.43 [−5.08 to −1.79]	43%
3D LV GAS	9	363	29.7 [29.2 to 30.1]	393	31.0 [30.4 to 31.6]	−1.45 [−2.01 to −0.90]	−1.42 [−2.20 to −0.64]	49%

3D indicates 3-dimensional; DM, diabetes mellitus; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; I^2, heterogeneity statistic; LV, left ventricular.

DISCUSSION

Based on the 12 eligible studies (544 patients with diabetes mellitus and 489 controls), the findings of this meta-analysis confirm that 3D LV systolic strain values are significantly reduced in all directions (longitudinal, circumferential, radial, and area) in patients with subclinical DCM. Three-dimensional GLS, as the most commonly used strain value, is 2.4 units (ie, 2.4 percentage points) lower in patients with diabetes mellitus compared with healthy controls and has the largest effect size. Our initial meta-regression results were driven by intervendor differences among the included studies. Subgroup meta-regression analysis of the studies that used the most common STE software showed a higher prevalence of hypertension and higher hemoglobin A1c as the main contributors to worse 3D GLS and GCS in patients with diabetes mellitus, respectively.

The Pattern of Change in Cardiac Mechanics of Subclinical DCM

Our meta-analysis confirms that subclinical DCM can be detected by 3D STE and exists in all directions of LV. The standard reduction in strain values was most prominent in 3D GLS. Therefore, 3D GLS can be used as the most sensitive marker in the detection of subclinical DCM among the 3D STE parameters. The relationship between early changes in cardiac mechanics in different directions in subclinical heart disease is still a matter of debate.[27–29] Unlike the theory of compensatory increase in circumferential deformation in early stages of myocardial dysfunction to preserve gross LVEF,[29] our meta-analysis showed that in patients with asymptomatic pure diabetes mellitus with normal LVEF, impairment of 3D GCS, GRS, and GAS occurs in addition to the impaired 3D GLS. More prospective studies can elucidate the relationship of changes in multiple directions during the evolvement of DCM.

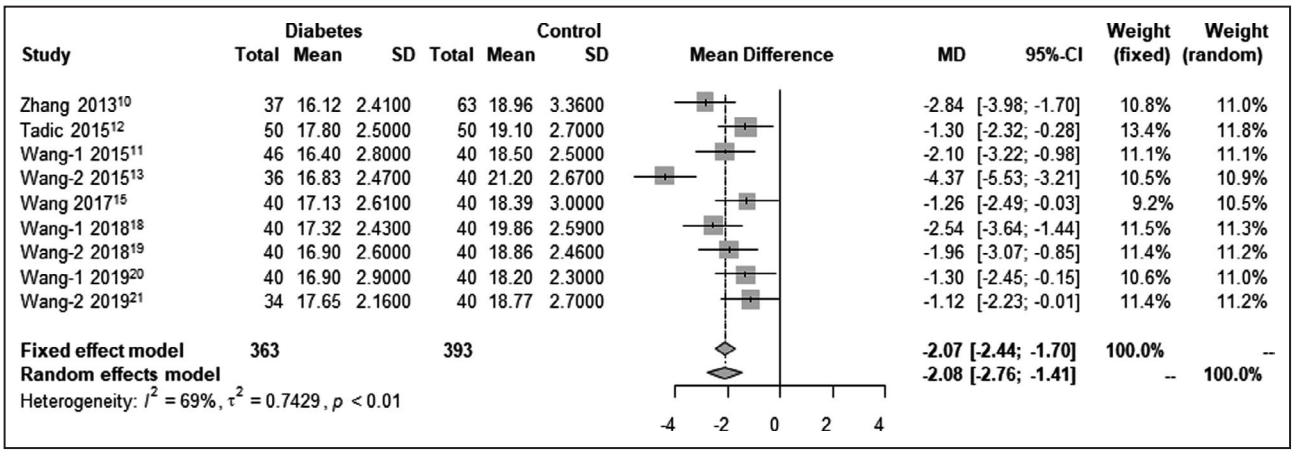

Figure 3. Forest plot of mean difference in 3D LV GLS in the group with diabetes mellitus and controls-subgroup analysis of 9 studies using the most popular vendor.
Overall GLS mean difference was less in the subgroup analysis (−2.07 fixed effect, −2.08 random effects) of most popular vendor (EchoPac, GE Healthcare). Heterogeneity between studies was only marginally improved in this subgroup analysis (I^2=69), indicating that other differences in study design or baseline characteristics may have contributed. 3D indicates 3-dimensional; GLS, global longitudinal strain; I^2, inconsistency factor; and MD, mean difference.

Table 7. Joanna Briggs Institute Critical Appraisal Checklist for Cross-Sectional Studies

Study	Year	Study Type	1	2	3	4	5	6	7	8
Zhang[10]	2013	CS	Y	N*	Y	Y	Y	Y	Y	Y
Wang-1[11]	2015	CS	Y	N*	N†	Y	Y	Y	Y	Y
Tadic[12]	2015	CS	Y	N*	N‡	N§	Y	Y	Y	Y
Wang-2[13]	2015	CS	Y	Y	Y	Y	Y	Y	Y	Y
Enomoto[14]	2016	CS	Y	N*	N‡	N§	Y	Y	Y	Y
Wang[15]	2017	CS	Y	N*	N†	Y	Y	Y	Y	Y
Wang[18]	2018	CS	Y	N*	Y	Y	Y	Y	Y	Y
Wang[19]	2018	CS	Y	N*	Y	Y	Y	Y	Y	Y
Wang[20]	2019	CS	Y	N*	N†	Y	Y	Y	Y	Y
Wang[21]	2019	CS	Y	N*	N†	Y	Y	Y	Y	Y

CS indicates cross sectional; N, no; and Y, yes.
*Recruitment setting for cases/controls not clearly stated.
†No hemoglobin A_{1c}.
‡Diabetes mellitus duration not provided.
§Diabetes mellitus not clearly defined. (1) Were the criteria for inclusion in the sample clearly defined? (2) Were the study subjects and the setting described in detail? (3) Was the exposure measured in a valid and reliable way? (4) Were objective standard criteria used for measurement of the condition? (5) Were confounding factors identified? (6) Were strategies to deal with confounding factors stated? (7) Were the outcomes measured in a valid and reliable way? (8) Was appropriate statistical analysis used?

The discrepancy between strain reduction in all directions with preserved ejection fraction may be explained by the inherent variability in LVEF measurement, where the minimum changes detectable are 11.1% in 2-dimensional ejection fraction and 7.5% in 3D ejection fraction.[30] Therefore, subtle differences in LVEF between the diabetes mellitus and control groups were not detected with LVEF.

Intervendor Variability in 3D-STE

Observed significant reduction in I^2 in subgroup analyses of STE software (eg, I^2 of 3D GAS reduced from 89.9% to 17.7%) suggests that vendor differences be one of the main sources of heterogeneity. This finding is corroborated with high intervendor variability and discordance of 3D-STE data reported in the literature.[31–33] A recent systematic review and meta-analysis on normal values of 3D-STE[33] showed variations in the normal ranges across studies were significantly associated with the vendor and software used for strain analysis. They suggested that these differences can be explained with technical differences among the software. For example, 3D wall motion tracking has drift compensation (ie, all curves of different segments are forced to reach the 0 baseline at end-diastole) and uses speckles located in the endocardial layer to calculate global strains. On the other hand, EchoPAC (GE Healthcare) does not have drift compensation and automatically rejects segments with >12% drift. In addition, EchoPAC (GE Healthcare) tracks speckles across the whole wall thickness and calculates global strains by weighted spatial averaging of segmental values.[31] Furthermore, the same strain parameters have different definitions between vendors.[34] However, our study showed that despite these vendor-dependent variabilities of 3D-STE data, all 3D LV strain values are significantly lower in patients with asymptomatic diabetes mellitus compared with healthy controls in all vendors. Therefore, irrespective of the used vendor, subclinical DCM can be detectable by 3D-STE in the early stages.

Subgroup Analysis

To find the possible sources of heterogeneity between studies irrespective of intervendor variabilities, we performed a subgroup analysis on 9 studies that used the most popular STE software. The main results of the subgroup meta-analysis were consistent with our initial

Table 8. Newcastle Ottawa Quality Assessment Scale for Cohort Studies

Study	Year	Study Type	Selection				Comparability	Outcome		
			1	2	3	4	5	6	7	8
Luo[16]	2018	PC	*	…	…	*	**	…	…	*
Ringle[17]	2018	PC	*	*	*	*	**	…	*	…

PC indicates prospective cohort. 1, Representativeness of the exposed cohort; 2, selection of the nonexposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at the start of study; 5, comparability of cohorts on the basis of the design or analysis; 6, assessment of outcome; 7, was follow-up long enough for outcomes to occur?; 8, adequacy of follow-up of cohorts. Each * represents one star according to the Newcastle Ottawa Quality Assessment Scale.

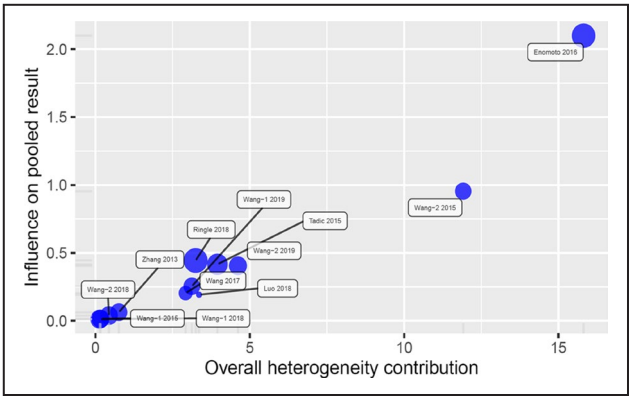

Figure 4. Baujat plot comparing included studies—contribution toward heterogeneity plotted against influence on pooled result.
The Baujat plot allows comparison of studies based on contribution of heterogeneity and extent of influence on the overall pooled mean difference. As seen, 2 studies (Wang, 2015,[11] and Enomoto, 2016[13]) contributed significantly to heterogeneity, while also having significant impact on the pooled result.

meta-analysis (all 3D LV strain values were significantly lower in patients with diabetes mellitus, with 3D GLS having the largest effect size). The significant reduction in heterogeneity in Figure 5 indicates that these 2 studies may have alternate underlying clinical characteristics that differentiate their cohorts from the remaining studies. Individual patient-level data would assist in reconciling these differences.

Subgroup meta-regression analysis could not find any additional consistent source of heterogeneity in both the group of patients with diabetes mellitus and the control group. However, a higher prevalence of hypertension was significantly associated with worse 3D GLS in patients with diabetes mellitus. The additional negative effect of hypertension on LV mechanics in patients with diabetes mellitus has been shown in studies that used 3D-STE[31] as well as 2-dimensional STE.[35–37] In addition, poor diabetes mellitus control (ie, higher hemoglobin A_{1c}) was the main contributor to worse 3D GCS in patients with diabetes mellitus. Zhang et al[10] compared LV strain values using 3D-STE among patients with diabetes mellitus with controlled and uncontrolled blood glucose and concluded that reduction in 3D GCS occurs only in patients with diabetes mellitus with hemoglobin A_{1c} ≥7%. Obesity has been suggested as one of the important factors that adversely affect cardiac mechanics in patients with diabetes mellitus.

Clinical Implications and Perspective

It has been shown in multiple clinical trials[38] that sodium-glucose cotransporter 2 inhibitors (such as empagliflozin, canagliflozin, and dapagliflozin) can reduce cardiovascular mortality as well as heart failure–related hospitalization in patients with type 2 diabetes mellitus. Findings of our study confirm that 3D-STE can be helpful to detect subclinical LV systolic dysfunction in patients with diabetes mellitus with normal LVEF. This therefore represents an opportunity for future randomized controlled trials to evaluate potential therapeutic options such as sodium-glucose cotransporter 2 inhibitors in the setting of subclinical diabetic cardiomyopathy, with 3D STE being used as surrogate end points to detect early changes in LV systolic function.

Modifiable factors such as glycemic control can have a significant impact on LV systolic function. Several studies

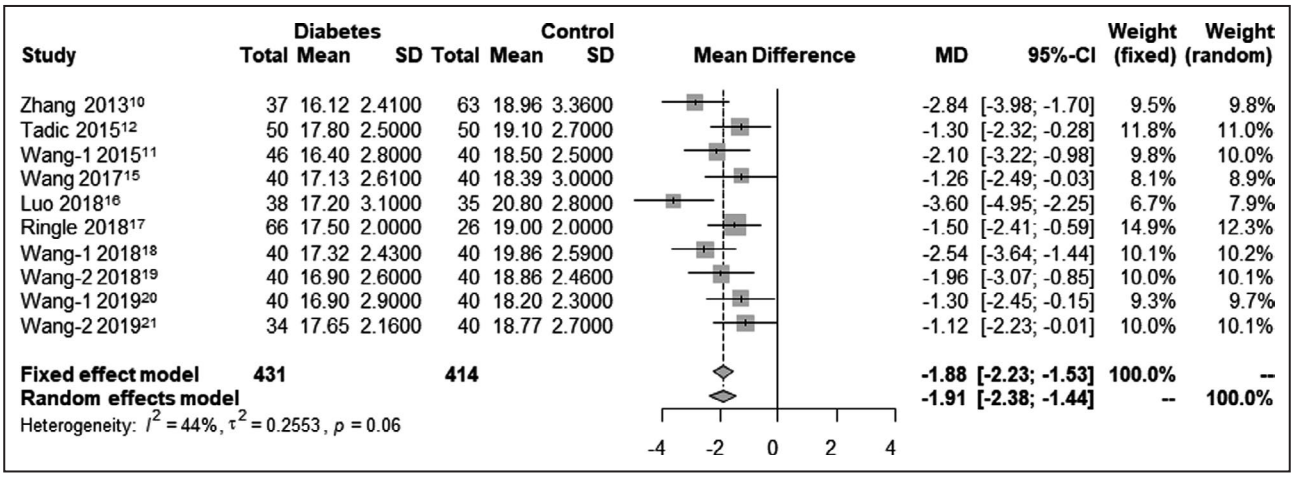

Figure 5. Forest plot of mean difference in 3D LV GLS in the group with diabetes mellitus and controls; sensitivity analysis removing most heterogeneous studies.
In response to the influence analysis performed, a sensitivity analysis was performed to determine the effect on pooled mean difference and overall heterogeneity when the 2 most heterogeneous studies (Wang, 2015,[13] and Enomoto, 2016[14]) were excluded. This forest plot shows a more modest reduction in 3D GLS in the diabetic pooled mean difference (–1.88 fixed, –1.91 random) when compared with control. Heterogeneity was significantly improved (I^2=44%). 3D indicates 3-dimensional; GLS, global longitudinal strain; and LV, left ventricular.

have shown that improved glycemic control leads to improvement in systolic and diastolic function.[39,40] Three-dimensional STE provides an important measurement that clinicians can use to effectively communicate early signs of cardiac involvement to improve motivation and compliance with diabetes mellitus control.

Early identification of subclinical diabetic cardiomyopathy is the key to preventing significant mortality and morbidity. Our review focused on the merits of 3D STE as a tool to detect myocardial deformation. Newer features in echocardiographic software, such as left ventricular myocardial work, may add further insight into the early manifestations of diabetic cardiomyopathy.[41] Future studies assessing the effect of diabetes mellitus on myocardial work are required before conclusions can be drawn.

Study Strengths and Limitations

Several factors merit consideration in the interpretation of our results. First, like all meta-analyses, this study is limited by variations within the original studies and publication bias, although we used standard approaches to find this. Additionally, observational studies may be restricted by biases within the recruitment method. Second, we assumed that all the measurements were performed by experts; however, the amount of expertise among people who have measured the strain is uncertain. Third, significant heterogeneities among studies were detected, the most prominent of which was the variation in definition of diabetes mellitus without clinical cardiac manifestation (Table S1). We performed subsequent meta-regression analyses to attempt to elucidate the sources of these variations; however, we were limited by the fact that this was a study-level meta-analysis, rather than a patient-level one. Furthermore, we were able to perform only univariate meta-regression analysis because of the number of included studies, so interactions between comorbidities such as hypertension and diabetes mellitus could not be explored in detail. There was also limited information regarding radial and area strain values from some of the included studies.

Finally, 7 studies had 2 groups of patients with diabetes mellitus, and we selected the lower-risk group to avoid extreme cases and report conservative estimates. The majority of the studies included patients with type 2 diabetes mellitus, meaning that generalizing our results to patients with type 1 diabetes mellitus should be done with caution. Nevertheless, this systematic review and meta-analysis in 3D-STE in subclinical DCM is the first of its kind and revealed the above important findings.

CONCLUSIONS

Three-dimensional STE may be useful in the diagnosis of subclinical DCM. Cardiac mechanics is impaired in all directions in patients with asymptomatic diabetes mellitus. The largest standardized reduction was observed in 3D GLS, which would be the most sensitive marker in detecting subclinical LV dysfunction in patients with diabetes mellitus. Intervendor discordance is a source of heterogeneity in included studies, emphasizing that this factor must be considered in the interpretation of 3D strain data. However, worse strain value in patients with diabetes mellitus can be detected with any vendor.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S8
Figures S1–S10

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Supplemental Material

Data S1.

Search criteria for the meta-analysis on 30/03/2020

Ovid MEDLINE(R) ALL (1946 to March 26, 2020)

#	Search Statement	Results
1	myocardial strain.mp.	1118
2	deformation imaging.mp.	305
3	speckle tracking echocardio*.mp.	2750
4	speckle tracking stud*.mp.	56
5	speckle tracking analys*.mp.	245
6	deformation analys*.mp.	379
7	diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/	299992
8	diabetes mellitus.mp.	427259
9	3 or 4 or 5	2946
10	7 or 8	427259
11	1 and 2 and 9	10
12	1 or 2 or 6 or 9	4330
13	10 and 12	160
14	(left ventric* or LV or right ventric* or RV or left atri* or LA or right atri* or RA).mp.	881773
15	(function* or dysfunction*).mp.	4093791
16	14 and 15	191576
17	strain.mp.	430336
18	16 and 17	8130
19	13 and 18	127
20	13 or 19	160
21	Filter by journal article and human studies	121

Embase Classic+Embase (1947 to March 27, 2020)

	Search Statement	Results
1	myocardial strain.mp.	2398
2	deformation imaging.mp.	683
3	speckle tracking echocardio*.mp.	8331
4	speckle tracking stud*.mp.	171
5	speckle tracking analys*.mp.	860
6	deformation analys*.mp.	689
7	diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/	659383
8	diabetes mellitus.mp.	954813
9	3 or 4 or 5	8984
10	7 or 8	954813
11	1 and 2 and 9	22
12	1 or 2 or 6 or 9	11581
13	10 and 12	794
14	(left ventric* or LV or right ventric* or RV or left atri* or LA or right atri* or RA).mp.	1443344
15	(function* or dysfunction*).mp.	5908112
16	14 and 15	350926
17	strain.mp.	842307
18	16 and 17	20484
19	13 and 18	574
20	13 or 19	794
21	Filter by journal articles and human studies	330

Cochrane central register of controlled trials (1991 to February 2020)

#	Search Statement	Results
1	myocardial strain.mp.	101
2	deformation imaging.mp.	16
3	speckle tracking echocardio*.mp.	300
4	speckle tracking stud*.mp.	3
5	speckle tracking analys*.mp.	33
6	deformation analys*.mp.	12
7	diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/	25548
8	diabetes mellitus.mp.	63955
9	3 or 4 or 5	324
10	7 or 8	63955
11	1 and 2 and 9	0
12	1 or 2 or 6 or 9	417
13	10 and 12	26
14	(left ventric* or LV or right ventric* or RV or left atri* or LA or right atri* or RA).mp.	55341
15	(function* or dysfunction*).mp.	278968
16	14 and 15	20338
17	strain.mp.	8265
18	16 and 17	803
19	13 and 18	19
20	13 or 19	26
21	Filter by journal articles and human studies	10

Scopus (March 30, 2020): 40 studies

(TITLE-ABS
KEY (myocardial AND strain OR deformation AND imaging OR speckle AND tracking AND stud* OR speckle AND tracking AND analys* OR deformation AND analys*))
AND (TITLE-ABS-
KEY (diabetes AND mellitus OR diabetes AND mellitus AND type 1 OR diabetes AN D mellitus AND type 2)) AND (LIMIT
TO (LANGUAGE , "English")) AND (LIMIT-
TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-
TO (EXACTKEYWORD , "Human"))

Web of Science (March 30, 2020): 290 studies

(myocardial AND strain OR deformation AND imaging OR speckle AND tracking AN D stud* OR speckle AND tracking AND analys* OR deformation AND analys*) AN D (diabetes AND mellitus OR diabetes AND mellitus AND type 1 OR diabetes AND mellitus AND type 2) Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (CARDIAC CARDIOVASCULAR SYSTEMS OR ENDOCRINOLOGY METABOLISM)

Table S1. Definition of study groups of included studies.

First Author	Year	DM group inclusion criteria	DM group exclusion criteria	Control group definition
Zhang	2013	Type 2 DM with LVEFs > 55%	Arrhythmias, ischemic heart disease (documented myocardial infarction, history of revascularization procedures, and positive findings on coronary angiography or computed tomography), other structural heart diseases, albumin/creatinine ratios > 30 mg/mg, uncontrolled hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg at rest), and one with other serious complications of DM (diabetic ketoacidosis or nonketotic hyperosmolar coma), inadequate echocardiographic image quality	Age-matched and gender-matched controls if they met the following criteria: no evidence of pre-existing cardiac disease on transthoracic echocardiography and other examinations, no clinical history of chronic diseases or chronic medications, and normal results on 12-lead electrocardiography. However, subjects with hypertension but well-controlled blood pressure (i.e., systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg on three separate measurements during the past month) were not excluded.
Wang-1	2015	Outpatients or inpatients diagnosed with type 2 diabetes according to the 2010 guidelines of the American Diabetes Association, and with left ventricular ejection fraction (LVEF) > 55%	Presence of coronary artery stenosis, atrial fibrillation, or poor acoustic window and image quality	Age- and gender-matched controls were recruited from the medical examination centre in our hospital based on the following criteria: no history of diabetes, hypertension, or coronary heart disease and no evidence of pre-existing cardiac diseases on conventional electrocardiogram (ECG), echocardiography, or laboratory examination
Tadic	2015	Normotensive patients ((blood pressure < 140/90 mm Hg measured on several separate occasions) untreated for type 2 diabetes	Symptoms or signs of cardiovascular disease (arterial hypertension, heart failure, myocardial infarction, significant valvular disease, atrial fibrillation, congenital heart disease), obesity (BMI ≥ 30 kg/m2), asthma, chronic obstructive lung disease, neoplastic disease, cirrhosis of the liver, or kidney failure	Controls of similar age and sex distributions
Wang-2	2015	Patients diagnosed with type 2 diabetes [left ventricular ejection fraction (LVEF) ≥55%]	History of coronary artery stenosis diagnosed by coronary angiography, arrhythmia, or poor acoustic windows and imaging qualities	Age- and sex-matched controls with BMIs of 18.5–24.5 kg/m2 who showed an absence of diabetes, hypertension, and coronary heart disease and in whom there was no evidence of pre-existing cardiac disease on conventional electrocardiography (ECG), transthoracic echocardiography (TTE), and laboratory examinations

Enomoto	2016	Hospitalized patients with type 2 DM requiring diabetes education	Patients with coronary artery disease or LV ejection fraction (LVEF) <50%, other than sinus rhythm, significant valvular disease, and inadequate echocardiographic image quality for analysis	Age-matched healthy subjects
Wang	2017	Type 2 diabetic patients aged 60 years or over	Arterial hypertension, coronary lesions, severe arrhythmia, and other heart disease with known causes	Sex-matched healthy volunteers aged over 60 years, without diabetes, hypertension, or pre-existing cardiac disease on conventional examinations
Luo	2018	T2DM complicated with microangiopathy. Microangiopathies were as follows: (1) diabetic retinopathy, (2) diabetic nephropathy, (3) diabetic neuropathy	Acute complications, severe hypoglycaemia during treatment, hypertension, coronary heart disease, and arrhythmia	Healthy volunteers not have a history of diabetes mellitus, hypertension and coronary heart disease
Ringle	2018	Patients aged older than 18 years with isolated type 1 diabetes	Recent diagnosis of diabetes (<1year), documented cardiac disease, diabetic nephropathy, cardiovascular risk factors (hypertension, hypercholesterolemia, active smoking, obesity, age over 60 years)	Age- and gender-matched healthy subjects that met the following criteria: no cardiovascular risk factors, no personal history of heart disease, no clinical history of chronic disease or chronic medication and normal transthoracic echocardiography
Wang-1	2018	(1) diagnosis of type 2 diabetes based on the 2014 guidelines of the American Diabetes Association10; and (2) a left ventricular ejection fraction (LVEF) of 55% or higher	(1) patients who had a history of hypertension or coronary artery stenosis diagnosed by coronary angiography and computed tomography; (2) patients with arrhythmia; (3) patients who had known causes of chronic liver disease (i.e., alcoholic or drug-induced liver disease and autoimmune or viral hepatitis); and (4) patients with a poor acoustic window and fuzzy 3D images	Age- and sex-matched healthy Volunteer, absence of diabetes, hypertension, and coronary heart disease and no evidence of pre-existing cardiac or hepatic disease in conventional radiologic, US, or laboratory tests
Wang-2	2018	Type 2 diabetic patients	Possibility of hypertension, coronary lesion, severe arrhythmia, and other heart diseases with known causes	Age-and sex-matched healthy volunteers from our medical examination centre were recruited as the control group. All of them showed the absence of diabetes, hypertension, or other pre-existing cardiac diseases using conventional examinations, and they also had serum concentrations of cholesterol and triglycerides within the normal range
Wang-1	2019	Diagnostic criteria of T2DM were in line with the guidelines	Presence of hypertension, coronary lesion, severe arrhythmia, and other heart diseases with known causes	Age- and gender-matched healthy physical examinees in our hospital were recruited as the

		promulgated by the American Diabetes Association (ADA) in 2016		control group. None of the controls had obviously positive signs of T2DM, hypertension, or other pre-existing cardiac diseases after routine examinations. Moreover, they all had SUA at normal levels.
Wang-2	2019	The diagnostic criteria of T2DM complied with the 2016 guidelines of the American Diabetes Association (ADA).	Hypertension, severe arrhythmia and valve lesion, as well as other cardiac disease with known causes	Age-and gender-matched healthy individuals who received regular check-ups in our hospital were recruited as the control subjects. They all had no history or positive signs of T2DM, hypertension, coronary disease, and other pre-existing heart diseases detected by routine examinations

Table S2. Haemodynamic parameters in included articles.

First Author	Year	Rest SBP Mean ± SD (DM)	Rest SBP Mean ± SD (Control)	Rest DBP Mean ± SD (DM)	Rest DBP Mean ± SD (Control)	Rest HR Mean ± SD (DM)	Rest HR Mean ± SD (Control)
Zhang	2013	128±8	129±12	76±15	77±7	76±15	74±13
Wang-1	2015	127±9.5	124±9.2	78±0.4	77±5.6	79±11	76±10
Tadic	2015	128±11	124±13	77±7	75±8	71±8	73±7
Wang-2	2015	127±10.2	126±8.4	77±7.3	78±4.5	78±12	75±11
Enomoto	2016	119.8±21.4	122.9±17.2	70.3±13.6	73.2±13.4	66.1±11.9	65.5±12.7
Wang	2017	128±7	123±9.2	78±5.3	75±6.4	77±12	74±13
Luo	2018	128.4±8.9	107.2±8.8	75.7±5.9	73.3±6	-	-
Ringle	2018	121±12	122±9	74±9	74±6	-	-
Wang-1	2018	127±9.8	126±6.8	78±5.8	76±6.4	77±12	75±10
Wang-2	2018	127.8±8.8	125.7±10	77.3±6.4	77.6±7.7	77±11	75±13
Wang-1	2019	128.7±5.7	126.5±6.9	75.6±7.3	75±6	76±10	77±9
Wang-2	2019	125±8.48	125±7.26	76±5.37	75±7.19	78±10	75±10

Table S3. Meta-regression results in diabetes mellitus group.

Variable		DM type (II vs I)	Vendor (Toshiba vs G.E)	Vendor (Philips vs G.E)	Age, per 1 year	%female, per 1%	SBP, per 1 mmHg	DBP, per 1 mmHg	HR, per 1 pm	%HTN, per 1%	BMI, per 1 kg/m2	HbA1C, per 1%
3D LV GLS	**N**	12	12	12	12	12	12	12	10	12	12	7
	β [95% CI]	-0.94 [-4.6, 2.7]	**-5.8 [-7, -4.6]**	-0.3 [-1.4, 0.7]	0 [-0.1, 0.1]	**0.1 [0, 0.2]**	0.3 [0, 0.6]	**0.5 [0.2, 0.9]**	**0.3 [0.1, 0.5]**	**-0.1 [-0.1, 0]**	0.7 [-0.2, 1.6]	-0.7 [-1.5, 0]
	***P*-value**	0.62	**<0.001**	0.46	0.97	**0.04**	0.07	**0.002**	**0.007**	**0.001**	0.1	0.06
3D LV GCS	**N**		11	11	11	11	11	11	10	11	11	7
	β [95% CI]		**8.8 [6.7, 10.9]**	**4 [2.3, 5.7]**	**-0.3 [-0.6, 0]**	**-0.4 [-0.6, -0.3]**	**-1 [-1.5, -0.4]**	**-1.3 [-1.8, -0.8]**	**-0.7 [-0.9, -0.4]**	0.1 [0, 0.1]	-0.7 [-2.1, 0.8]	**1.8 [0.6, 3.1]**
	***P*-value**		**<0.0001**	**<0.0001**	**0.03**	**<0.0001**	**0.0005**	**<0.0001**	**<0.0001**	0.2	0.4	**0.003**
3D LV GRS	**N**		10		10	10	10	10	10	10	10	6
	β [95% CI]		**-14.7 [-18, -11.6]**		**1 [0.2, 1.7]**	**1.1 [0.7, 1.5]**	**2.2 [1, 3.5]**	**2.8 [1.6, 3.9]**	**1.7 [1.3, 2.1]**	**-0.2 [-0.4, 0]**	0.8 [-3.7, 5.2]	**-4.7 [-7.7, -1.7]**
	***P*-value**		**<0.0001**		**0.01**	**<0.0001**	**0.0004**	**<0.0001**	**<0.0001**	**0.04**	0.7	**0.002**
3D LV GAS	**N**		10		10	10	10	10	10	10	10	6
	β [95% CI]		**8.4 [6.3, 10.5]**		-0.2 [-0.4, 0.1]	**-0.4 [-0.5, -0.2]**	**-0.9 [-1.2, -0.7]**	**-1 [-1.3, -0.6]**	**-0.5 [-0.8, -0.2]**	0.1 [0, 0.1]	-1 [-2.1, 0.1]	**1.5 [0.2, 2.7]**
	***P*-value**		**<0.0001**		0.24	**<0.0001**	**<0.0001**	**<0.0001**	**0.001**	0.09	0.07	**0.02**

Table S4. Meta-regression results in control group.

Variable		DM type (II vs I)	Vendor (Toshiba vs G.E)	Vendor (Philips vs G.E)	Age, per 1 year	%female, per 1%	SBP, per 1 mmHg	DBP, per 1 mmHg	HR, per 1 pm	%HTN, per 1%	BMI, per 1 kg/m2	HbA1C, per 1%
3D LV GLS	**N**	12	12	12	12	12	12	12	10	12	12	4
	β [95% CI]	0 [-3, 3]	**-2.9 [-5.7, -0.1]**	0.8 [-1.7, 3.2]	0 [-0.1, 0.1]	0 [-0.1, 0.1]	-0.1 [-0.2, 0.1]	0.3 [-0.2, 0.8]	**0.3 [0, 0.4]**	0 [-0.1, 0.1]	0.3 [-0.6, 1.2]	0 [-4, 4]
	***P*-value**	0.9	**0.04**	0.53	0.66	0.53	0.4	0.2	**0.02**	0.9	0.5	0.9
3D LV GCS	**N**		11	11	11	11	11	11	10	11	11	4
	β [95% CI]		**11.8 [9.5, 14.1]**	**5.5 [3.8, 7.2]**	**-0.4 [-0.7, -0.2]**	**-0.4 [-0.7, -0.1]**	**-0.4 [-0.6, -0.2]**	**-1.8 [-2.7, -0.9]**	**-1.3 [-1.5, -1]**	0 [-0.2, 0.1]	-2.2 [-4.1, -0.3]	**-1.9 [-3.4, 0.4]**
	***P*-value**		**<0.0001**	**<0.0001**	**0.0005**	**0.005**	**0.0008**	**0.0001**	**<0.0001**	0.5	0.02	**0.01**
3D LV GRS	**N**		10		10	10	10	10	10	10	10	4
	β [95% CI]		**-13.5 [-20.2, -6.9]**		**0.7 [0.2, 1.2]**	1.7 [-0.8, 4.2]	**2.3 [0.7, 4.1]**	**3.4 [1.4, 5.4]**	**1.9 [1, 2.8]**	0.2 [-0.1, 0.4]	3.9 [0, 7.8]	**11.6 [2.4, 20.8]**
	***P*-value**		**<0.0001**		**0.006**	0.18	**0.006**	**0.001**	**<0.0001**	0.2	0.05	**0.01**
3D LV GAS	**N**		10		10	10	10	10	10	10	10	4
	β [95% CI]		**13 [9.7, 16.3]**		**-0.4 [-0.6, -0.1]**	-0.8 [-2, 0.4]	-0.6 [-1.7, 0.4]	**-1.4 [-2.6, -0.2]**	**-1.2 [-1.5, -0.9]**	0 [-0.1, 0.1]	**-2.6 [-4.3, -0.9]**	-0.4 [-2.5, 1.7]
	***P*-value**		**<0.0001**		**0.007**	0.2	0.2	**0.02**	**<0.0001**	0.8	**0.003**	0.7

Table S5. Meta-regression results in diabetes mellitus group in subgroup analysis of studies using the most popular vendor.

Variable		Age, per 1 year	%female, per 1%	SBP, per 1 mmHg	DBP, per 1 mmHg	HR, per 1 pm	%HTN, per 1%	BMI, per 1 kg/m2	HbA1C, per 1%
3D LV GLS	**N**	9	9	9	9	9	9	9	5
	β [95% CI]	0. [-0.1, 0]	0.1 [0, 0.3]	-0.2 [-0.5, 0.2]	0 [-0.4, 0.5]	-0.1 [-0.3, 0]	**-0.02 [-0.04, 0]**	0.2 [-0.2, 0.5]	-0.4 [-1, 0.2]
	***P*-value**	0.4	0.1	0.4	0.9	0.2	**0.04**	0.3	0.2
3D LV GCS	**N**	8	8	8	8	8	8	8	4
	β [95% CI]	**0.1 [0, 0.3]**	**0.2 [0.1, 0.3]**	-0.2 [-0.6, 0.2]	0.1 [-0.3, -0.6]	0.3 [-0.1, 0.7]	**-0.02 [-0.04, -0.01]**	-0.1 [-0.8, 0.6]	**-0.5 [-0.9, -0.1]**
	***P*-value**	**0.01**	**0.0006**	0.3	0.6	0.2	**0.0009**	0.8	**0.007**
3D LV GRS	**N**	8	8	8	8	8	8	8	4
	β [95% CI]	0.2 [-0.1, 0.6]	0.4 [0, 0.8]	-0.6 [-1.5, 0.4]	0.3 [-0.7, 1.4]	0.4 [-0.5, 1.4]	-0.04 [-0.1, 0]	-0.4 [-1.8, 1]	-1 [-2.4, 0.3]
	***P*-value**	0.2	0.05	0.2	0.5	0.4	0.08	0.5	0.1
3D LV GAS	**N**	8	8	8	8	8	8	8	4
	β [95% CI]	0.1 [-0.1, 0.2]	0.2 [0, 0.3]	**-0.4 [-0.8, 0]**	0 [0.6, 0.5]	0.2 [-0.3, 0.7]	-0.02[-0.04, 0]	-0.2 [-0.9, 0.5]	-0.6 [-1.1, 0]
	***P*-value**	0.4	0.08	**0.03**	0.9	0.4	0.06	0.5	0.05

Table S6. Meta-regression results in control group in subgroup analysis of studies using the most popular vendor.

Variable		Age, per 1 year	%female, per 1%	SBP, per 1 mmHg	DBP, per 1 mmHg	HR, per 1 pm	%HTN, per 1%	BMI, per 1 kg/m2	HbA1C, per 1%
3D LV GLS	N	8	8	8	8	8	8	8	3
	β [95% CI]	0 [-0.1, 0.1]	0 [-0.5, 0.5]	0.1 [-0.3, 0.6]	0.5 [-0.1, 1]	**-0.2 [-1, 0.5]**	0 [0, 0]	-0.5 [-1.3, 0.2]	-2.9 [-10.1, 4.3]
	***P*-value**	0.8	0.9	0.6	0.08	**0.5**	0.9	0.2	0.4
3D LV GCS	N	8	8	8	8	8	8	8	3
	β [95% CI]	0 [-0.1, 0.1]	0.1 [-0.1, 0.4]	0 [-0.2, 0.3]	0.2 [-0.1, 0.5]	-0.3 [-0.6, 0]	0 [-0.03, 0.03]	-0.2 [-0.6, 0.2]	-0.9 [-3.2, 1.5]
	***P*-value**	0.9	0.3	0.8	0.3	0.1	0.9	0.4	0.5
3D LV GRS	N	8	8	8	8	8	8	8	3
	β [95% CI]	**-0.4 [-0.8, -0.1]**	1 [0.2, 2]	0.7 [-0.2, 1.6]	0.7 [-0.6, 2]	**-1.6 [-2.5, -0.6]**	**0.1 [0, 0.2]**	-0.1 [-2.1, 1.9]	2.4 [-5.5, 10.3]
	***P*-value**	**0.03**	0.05	0.1	0.3	**0.001**	**0.04**	0.9	0.6
3D LV GAS	N	8	8	8	8	8	8	8	3
	β [95% CI]	**-0.2 [-0.4, -0.1]**	0.3 [-0.2, 0.7]	**0.3 [0.1, 0.7]**	0.4 [-0.2, 1]	-0.5 [-1.2, -0.1]	0.05 [0.02, 0.08]	-0.3 [-1.2, 0.6]	-2.2 [-6, 1.6]
	***P*-value**	**0.002**	0.3	**0.02**	0.2	0.09	0.002	0.5	0.3

Table S7. Observer variability and strain reproducibility for included studies.

Study	N	Intra-observer variability				Inter-observer variability			
		GLS	GCS	GRS	GAS	GLS	GCS	GRS	GAS
Zhang[10] 2013	20	0.940	0.849	0.902	0.913	0.834	0.838	0.829	0.822
Wang-1[26] 2015	18	0.967	0.923	0.993	0.979	0.966	0.906	0.988	0.963
Tadic[12] 2015	-	0.95	0.87	0.7	0.89	0.91	0.83	0.65	0.86
Wang-2[11] 2015	15	0.951	0.945	0.986	0.977	0.964	0.956	0.992	0.988
Enomoto[13] 2016	10	#							
Wang[14] 2017	12	0.975	0.988	0.982	0.986	0.962	0.929	0.979	0.967
Luo[15] 2018	16	†							
Ringle[16] 2018	20	0.967	-	-	-	0.893	-	-	-
Wang-1[18] 2018	18	0.913	0.903	0.904	0.930	0.856	0.872	0.851	0.879
Wang-2[17] 2018	18	0.956	0.969	0.983	0.980	0.929	0.916	0.967	0.941
Wang-1[20] 2019	12	0.974	0.968	0.982	0.969	0.932	0.944	0.963	0.930
Wang-2[19] 2019	12	0.951	0.965	0.950	0.953	0.937	0.930	0.934	0.931

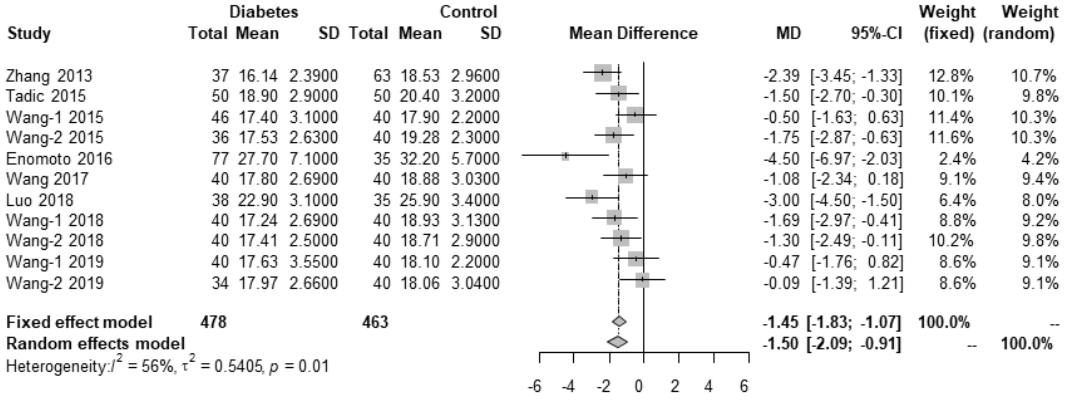
N – Number of patients assessed for variability in each study, GLS – Global Longtitudinal Strain, GCS – Global Circumferential Strain, GRS – Global Radial Strain, GAS – Global Area Strain. # - Only percent variability reported, † - Graphically represented without correlation coefficients,

Table S8. Leave-One-Out Analysis.

Study Omission	Effect	LLCI 95%	ULCI 95%	I^2
Omitting Enomoto 2016	-2.15	-2.75	-1.54	69%
Omitting Wang-2 2015	-2.16	-2.79	-1.52	73%
Omitting Wang-2 2019	-2.45	-3.15	-1.74	78%
Omitting Tadic 2015	-2.43	-3.15	-1.7	78%
Omitting Ringle 2018	-2.42	-3.15	-1.69	79%
Omitting Luo 2018	-2.23	-2.94	-1.53	79%
Omitting Wang-1 2019	-2.43	-3.14	-1.71	79%
Omitting Wang 2017	-2.43	-3.14	-1.72	79%
Omitting Zhang 2013	-2.29	-3.03	-1.56	80%
Omitting Wang-2 2018	-2.37	-3.11	-1.63	80%
Omitting Wang-1 2015	-2.36	-3.10	-1.62	80%
Omitting Wang-1 2018	-2.32	-3.06	-1.58	80%

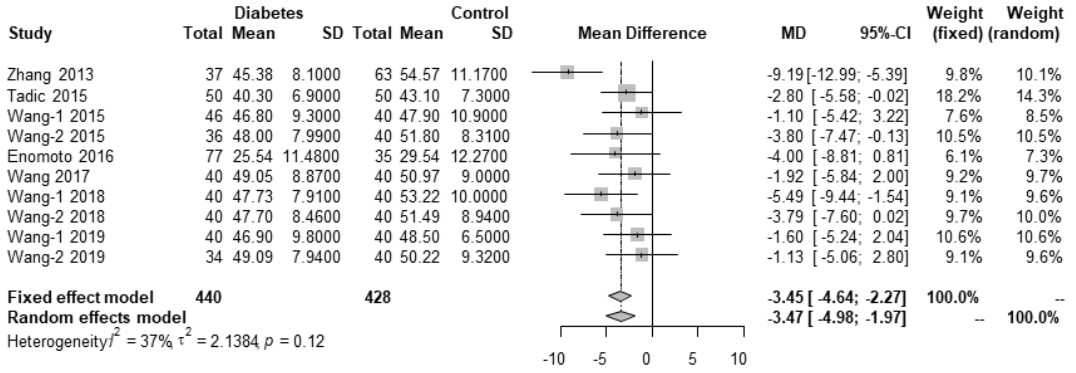
LLCI – Lower Limit Confidence Interval, ULCI – Upper Limit Confidence Interval, I^2 – Heterogeneity statistic

Figure S1. Forest plots for 3D LV GCS in diabetic and healthy controls and MD of 3D LV GCS.



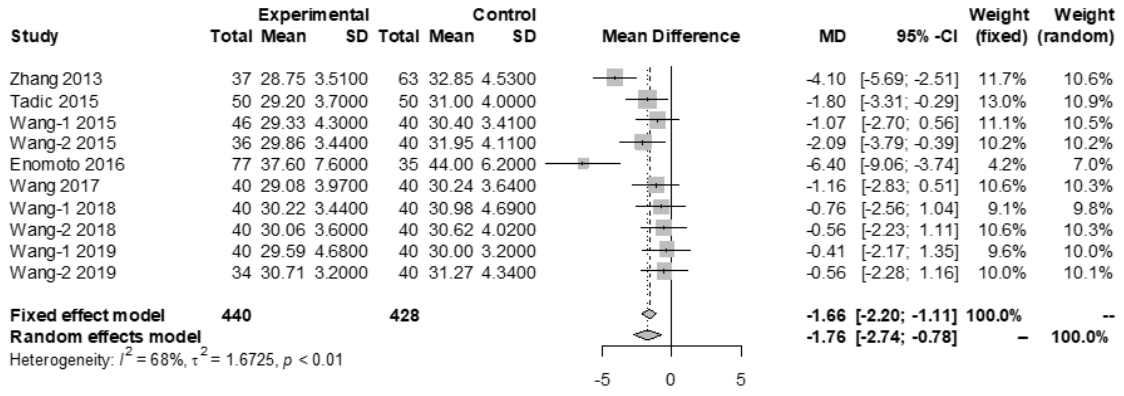
3D -three dimensional, GCS -global circumferential strain, LV - left ventricular, MD - mean difference.

Figure S2. Forest plots for 3D LV GRS in diabetic and healthy controls and MD of LV GRS.



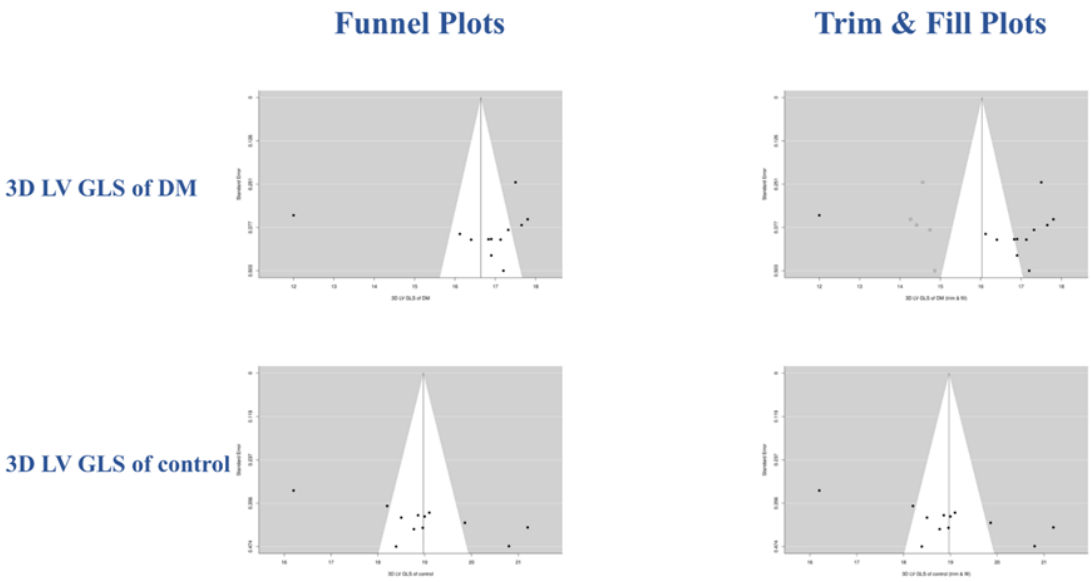
3D - three dimensional, GRS - global radial strain, LV -left ventricular, MD - mean difference.

Figure S3. Forest plots for 3D LV GAS in diabetic and healthy controls and MD of LV GAS.



3D - three dimensional, GAS - global area strain, LV - left ventricular, MD - mean difference.

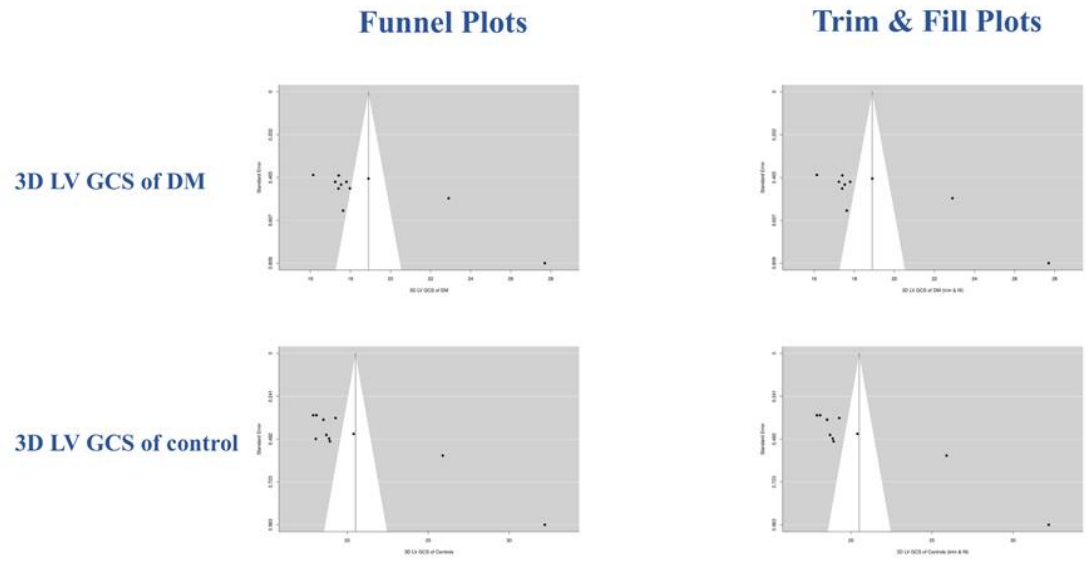
Figure S4. Funnel plots with Trim and Fill plots for 3D LV GLS in diabetic and healthy controls.



For assessment of publication bias, funnel plots of each strain parameter are shown with their trim and fill plots.

3D - three dimensional, GLS -global longitudinal strain, LV - left ventricular, MD - mean difference.

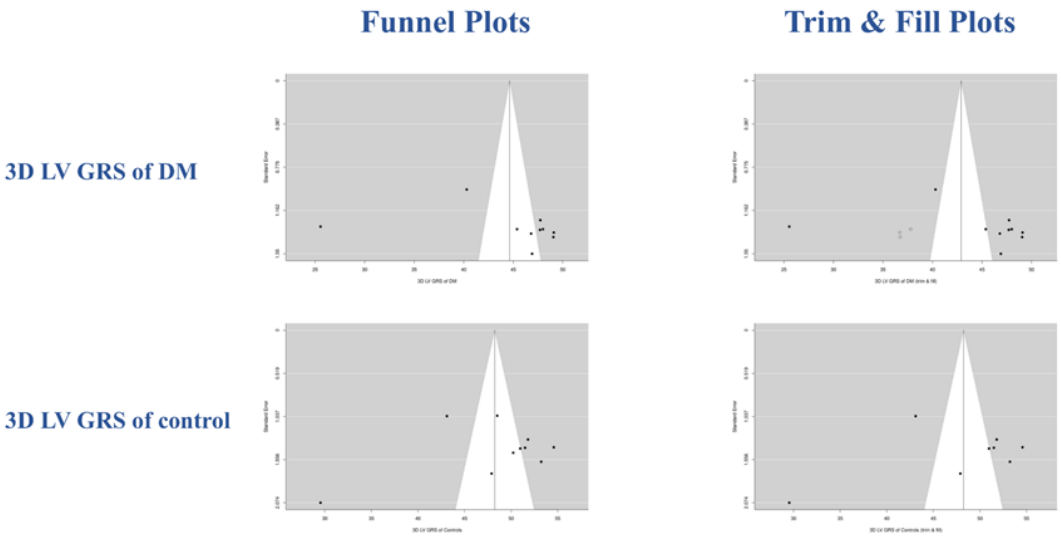
Figure S5. Funnel plots with Trim and Fill plots for 3D LV GCS in diabetic and healthy controls.



For assessment of publication bias, funnel plots of each strain parameter are shown with their trim and fill plots.

3D - three dimensional, GCS - global circumferential strain, LV - left ventricular, MD - mean difference.

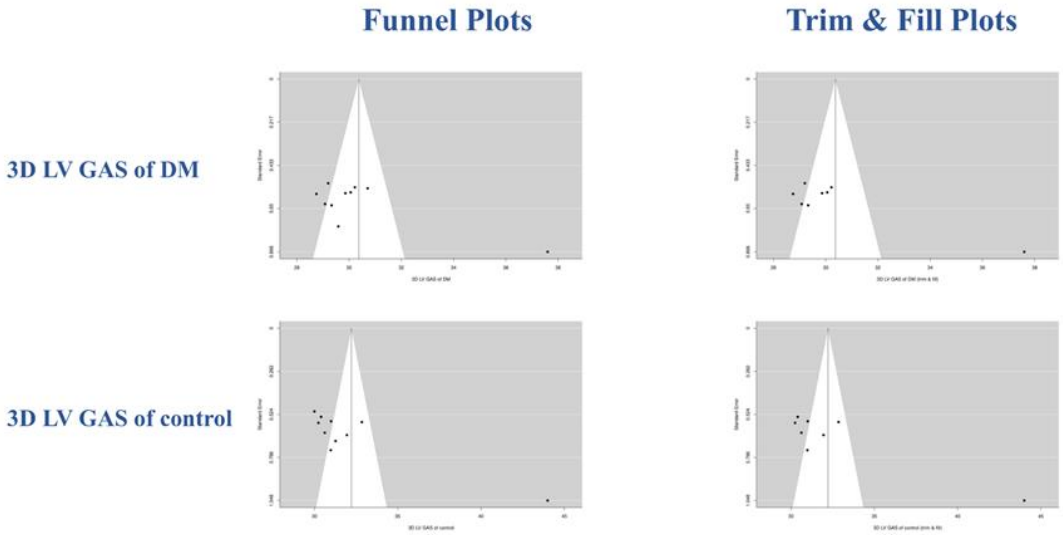
Figure S6. Funnel plots with Trim and Fill plots for 3D LV GRS in diabetic and healthy controls.



For assessment of publication bias, funnel plots of each strain parameter are shown with their trim and fill plots.

3D - three dimensional; GRS - global radial strain, LV - left ventricular, MD - mean difference.

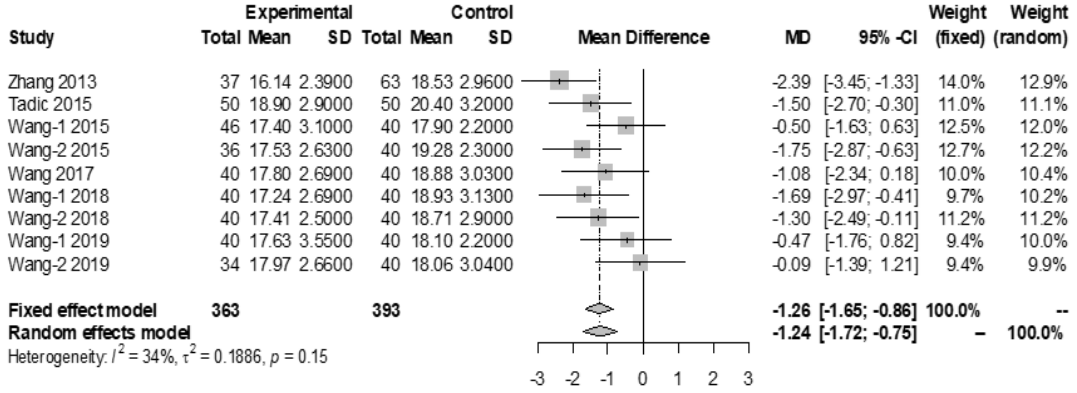
Figure S7. Funnel plots with Trim and Fill plots for 3D LV GAS in diabetic and healthy controls.



For assessment of publication bias, funnel plots of each strain parameter are shown with their trim and fill plots.

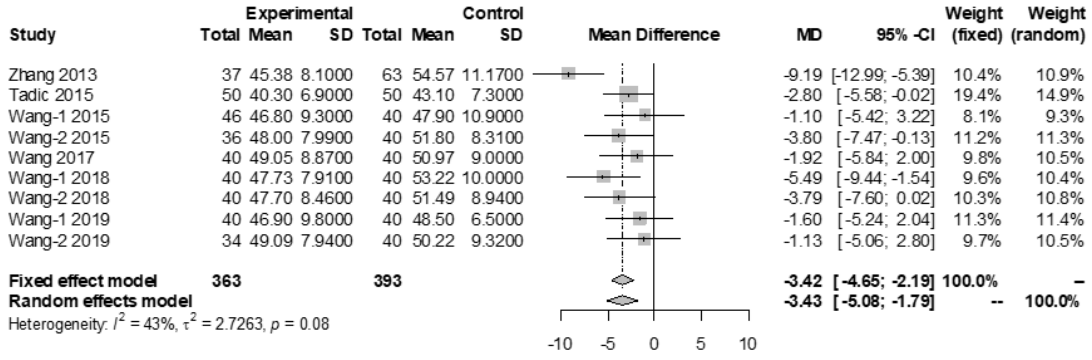
3D - three dimensional; GAS - global area strain, LV - left ventricular, MD - mean difference.

Figure S8. Forest plots of subgroup analysis of mean 3D LV GCS and MD in diabetes mellitus and control groups in studies using the most popular vendor.



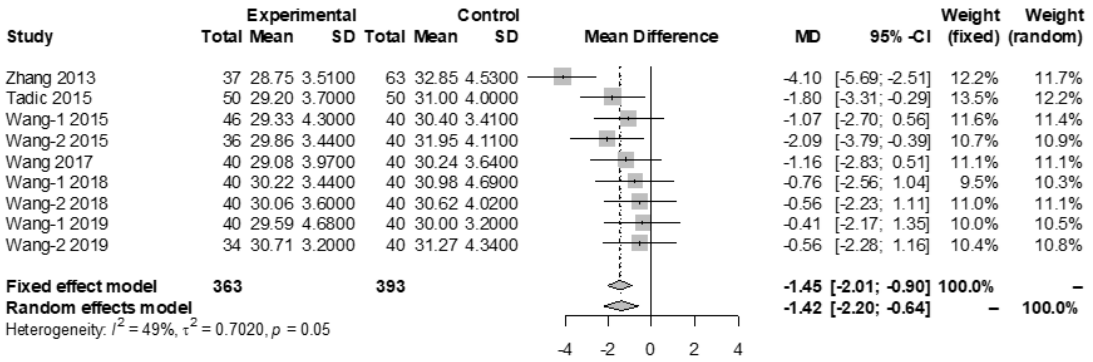
3D - three dimensional, GRS - global radial strain, LV - left ventricular.

Figure S9. Forest plots of subgroup analysis of mean 3D LV GRS and MD in diabetes mellitus and control groups in studies using the most popular vendor.



3D - three dimensional, GRS - global radial strain, LV - left ventricular.

Figure S10. Forest plots of subgroup analysis of mean 3D LV GAS and MD in diabetes mellitus and control groups in studies using the most popular vendor.



3D - three dimensional, GRS - global radial strain, LV - left ventricular.