



ORIGINAL ARTICLE

The impact of diastolic dysfunction as a predictor of cardiovascular events: A systematic review and meta-analysis



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KEYWORDS

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Myocardial relaxation;
Diastolic dysfunction;
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Heart failure

Abstract

Introduction: Diastolic dysfunction is highly prevalent and a key pathophysiological contributor to several cardiovascular diseases, especially heart failure with preserved ejection fraction. In addition, some evidence suggests diastolic dysfunction is a risk factor for major adverse cardiovascular events. This study aimed to systematically review the evidence and to quantify the association between diastolic dysfunction and risk of cardiovascular events and death.

Methods: MEDLINE was systematically searched from 1974 up to October 2017. We included cohort studies that assessed diastolic function in adults in the community, providing a definition of diastolic dysfunction regarding the occurrence of any cardiovascular event or mortality. For the quantitative analysis, relative risk estimates comparing individuals with versus without diastolic dysfunction were combined using a random effects model.

Results: Nineteen studies were identified for inclusion in the systematic review, assessing a total of 63 802 participants. Nine studies were included in the meta-analysis. Diagnostic criteria and classification of diastolic dysfunction differed substantially between studies. The median prevalence of diastolic dysfunction in studies including individuals with and without diastolic dysfunction was 35.1% (range 5.3-65.2%). Comparing diastolic dysfunction with normal diastolic function, the summary relative risk estimate for cardiovascular events or mortality was 3.53 (95% CI: 2.75-4.53; $I^2=85.5%$; nine studies).

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PALAVRAS-CHAVE

Diástole;
Relaxamento
miocárdico;
Disfunção diastólica;
Prognóstico;
Eventos
cardiovasculares;
Insuficiência cardíaca

Conclusions: Although the definitions found in the literature differ, the diagnosis of diastolic dysfunction is associated with a 3.53-fold increased risk of cardiovascular events or death. This finding highlights the importance of developing easily applicable and consensual diagnostic criteria, as well as fostering research on effective treatment strategies when diastolic dysfunction is identified in the subclinical stage.

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O impacto da disfunção diastólica como preditor de eventos cardiovasculares: uma revisão sistemática e meta-análise

Resumo

Introdução: A disfunção diastólica (DD) é muito prevalente e representa um mecanismo fisiopatológico central para várias doenças cardiovasculares, especialmente para a insuficiência cardíaca com fração de ejeção preservada. Além disso, alguns estudos sugerem que a DD se associa a um aumento do risco de eventos cardiovasculares. Este estudo pretende determinar se a DD é um preditor de eventos cardiovasculares e mortalidade através de uma revisão sistemática e meta-análise.

Métodos: Foi realizada uma pesquisa na Medline, desde 1974 até outubro de 2017. Foram incluídos estudos de coorte que avaliassem a função diastólica em adultos da comunidade, comparando participantes com e sem DD, no que diz respeito ao desenvolvimento de eventos cardiovasculares ou morte. Na meta-análise, os riscos relativos foram combinados usando um modelo de *random-effects analysis*.

Resultados: Foram identificados dezanove estudos para a revisão sistemática, avaliando um total de 63 802 participantes, dos quais nove foram incluídos na meta-análise. Observamos que os critérios de diagnóstico e classificação de DD foram bastante diferentes entre os estudos. A prevalência mediana de DD foi 35,1% (variabilidade 5,3%-65,2%). A presença de DD associou-se a um aumento significativo do risco relativo combinado de evento cardiovascular ou mortalidade (3,53; IC 95%: 2,75-4,53; I²=85,5%; 9 estudos).

Conclusões: Apesar da heterogeneidade na definição de DD, a sua presença está associada a um aumento marcado do risco de eventos cardiovasculares ou morte. Este resultado realça a importância de desenvolver critérios objetivos e consensuais para o diagnóstico de DD, de modo a promover a sua identificação numa fase subclínica e eventualmente estimular uma investigação dirigida à abordagem terapêutica precoce.

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Introduction

Diastolic dysfunction (DD) is a commonly used term that denotes the presence of pathophysiological changes in cardiac function which include abnormal relaxation, increased myocardial stiffness and increased end-diastolic pressure.¹

The prevalence of DD is increasing and is now higher than that of systolic dysfunction.² According to a recent systematic review, DD affects approximately 36% of the population older than 60 years.³ Echocardiography is often used to assess diastolic function. However, no single echocardiographic parameter is considered sufficiently accurate and reproducible to establish the diagnosis of DD and several parameters must be combined for the diagnosis. Recently, a joint effort involving the European Association of Cardiovascular Imaging and the American Society of Echocardiography

set out to harmonize the assessment of diastolic function and to develop a new definition of DD.⁴

DD is closely associated with several cardiovascular risk factors, including hypertension, obesity and diabetes.⁵⁻⁸ Furthermore, DD is mechanistically involved in the cardiovascular changes that accompany common cardiac diseases, such as stable coronary artery disease, myocardial infarction and cardiomyopathies, with a very strong link to heart failure with preserved ejection fraction (HFpEF).⁹ DD is one of the best predictors of exercise capacity in patients with heart failure and after myocardial infarction.¹⁰ More interestingly, it has also been suggested that increasing severity of DD increases the risk of heart failure¹ and is predictive of all-cause mortality.¹¹ However, to the best of our knowledge, the available evidence has not yet been systematically reviewed.

This study aimed to systematically review cohort studies assessing the association between DD and the incidence of major adverse cardiovascular events (MACE) and death, and to quantify the strength of this association using meta-analytical methods.

Methods

Data sources and query

This study was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.¹² Studies were identified by searching the PubMed electronic database (MEDLINE) and scanning reference lists of articles. The following search terms were used: ("Diastole"[MeSH] OR diastolic OR "myocardial relaxation" OR "cardiac relaxation" OR "myocardial stiffness" OR "cardiac stiffness") AND ("Prognosis"[MeSH] OR "Heart Failure"[MeSH] OR "Mortality"[MeSH]) AND (community OR "general population"). A language filter was used to restrict the search to English, Portuguese and Spanish papers. There were no date restrictions applied to the electronic searches – all reports from 1974 until October 26 2017 (when the last search was conducted) were eligible. There were no other methodological filters.

Eligibility criteria

Cohort studies that included adults from the community assessing the impact of DD on cardiovascular events (including heart failure, myocardial infarction, and hospitalization from cardiovascular cause) and/or mortality (both cardiac and all-cause) over time were eligible. Studies in specific population groups, such as end-stage renal disease on dialysis, were excluded. Only studies clearly describing how DD was defined and providing data on incident MACE and/or mortality were selected for inclusion. Studies comparing outcomes between individuals with and without DD were eligible for meta-analysis. Studies that only assessed diastolic function parameters as continuous variables, without defining a cut-off to distinguish DD from normal diastolic function, were excluded.

Study selection and data collection

After studies were identified using the search query, they were screened by one investigator (M.A.) based on the title and abstract. Eligibility was assessed and article data were extracted by two reviewers independently (M.A., R.L.) using a standardized form. Any disagreement was subsequently resolved by the two authors. Information was extracted from each included report on the following: characteristics of participants (number of individuals, age, gender, ethnicity, risk factors such as hypertension, diabetes, smoking, body mass index, systolic blood pressure, diastolic blood pressure, medication, left ventricular [LV] hypertrophy, systolic dysfunction, heart failure, coronary artery disease) and diastolic echocardiographic measures (e' velocity, E/e' ratio, left atrial size, tricuspid regurgitation velocity, E/A ratio); imaging method used for the diagnosis of DD and

diagnostic criteria; and type of outcome measure (MACE and/or mortality).

To avoid double counting of a cohort, one set of results was selected when multiple publications were available for the same cohort. Priority was given to the study with the longest follow-up.

Regarding the studies eligible for meta-analysis and not providing the required data in the full-text and supplementary material publications, the first and/or corresponding authors were contacted by email in order to provide the required information.

The methodological quality of all studies was assessed using the revised and validated version of the Methodological Index for Non-Randomized Studies (MINORS),¹³ as detailed in Supplementary Table 1.

Statistical analysis

Study-specific measures were pooled using random-effects model meta-analysis to provide a single summary estimate. Random-effects model meta-analysis makes allowance for between-study heterogeneity. Pooled estimates along with their 95% confidence intervals (CI) were provided. Heterogeneity between studies was assessed using Q and I^2 statistics (I^2 values of $\leq 25\%$, 50% , and $\geq 75\%$ represent low, moderate, and high levels of heterogeneity, respectively (www.cochrane-handbook.org).

A forest plot was constructed showing the individual studies with the pooled estimates. Publication bias was assessed using the Egger test and the funnel plot analysis. All statistical analyses were performed using STATA software (version 13.1, StataCorp LP, College Station, TX, USA).

Results

General characteristics of the included studies

Of a total of 604 initially identified studies, only 12 matched our eligibility criteria and were included (Figure 1). Seven additional studies were included after checking the reference list of the articles, yielding 19 studies for the qualitative analysis. Ten studies were excluded from quantitative analysis (meta-analysis) because they provided data only for patients with DD without a clearly defined group with normal diastolic function ($n=4$), or provided insufficient data for the required calculations (as full-text and supplementary material publications) and did not respond to multiple contact attempts ($n=6$).

Nine studies were eventually included in the meta-analysis. For the 19 studies included in the qualitative analysis, the mean follow-up period ranged from one year¹⁴ to 11 years.¹⁵ Eleven studies were conducted in the USA,^{11,15-24} six in Europe,^{14,25-29} one in Israel³⁰ and one in Japan.³¹ Six of the included studies^{14,17,21-23,31} were retrospective. Included studies were assessed as high-quality publications (median MINORS score of 17; 25th and 75th percentile of 16 and 18, respectively).

The included studies provided data on 63 802 participants from community-based cohorts, with mean ages ranging from 50.929 to 82 years,¹⁴ with some studies focusing on the elderly population.^{16,20,21,30} Most of the studies had a balanced gender distribution, except for Ren et al.,¹⁹ which

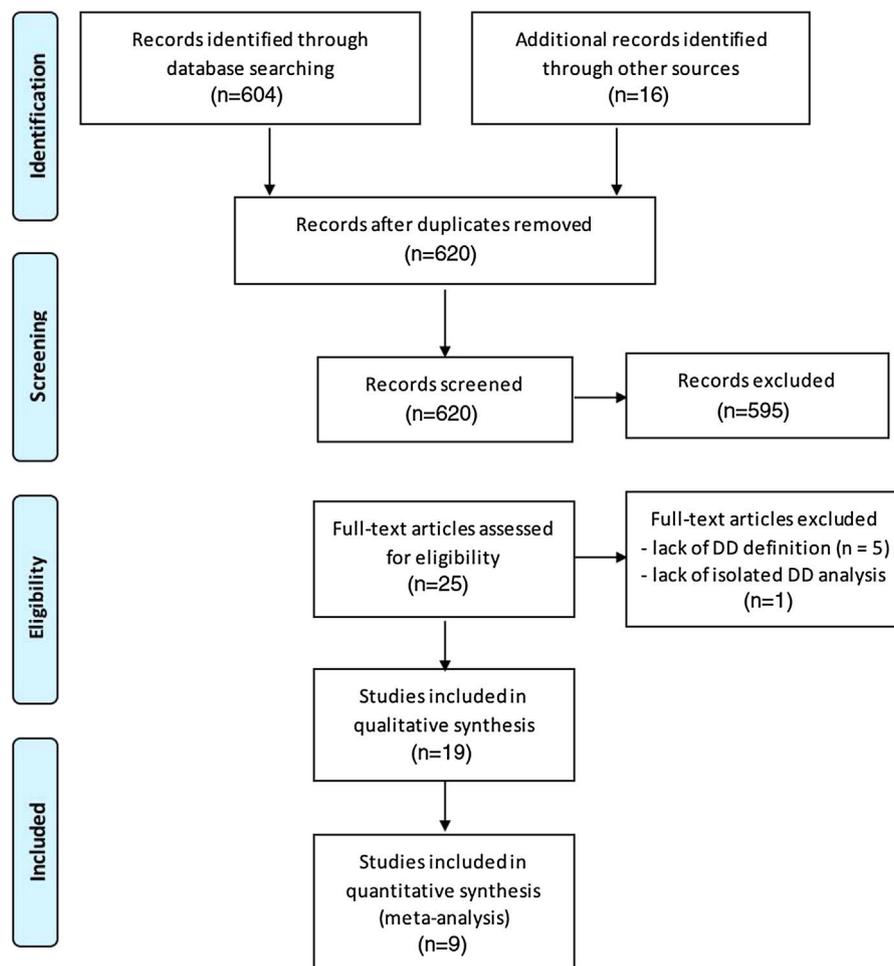


Figure 1 Flowchart showing search strategy for published data and selection process for inclusion in the systematic review and meta-analysis (according to the PRISMA flow Diagram¹²).

included 81% males. Kuznetsova et al.²⁹ included only white participants and Brady et al.²² had 57% black participants. As depicted in Table 1, the prevalence of major cardiovascular risk factors was in agreement with what would be expected in cohorts coming from the community. However, Blomstrand et al.²⁵ and From et al.¹⁷ focused only on subjects with diabetes. Most of the studies included individuals with systolic dysfunction and only six studies excluded this population.^{14,19,22–24,31} Kardys et al.²⁸ reported as much as 39% of systolic dysfunction in their baseline population. Symptomatic heart failure was present in eight studies,^{11,14,18,22,24,25,30,31} and most included individuals with known coronary artery disease (only Aurigemma et al.,¹⁶ Tsang et al.,²¹ Brady et al.²² and Kardys et al.²⁸ used this as an exclusion criterion).

Assessment and definition of diastolic dysfunction

All studies used echocardiography (pulsed-wave Doppler and/or tissue Doppler imaging) to assess diastole and to define DD, except Brady et al.,²² who used cardiac catheterization and measurement of LV pressure. The prevalence of DD in the studies ranged from 5.3%²⁰ to 65.2%,²⁴ with a median prevalence of 35.1%.

Significant heterogeneity was observed regarding the definition and grading of DD. Ten studies^{11,15,16,18,19,21,23,24,28,29} used a one-level classification tree (criteria were presented for each grade and DD was defined as fulfillment of the criteria for any of these grades), two studies^{26,27} used a two-level classification tree (criteria for DD were defined and, if fulfilled, subsequent grading took place with additional variables), and seven studies^{14,17,20,22,25,30,31} only defined the criteria for DD, without grading. As shown in Table 2, there was also significant variability in the core echocardiographic parameters for diagnosis of DD. The most used variable was E/A ratio (10 studies^{11,15,16,18,19,21,23,27–29}), followed by E/e' ratio (eight studies^{11,17,20,23,25,27,29,30}), E-wave deceleration time (seven studies^{11,15,18,21,23,28,31}), left atrial size (five studies^{15,20,21,27,29}) and pulmonary vein flow indices (five studies^{11,19,23,29,31}), e' velocity (two studies^{20,27}) and LV end-diastolic pressure (one study²²).

Association between diastolic dysfunction and risk of cardiovascular events and mortality

The median incidence of the primary outcome among individuals with normal diastolic function and participants with

Table 1 General characteristics of cohort studies assessing the association between diastolic dysfunction and risk of cardiovascular events and/or mortality.

Study	Cohort (acronym)	n	Patients with LVSD, Yes/No; (criteria), percentage	Patients with HF, Yes/No; percentage according to NYHA	Patients with known CAD, Yes/No; percentage	Patients with LVH, percentage; criteria	Age, years (mean/median, SD/IQR)	Male gender, %	Ethnicity, %	Hypertension, %	Diabetes, %	Smokers, %	Mean BMI, kg/m ²	Mean SBP, mmHg	Mean DBP, mmHg	ACEi/ARB, %	Beta-blockers, %
Johansen et al. ²⁷	CCHS	1851	Yes (LVEF <50%); 0.8%	No	Yes; 16%	11%; LVMI ≥104 g/m ² (women); ≥116 g/m ² (men)	57.9 (SD 16.1) ^a	43	N/A	43 ^a	10 ^a	NA	25.4 (SD 3.9) ^a	136 (SD 23) ^a	79 (SD 12) ^a	NA	NA
Shah et al. ²⁰	ARIC	5801	NA	No	NA	NA	76 (SD 5.1)	42	23% black	89	39	6	28.8 (SD 5.6)	131 (SD 18)	67 (SD 11)	NA	NA
Banerjee et al. ¹⁴	N/A	80	No (LVEF ≤45%)	Yes (100%); NYHA I: 22.5%; II: 43.8%; III: 25%; IV: 8.8%	Yes; 9%	N/A	82 (SD 8.1)	34	N/A	83	24	N/A	N/A	N/A	N/A	53	44
Blomstrand et al. ²⁵	CARDIPP	406	Yes (GLS <-15%); 13%	Yes; 1.5%	Yes; 7.4%	N/A	60.7 (SD 3.1)	68	N/A	65	100	N/A	29.8 (SD 4.5)	136 (SD 15)	81 (SD 10)	48	35
Kuznetsova et al. ²⁹	FLEMENGHO	793	Yes (LVEF ≤50%); 0.8%	N/A	Yes; 3.2%	N/A	50.9 (SD 15.5)	49	100% white	41	3	21	Women: 26.3 (SD 4.7); men: 26.6 (SD 3.7)	Women: 128 (SD 19); men: 131 (SD 15)	Women: 78 (SD 9); men: 82 (SD 10)	8	15
Di Bello et al. ²⁶	D.A.V.E.S	2142	Yes (LVEF ≤50%); N/A	No	Yes; 14.8%	3.5%; LVMI >49.2 g/m ² (men) and >46.2 g/m ² (women)	63 (IQR 56-68)	54	N/A	57	14	23	25 (IQR 23-29)	140 (IQR 130-150)	80 (SD 80-90)	41	25
Leibowitz et al. ³⁰	JLCS	502	Yes (LVEF <55%); N/A	Yes (11.2%); NYHA I 90.7%; II 7.7%; III 1.4%; IV 0.2%	Yes; 36.8%	N/A	N/A (all individuals >85)	47	N/A	71	19	3	27.2 (SD 4.4)	N/A	N/A	N/A	N/A
Vogel et al. ²³	RES	388	No (LVEF <50%)	No	Yes; 52%	N/A	67.1 (SD 12.4)	43	N/A	87	30	N/A	29.2 (SD 6.9)	N/A	N/A	N/A	N/A
Halley et al. ²⁴	N/A	36261	No (LVEF <55%)	Yes; 3.5%	Yes; 0.6%	N/A	58.3 (SD 15.4)	45.6	N/A	14.9	11.6	N/A	N/A	140 (SD 21.6)	82.1 (SD 11.2)	N/A	N/A
Kane et al. ¹⁸	OCHF5	1402	Yes (LVEF <50%); 2.4%	Yes; 2.2%	Yes; 16.7%	N/A	65.2 (SD 9.5)	49	>95% white	42	10	N/A	28.5 (SD 5.2)	126 (SD 19.1)	69.5 (SD 10.4)	18	22
Lam et al. ¹⁵	FHS	1038	Yes (LVEF ≤45%); 5%	No	Yes; 9%	N/A	76 (SD 5)	39	N/A	77	10	N/A	26.6 (SD 4.5)	147 (SD 22)	N/A	N/A	N/A
From et al. ¹⁷	N/A	1760	N/A	No	Yes; 36%	33%; LVMI ≥104 g/m ² (women); ≥116 g/m ² (men)	60 (SD 14)	49	N/A	86	100	N/A	33 (SD 14)	N/A	N/A	N/A	N/A
Kardys et al. ²⁸	Rotterdam Study	4425	Yes ("qualitative assessment"); 39%	No	No	N/A	71.4 (SD 7.3)	39	N/A	N/A	13	16	27.5 (SD 4.1)	150 (SD 21)	80 (SD 11)	11	14
Okura et al. ³¹	SHFS	272	No (LVEF <40%)	Yes; NYHA I 41%; II 58%; IV 1%	Yes; 19% (men), 15% (women)	61%; LVMI ≥116 g/m ² (men); ≥104 g/m ² (women)	68.5 (SD 8.7) (men); 69.3 (SD 10.6) (women)	58	N/A	46	24	N/A	N/A	N/A	N/A	39	N/A

Table 1 (Continued)

Study	Cohort (acronym)	n	Patients with LVSD, Yes/No (criteria), percentage	Patients with HF, Yes/No; percentage according to NYHA	Patients with known CAD, Yes/No; percentage	Patients with LVH, percentage; criteria	Age, years (mean/median, SD/IQR)	Male gender, %	Ethnicity, %	Hypertension, %	Diabetes, %	Smokers, %	Mean BMI, kg/m ²	Mean SBP, mmHg	Mean DBP, mmHg	ACEi/ARB, %	Beta-blockers, %
Ren et al. ¹⁹	HSS	693	No (LVEF <50%)	No	Yes; 100%	49%; LVMI >90 g/m ²	65 (SD 10) normal diastole; 72 (SD 9) impaired relaxation; 70 (SD 12) pseudonormal or restrictive	81	59% white, 32% African-American, 13% Asian, 14% other	71	26	18	28.5 (SD 5.0) normal diastole; 28.2 (SD 4.9) impaired relaxation; 28.6 (SD 5.8) pseudonormal or restrictive	132 (SD 21) normal diastole; 138 (SD 22) impaired relaxation; 134 (SD 24) pseudonormal or restrictive	75 (SD 11) normal diastole; 76 (SD 11) impaired relaxation; 71 (SD 11) pseudonormal or restrictive	46	57
Brady et al. ²²	N/A	115	No (LVEF <50%)	Yes; <0.035%	No	N/A	58	37	18% white, 57% black, 22% Hispanic majority white	71	21	N/A	31	N/A	N/A	N/A	N/A
Redfield et al. ¹¹	Rochester Epidemiology Project	2042	Yes (LVEF ≤50%); 6%	Yes; 2.2%	Yes; 12.2%	N/A	62.8 (SD 10.6)	41		25	4.5	8.9	28.4 (5.41)	N/A	N/A	47.5% LVEF ≤40%; 14.2% moderate or severe DD	22.5% LVEF ≤40%; 40.2% moderate or severe DD
Tsang et al. ²¹	N/A	1160	Yes (LVEF <50%); 4%	No	No	3% in group with no events, 6% in group with events; ECG	75 (SD 7)	36	N/A	48% in group with no events, 63% in group with events	7% in group with no events, 11% in group with events	N/A	N/A	142 (SD 23) in group with no events, 146 (SD 23) in group with events	N/A	N/A	N/A
Aurigemma et al. ¹⁶	CHS	2671	Yes (LVEF <45%); 4%	No	No	7.6% in group with no events, 24.3% in group with events; ratio of observed to expected LV mass/height ratio >1.45	72 (SD 5) in group with no events, 74 (SD 6) in group with events	36% in group with no events, 45% in group with events	94% white (in group with no events) 94% white (in group with events)	28% in group with no events, 47% in group with events	5% in group with no events, 12% in group with events	12% in group with no events, 12% in group with events	26 (SD 4) in group with no events, 27 (SD 5) in group with events	134 (SD 21) in group with no events, 145 (SD 22) in group with events	70 (SD 11) in group with no events, 73 (SD 13) in group with events	N/A	N/A

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; DD: diastolic dysfunction; ECG: electrocardiography; GLS: global longitudinal strain; HF: heart failure; IQR: interquartile range; LV: left ventricular; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; LVSD: left ventricular systolic dysfunction; N/A: not available; NYHA: New York Heart Association functional class; SBP: systolic blood pressure; SD: standard deviation.

^a Unpublished data.

Table 2 Method of assessment of diastolic dysfunction and magnitude of the association with incident cardiovascular events and/or mortality.

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Johansen et al. ²⁷	Echocardiography (including TDI)	e' <7 cm/s (mean of septal and lateral); grading: E/A >2 and/or LAVi ≥34 ml/m ² and/or E/e' ≥17	52.5	7.1 (SD 2.7) (mean of septal and lateral) ^a	N/A	N/A	LAVi 19.1 ml/m ² (SD 6.5)	N/A	1.11 (SD 0.46) ^a	10.9 years	CV death, MI and hospitalization due to HF	HR 2.54 (95% CI 1.61-4)
Shah et al. ²⁰	Echocardiography (including TDI)	According to 2016 guidelines ³	5.3	N/A	N/A	N/A	N/A	N/A	N/A	610 days	All-cause mortality and hospitalization due to HF	Event rate ratio (calculated) 5.36
Banerjee et al. ¹⁴	Echocardiography (including TDI)	According to 2007 diastolic heart failure consensus ³³	100 (only patients with DD)	N/A	N/A	16 (SD 5.74)	N/A	N/A	N/A	1 year	CV death or hospitalization due to CV event	Incidence 25%
Blomstrand et al. ²⁵	Echocardiography (including TDI)	E/e' ratio >15	34.2	N/A	N/A	14.4 (SD 4.5) (septal)	N/A	N/A	N/A	67 (SD 17) months	CV death, myocardial infarction and stroke	HR 3.05 (95% CI 1.18-7.85)
Kuznetsova et al. ²⁹	Echocardiography (including TDI)	Impaired relaxation (group 1): ↓ E/A ratio (age-specific) and E/e' ≤8.5; elevated filling pressure (group 2): normal E/A ratio (age-specific), E/e' >8.5 or Adur <ARDur+10 or LAVi ≥28 ml/m ² ; combined dysfunction (group 3): ↓ E/A ratio (age-specific) and E/e' >8.5	25.1	Women: 11.3 (SD 3.6); men: 11.5 (SD 3.8) (mean of septum, lateral, inferior, posterior)	Women: 7.5 (SD 2.4); men: 6.7 (SD 1.9) (mean of septum, lateral, inferior, posterior)	Women: 21.8 ml/m ² (SD 6.0); men: 24.0 ml/m ² (SD 6.3)	LAVi: women: 21.8 ml/m ² (SD 6.0); men: 24.0 ml/m ² (SD 6.3)	N/A	Women: 1.2 (SD 0.4); men: 1.3 (SD 0.4)	4.8 years	Cardiac events (MI, coronary revascularization, HF, new-onset angina, cor pulmonale, new-onset AF, life-threatening arrhythmias); CV events (cardiac events plus stroke, TIA, aortic aneurysm, arterial embolism, and peripheral artery revascularization)	HR 1.77 (95% CI: 0.75-4.17) for CV events in group 1 and 2.21 (95% CI: 1.01-3.83) in groups 2+3; HR 2.13 (95% CI: 0.70-6.48) for cardiac events in group 1 and 4.50 (95% CI: 1.73-11.7) in groups 2+3

Table 2 (Continued)

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Di Bello et al. ²⁶	Echocardiography (including TDI)	According to 2009 guidelines ³⁰	N/A	N/A	N/A	N/A	LA diameter 38 mm (IQR 34-45); LA area 15 cm ² (14-18)	N/A	N/A	26 (SD 11) months	Cardiac death, MI, CABG or PTCA, stroke, TIA, acute pulmonary edema	OR 1.392 (95% CI 1.313-1.712)
Leibowitz et al. ³⁰	Echocardiography (including TDI)	E/e' >13	N/A	N/A	N/A	12.2 (SD 4.9) (mean of septal and lateral tissue velocities) [survivor]	LAVi 36.6 ml/m ² (SD 12.5) [survivor]	N/A	0.97 (SD1.1) [survivor]	5 years	All-cause mortality	HR 1.028 (95% CI 0.98-1.084) (E/e' ratio included as continuous variable in the model)
Vogel et al. ²³	Echocardiography (including TDI)	Impaired relaxation: grade 1 - E/A ≤0.75, E/e' <10; grade 1a - E/A ≤0.75, E/e' >10; pseudonormal pattern: grade 2 - 0.75 <E/A <1.5, DT >140, PV S/D ≥1 or E/e' ≥10; restrictive (grade 3/4): E/A >1.5 and/or DT <140 ms and/or PV S/D <1 and/or E/e' ≥10	100 (only patients with DD)	N/A	N/A	15.5 (SD 5.4) (not specified)	LAVi 41.5 ml/m ² (SD 12.1)	N/A	1.3 (SD 0.7)	3.9 years	HF	Cumulative probability of 2.2%, 5.7% and 11.6% at 1, 2 and 3 years, respectively
Halley et al. ²⁴	Echocardiography (including TDI)	According to 2002 guidelines ³⁴	65.2	N/A	N/A	N/A	N/A	N/A	N/A	6.2 (SD 2.3) years	All-cause mortality	Mild DD: HR 1.11 (95% CI 0.85-1.47); moderate DD: HR 1.58 (95% CI 1.20-2.08); severe DD: HR 1.84 (95% CI 1.29-2.62)

Table 2 (Continued)

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Kane et al. ¹⁸	Echocardiography (including TDI)	Mild DD: E/A ratio <0.75; moderate or pseudonormal DD: E/A 0.75 to 1.5, DT >140 ms, plus 2 other Doppler indices of elevated end-diastolic filling pressure; severe DD: E/A ratio >1.5, DT <140 ms, and Doppler indices of elevated LV end-diastolic filling pressure	39.2	N/A	0.08 (SD 0.05)	10.7 (SD 4.5) (septal)	LAVi 24.7 ml/m ² (SD 8.5)	N/A	N/A	6.3 (SD 2.3) years	HF	HR 1.81 (95% CI 1.01-3.48)
Lam et al. ¹⁵	Echocardiography (PW Doppler imaging)	Abnormal relaxation: E/A <0.5, DT >280 ms; restrictive filling: mitral E/A >2.0, DT <120 ms; pseudonormal LV filling: distinguished from normal if LA size ≥sex-specific 80th percentile or LV mass ≥sex-specific 80th percentile or any AF	36	N/A	N/A	N/A	N/A	N/A	N/A	11 years	HF	HR 1.32 (95% CI 1.01-1.71)
From et al. ¹⁷	Echocardiography (including TDI)	E/e' ratio >15	23	N/A	N/A	13 (SD 6) (septal)	LAVi 63 ml/m ² (SD 24)	N/A	N/A	2.9 (SD 1.8) years	HF	HR 1.61 (95% CI 1.17-2.2)
Kardys et al. ²⁸	Echocardiography (PW Doppler imaging)	Impaired relaxation: E/A <0.75 and DT >240 ms; restrictive pattern: E/A >1.50 and DT <150 ms	11.5	N/A	N/A	N/A	LA diameter 40 mm (SD 5)	N/A	0.83 (IQR 0.71-1.00)	3 years	All-cause mortality	Impaired relaxation: HR 1.55 (95% CI 1.04-2.33); restrictive pattern: HR 7.23 (95% CI 2.16-24.2)

Table 2 (Continued)

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Okura et al. ³¹	Echocardiography (PW Doppler imaging)	LVEF $\geq 40\%$ + ≥ 1 of: (1) DT <140 ms; (2) S/D ratio <1; (3) ARdur-Adur >30 ms	100 (only patients with DD)	N/A	N/A	N/A	LA diameter 42.9 mm (SD 7.5) males; 40.8 (8.0) females	N/A	1.3 (SD 0.5) males; 1.2 (SD 0.4) females	4.4 (SD 1.7) years	All-cause mortality	Incidence rate 6.3%
Ren et al. ¹⁹	Echocardiography (PW Doppler imaging)	Impaired relaxation: E/A ≤ 0.75 and systolic dominant pulmonary venous flow; Pseudonormal pattern: E/A=0.75-1.5 and LV diastolic dominant pulmonary venous flow; restrictive pattern: E/A >1.5 and LV diastolic dominant pulmonary venous flow	52	N/A	N/A	N/A	N/A	N/A	N/A	3 years	All-cause mortality, heart disease death, non-fatal MI, hospitalization for HF	Impaired relaxation: HR 0.7 (95% CI 0.4-1.3) for all-cause mortality; HR 1.0 (95% CI 0.3-3.8) for heart disease death; HR 1.7 (95% CI 0.7-4.5) for hospitalization for HF; HR 1.7 (95% CI 0.8-3.7) for non-fatal MI; pseudonormal or restrictive: HR 1.2 (95% CI 0.6-2.4) for all-cause mortality; HR 3.9 (95% CI 1.0-14.8) for heart disease death; HR 6.3 (95% CI 2.4-16.1) for hospitalization for HF; HR 1.3 (95% CI 0.5-3.2) for non-fatal MI

Table 2 (Continued)

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Brady et al. ²²	Cardiac catheterization and LV pressure measurement	LVEDP \geq 15 mmHg and LVEF \geq 50%	100 (only patients with DD)	N/A	N/A	N/A	N/A	N/A	N/A	63 months	All-cause mortality	Incidence 5%
Redfield et al. ¹¹	Echocardiography (including TDI)	Mild DD (impaired relaxation): E/A \leq 0.75, Δ E/A $<$ 0.5, E/e' $<$ 10, S $>$ D, ARdur $<$ Adur; moderate DD (pseudonormal): 0.75 $<$ E/A $<$ 1.5, DT $>$ 140 ms, Δ E/A \geq 0.5, E/e' \geq 10, S $<$ D or ARdur $>$ Adur+30 ms; severe DD - reversible restrictive: E/A $>$ 1.5, DT $<$ 140 ms, Δ E/A \geq 0.5, E/e' \geq 10, S $<$ D or ARdur $>$ Adur+30 ms; fixed restrictive: E/A $>$ 1.5, DT $<$ 140 ms, Δ E/A $<$ 0.5, E/e' \geq 10, S $<$ D or ARdur $>$ Adur+30 ms (2 criteria necessary for moderate or severe DD classification)	24.6	N/A	N/A	N/A	N/A	N/A	N/A	5 years (longest)	All-cause mortality	Mild DD: HR 8.31 (95% CI 3.00-23.1); moderate or severe DD: HR 10.17 (95% CI 3.28-31.00)

Table 2 (Continued)

Study	DD imaging technique	DD criteria	DD prevalence, %	Mean lateral e', cm/s	Mean septal e'e, cm/s	Mean E/e' ratio (septal or lateral e')	Mean LA size	TR jet velocity (mean)	Mean E/A ratio	Follow-up (mean)	Primary endpoint	Association measure (HR/RR/OR (95% CI))
Tsang et al. ²¹	Echocardiography (PW Doppler imaging)	Abnormal relaxation: mitral E/A <0.75 or DT >240 ms; pseudonormal LV filling: mitral E/A=0.75-1.5 and DT 151-240 ms, but LA volume ≥28 ml/m ² ; restrictive filling: E/A >1.5 or DT ≤150 ms	60.1	N/A	N/A	N/A	LAVi 31 ml/m ² (SD 12) in group with no events; 36 ml/m ² (SD 12) in group with events	N/A	N/A	3.8 (SD 2.7) years	CV death, MI, coronary revascularization, AF, HF, TIA, stroke	HR 1.64 (95% CI 1.1-2.55)
Aurigemma et al. ¹⁶	Echocardiography (PW Doppler imaging)	E/A <0.7 or >1.5	N/A	N/A	N/A	N/A	LA diameter 3.8 cm (SD 0.6) in group with no events; 4.0 cm (SD 0.7) in group with events	N/A	0.95 (SD 0.3) in group with no events; 0.88 (SD 0.4) in group with events	5.2 years	HF	RR 1.88 (95% CI 1.33-2.68) for E/A ratio <0.7; RR 3.5 (95% CI 1.8-6.8) for E/A >1.5

Adur: mitral A-wave flow duration; ARdur: reverse pulmonary vein flow duration; AF: atrial fibrillation; CABG: coronary artery bypass grafting; CI: confidence interval; CV: cardiovascular; DD: diastolic dysfunction; DT: deceleration time; HF: heart failure; HR: hazard ratio; IQR: interquartile range; LA: left atrial; LAVi: left atrial volume index; LV: left ventricle; LVEF: left ventricular ejection fraction; MI: myocardial infarction; N/A: not available; OR: odds ratio; PW: pulsed-wave; PTCA: percutaneous transluminal coronary angioplasty; PV S/D: pulmonary vein systolic forward flow/diastolic forward flow; RR: risk ratio; SD: standard deviation; TDI: tissue-Doppler imaging; TIA: transient ischemic attack; TR: tricuspid regurgitation.

^a Unpublished data.

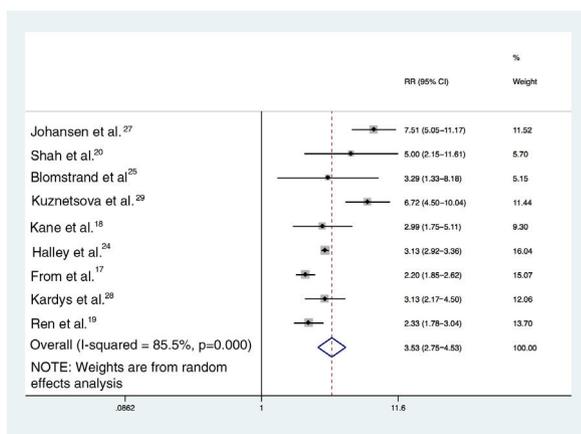


Figure 2 Forest plot showing the overall estimate of the association between diastolic dysfunction and cardiovascular events and/or mortality. CI: confidence interval; RR: relative risk.

DD was 3% (range 2.6-16.8%) and 13.1% (range 5.2-37.4%), respectively. Of the 14 studies providing an association measure, 13 showed a significant association between DD and MACE and/or mortality in the multivariate analysis. The strongest association was reported by Redfield et al.,¹¹ with an HR of 8.31 (95% CI 3.00-23.1) for all-cause mortality in individuals with mild DD and an HR of 10.17 (95% CI 3.28-31.00) for patients with moderate or severe DD. Only Leibowitz et al.³⁰ did not find an association (HR 1.028; 95% CI 0.98-1.084) between E/e' ratio (as a continuous variable) and all-cause mortality.

Two studies found an association between diastolic function variables and cardiovascular events and/or mortality: Shah et al.²⁰ found that abnormal e', E/e' ratio, left atrial dimension and left atrial volume index (LAVi) were significantly associated with incident death or heart failure hospitalization, while Vogel et al.²³ correlated E/A ratio with incident atrial fibrillation.

Banerjee et al.¹⁴ found a significantly worse combined outcome of all-cause mortality and hospitalization in a cohort of patients with DD and increased E/e' ratio. Okura et al.³¹ reported that the cumulative survival rate of DD patients, irrespective of a history of heart failure, was significantly lower than in the general population. However, Brady et al.²² showed that the mean mortality in the DD group was similar to the general population, and therefore DD with a normal LVEF, in the absence of coronary artery disease and systolic dysfunction, had an excellent prognosis over a long period (5-6 years). Overall, 17 studies showed that DD was a significant predictor of MACE and/or mortality, while two studies did not find this association.

Based on random-effects model meta-analysis, the pooled estimate for relative risk of MACE/mortality for individuals with DD across nine studies was 3.53 (95% CI 2.75-4.53; $I^2=85.5\%$) (Figure 2). Including the studies providing data on hospitalizations and/or mortality (six studies), the pooled estimate using the random-effects model was 3.98 (95% CI 2.91-5.44; $I^2=84.2\%$); in addition, including only the two studies providing all-cause mortality as the primary outcome (Halley et al.²⁴ and Kardys et al.²⁸), DD was associated with a 3.13-fold (95% CI 2.92-3.35; $I^2=0\%$) increased risk of death.

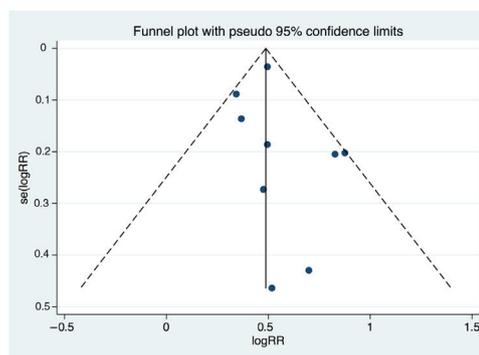


Figure 3 Funnel plot of the studies included in the meta-analysis for assessment of potential asymmetry and risk of publication bias.

Heterogeneity and publication bias

There were significant differences between individual studies in the magnitude of the association between DD and MACE, as indicated by the statistical test for heterogeneity ($Q=55.0$, $I^2=85.5\%$, $p < 0.001$). Figure 3 illustrates the funnel plot of studies that excluded small-study effects coming from publication bias ($p=0.480$ from the Egger test for funnel plot symmetry).

Discussion

This is the most comprehensive systematic review of cohort studies assessing the association between DD and risk of MACE and death. Overall, most studies (17 studies out of 19) showed DD as a significant predictor of cardiovascular events and death. The quantitative analysis using random-effects model meta-analysis yielded a combined risk of MACE and/or death 3.53-fold higher in the presence of DD; in addition, DD was associated with a 3.13-fold increased risk of death.

Diastolic dysfunction as a predictor of increased risk of cardiovascular events and mortality

Research during the last decade has shed some light on the pathophysiological changes leading to DD and its deleterious impact on cardiac function. Common risk factors for cardiovascular disease (such as hypertension, obesity, hypercholesterolemia and diabetes) are associated with systemic inflammation, myocardial oxidative stress and coronary microvascular dysfunction, and are significant contributors to myocardial stiffening and LV DD.³² In the cardiovascular risk continuum, intermediate stages of risk such as pre-hypertension⁶ and non-diabetic metabolic syndrome³³ are already associated with deterioration in indices of diastolic function measured by echocardiography and cardiac MRI, which suggests that there is also a continuum of myocardial structural and functional changes that impact on diastole. Indeed, the complex interplay between a systemic low-grade proinflammatory state, endothelial dysfunction and changes in myocardial extracellular space and intrinsic cardiomyocyte properties are now accepted as the new pathophysiological paradigm for HFpEF.³⁴ A previous

systematic review and meta-analysis³⁵ showed that asymptomatic LV DD was associated with an increased risk for incident HF (relative risk 1.7; 95% CI: 1.3-2.2), including data from five studies.¹⁵⁻¹⁹ Therefore, even subclinical DD seems to be strongly involved in the pathophysiology of HF. That being said, both in patients without symptomatic cardiovascular disease and in patients with full-blown cardiovascular disease (such as coronary artery disease), the presence of DD may indicate a more advanced degree of a specific but complex low-grade inflammatory state and structural and functional myocardial changes that appear to be associated with increased risk of CV events and death.

Causes of heterogeneity

In this meta-analysis significant heterogeneity was observed between studies, which may result from three key factors: different study populations, significant differences in the definition of DD, and different definitions of the primary outcome in each of the studies. All of these are potential limitations of this study and are inherent to the methodological approach adopted, especially regarding the quantitative meta-analysis.

Study population

This systematic review included different study populations, coming from different countries and continents and including community-derived individuals, elderly populations, and diabetes cohorts. The mean age differed between the study populations, as did gender distribution and ethnicity. As these were community-derived cohorts, the prevalence of cardiovascular risk factors, such as hypertension, diabetes, smoking and obesity, and cardiac diseases (especially coronary artery disease and heart failure) differed significantly between cohorts. This variability in study populations certainly explains a part of the heterogeneity observed in this meta-analysis. On the other hand, it is interesting to observe that despite the variability in the types of individuals included in this analysis, almost all studies showed a consistent association between DD and increased risk of cardiovascular events.

Diastolic dysfunction criteria

Given the complexity of the pathophysiology of DD, no single echocardiographic parameter can be used to quantify diastole.³⁶ Therefore, over the last two decades, various parameters and classifications of DD have been used in different studies and in different guidelines, which may also explain some of the heterogeneity observed in this study.

As detailed in [Table 2](#), in our systematic review we critically appraised the DD criteria used in different studies and observed striking differences between studies, even though there are published guidelines on diagnosis and grading. For example, the study by Di Bello et al.²⁶ cited the 2009 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines,³⁷ but never clarified which variables were used for DD diagnosis. Even Shah et al.,²⁰ who cited the 2016 ASE/EACVI guidelines,⁴ did not proceed exactly as suggested because they used LA diameter >4 cm to define LA dilatation (the guidelines use indexed volumes) and did not include tricuspid regurgitation

jet velocity >2.8 m/s, which is one of the four main parameters in the 2016 guidelines. Moreover, in some studies it was difficult to code diastolic function because of the vagueness of definitions and classifications of DD.

Selmeryd et al.³⁸ examined how the 2009 ASE/EACVI guidelines on the classification of DD were interpreted in the medical community and how variations in the definition of DD affected the reported prevalence. They found that these guidelines have been interpreted differently across studies that cite them with respect to the variables and logical operators used, and that these differences had a substantial impact on the prevalence of DD (range 12-84%).

On the other hand, the 2016 EACVI/ASE consensus on diastolic function⁴ was intended to simplify the approach to DD classification. It proposes that four variables with high specificity for myocardial disease should be assessed when determining whether LV diastolic function is normal or abnormal, in order to decrease false positive diagnoses of DD: e' velocity, E/e' ratio, LAVi and peak tricuspid regurgitation (TR) jet velocity. LV DD is present if three or four parameters are abnormal and inconclusive if only two variables are abnormal. A comparison of the impact of the 2016 ASE/EACVI guidelines on the prevalence and grades of DD in comparison with the 2009 ASE/EACVI guidelines showed that the concordance between the classifications is poor and that the former result in a much lower prevalence of DD, apparently only diagnosing the most advanced cases, leaving many patients diagnosed as having indeterminate diastolic function. One possible explanation might be the inclusion of TR jet velocity, which reflects more advanced and severe DD, resulting in lower sensitivity and higher specificity.³⁹ None of the studies included in this meta-analysis assessed DD using the exact criteria of the 2016 guidelines.

In summary, we strongly believe that it is important to clarify the definition of DD, to correctly assess diastolic function, and to persist in the search for new therapeutic options for DD.

Outcome definitions

In order to assess the prognosis of DD, we included studies that used diverse outcome definitions, such as different combinations of cardiovascular events, HF hospitalization, the combined endpoint of HF hospitalization and mortality, all-cause mortality or cardiac deaths. Since different outcomes were being assessed, some more comprehensive than others, the strength of the associations will inevitably be different.

Clinical relevance

Despite the heterogeneity between the studies included in this work as discussed above, our findings are significant for daily clinical practice and should drive a shift towards a rapid but careful assessment of diastolic function in most patients, as DD was found to be a consistent predictor of cardiovascular events and death. Therefore, we favor the inclusion of a statement concerning diastolic function in all echocardiography reports, when feasible. Notwithstanding, a universal definition of DD is still lacking and therefore most echocardiography laboratories should adopt the one

they feel most confident with and use it for consistency and reproducibility.

Conclusions

In this systematic review we found a consistent association between DD and the risk of cardiovascular events and death in community-based populations with different risk factors and prevalence of cardiac diseases. Individuals with DD showed a 3.53-fold higher risk of cardiac events or death and a 3.13-fold increased risk of mortality. A simple and widely used definition of DD is urgently needed, not only for user-friendly clinical application but also for the development of new therapeutic trials specifically targeting DD in the subclinical phase.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2019.03.007.

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