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Review article

A systematic review and meta-analysis of human population studies on the association between exposure to toxic environmental chemicals and left ventricular dysfunction (LVD)

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ABSTRACT

Background: Exposure to environmental chemicals has been associated with an elevated risk of heart failure (HF). However, the impact on early markers of HF, such as left ventricular dysfunction (LVD), remains limited.
Objective: To establish a foundation of evidence regarding early HF markers and their association with environmental pollutants, a systematic review and meta-analysis was conducted.
Methods: The search, conducted on October 13th, 2023, encompassed PubMed, Embase, and Web of Science without filters, focusing on observational studies reporting myocardial geometrical, structural, or functional alterations in individuals without a history of heart disease. This included the general adult population, workers, young people, and the elderly. The risk of bias was assessed using the ROBINS-I tool at both study and item levels.
Results: The systematic review included 17 studies involving 43.358 individuals exposed to air pollution and 2038 exposed to heavy metals. Approximately 41% of the effect measures of associations reported significant abnormalities in myocardial structure or function. The metanalyses by pollutants categories indicated positive associations between LV systolic and diastolic abnormalities and exposure to PM2.5 [-0.069 (−0.104, −0.033); −0.044 (−0.062, −0.025)] and PM10 [-0.055 (−0.087, −0.022); −0.030 (−0.050, −0.010)] and NO2 [-0.042 (−0.071, −0.013); −0.021 (−0.037, −0.004)], as well as positive associations between lead exposure and LV systolic abnormalities [-0.033 (−0.051, −0.016)].
Conclusions: Existing evidence shows that specific early markers of HF may be associated with exposure to chemical pollutants. It is recommended to include such endpoints in new longitudinal and case-control studies to confirm further risk associations. These studies should consider co-exposures, account for vulnerable groups, and identify cardiotoxic compounds that may require regulation. When examining the link between myocardial abnormalities and environmental exposure, it is also advisable to explore the supportive use of Adverse Outcome Pathway (AOP) approaches to confirm a causal relationship.

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1. Introduction

1.1. Background

The widespread presence of chemicals in the environment is of great concern for specific human diseases and conditions, caused or exacerbated by exposures to environmental contaminants, including CVDs (Bijlsma and Cohen, 2016). In past years, the association between exposure to toxic environmental pollutants and cardiovascular morbidity and mortality in humans were investigated mainly with an ecological approach on the basis of incidence and prevalence data over time. More recently, the quality of the observational studies, designed to improve the etiological knowledge of the exposure-to-diseases pathways, has been greatly improved (Gilmartin-Thomas et al., 2018). Relying on more data on the exposure characterization and the co-exposures, and on the determinants of health individual and socio-economic the certainty of the evidence of the observational studies has been upgraded at least as sufficient. Above all, air pollution, especially PM2.5, was associated in the literature with the risk of elevated blood pressure, acute coronary syndrome, myocardial infarction, cardiac arrhythmia, and heart failure (Lederer et al., 2021a). A metanalysis of 35 studies estimating the association between heart failure and air pollution, showed that every 10 μg/m3 increment in short-term exposure to PM2.5 was associated with a 2.1% relative increase in heart failure hospitalization or death. The authors estimated that a mean reduction in PM2.5 of 3.9 μg/m3 would prevent 7978 heart failure hospitalizations in the USA (Shah et al., 2013). Also, inorganic pollutants, particularly heavy metals and pesticides, significantly contribute to environmental pollution with consequences to human health, as reported in the study by Alengebawy et al., 2021) (Alengebawy et al., 2021). Pesticide pollution from metal-containing pesticides, such as arsenic, copper, lead, and chromium, is still a significant risk in the EU according to a report published by the EEA in September 2021 (How pesticides impact human health). A concern for the public health is raised by a recent systematic review conducted by Zago et al., 2022), which indicates a heightened risk of acute myocardial infarction associated with occupational exposure and environmental contamination from organochlorine pesticides and pesticides containing metals (Zago et al., 2022). A scientific statement from the American Heart Association on Contaminant Metals as Cardiovascular Risk Factors underscores that epidemiological studies show that exposure to these metals is linked to cardiovascular deaths, mainly attributed to ischemic heart disease. Specifically, lead, cadmium, and arsenic are associated with subclinical atherosclerosis, coronary artery blockages, ischemic heart disease, stroke, heart hypertrophy, heart failure, and peripheral artery disease (Lamas et al., 2023).

Due to the wide variety of chemical combinations encountered by humans and the environment, there is a critical need of information about their mode of action particularly to determine if interactions could lead to enhanced effects. While a list of cardiotoxic substances has been compiled and ranked by risk, it's important to acknowledge the challenges in directly applying mechanistic information for the protection of human health (Krishna et al., 2021).

Currently, the environmental factors causing direct damage to the heart muscle have not been fully understood and require a deeper understanding of the mechanisms that lead to heart failure, which can precede or increase the risk of developing other heart diseases. This field of knowledge lacks systematic reviews and meta-analyses to consolidate existing evidence. Heart failure (HF) has been recognized as a "global pandemic," impacting 64.3 million people worldwide in 2017, constituting a significant portion of cardiovascular diseases (CVDs). The prevalence of HF varies between 1% and 3% in the general adult population in developed countries, and it is expected to rise considerably due to improved diagnostic tools and a higher prevalence among older individuals (Landrigan et al., 2018). HF is a clinical syndrome that universally begins with an asymptomatic stage and progresses to symptomatic stages according to the consensus agreement reached in 2021. Asymptomatic heart failure is defined as depressed left ventricular systolic function in the absence of clinical heart failure and it is classified as stage B heart failure (Sara et al., 2020). One of the clinical characteristics of asymptomatic heart failure is lack of specific signs in the early stages progressing to symptomatic clinical HF. The early diagnosis of HF is challenging due to the involvement of multiple pathogenic mechanisms contributing to the development of HF including neurohormonal activation, inflammation, myocardial stretch, matrix remodeling, and myocyte injury (Ibrahim and Januzzi, 2018). These triggering mechanisms can be activated by external stressors and directly or indirectly lead to an increase in ventricular wall pressure, release of neurohumoral factors, energy deficiency in cardiac cells, and myocardial injury (Fig. 1). For example, the response to increased ventricular wall pressure initiates myocardial cell signaling, which, along with the influence of neurohumoral factors, triggers changes in gene expression, protein synthesis, and cellular remodeling, ultimately promoting cell growth and hypertrophy (Glennon et al., 1995). Energy-deficient and injured cells exhibit reduced protein synthesis and alterations in gene expression, resulting in decreased cell size and myocardial thinning/atrophy (Chen et al., 2022). Myocardial cell death stimulates an inflammatory response, further contributing to cellular remodeling and hypertrophy (Xu and Brink, 2016), and activates fibroblasts, which promote excessive collagen deposition and cardiac fibrosis (Thomas and Grisanti, 2020). All these processes collectively contribute to generate the cardiac remodeling. Remodeling refers to cellular, molecular, and interstitial changes that occur after injury and manifest as alterations in left ventricular (LV) size, mass, geometry, and ultimately function (O'Grady et al., 2019). LV geometry is generally classified by assessing the LV mass index and relative wall thickness (Lang et al., 2015). In turn, structural changes in the ventricular wall, such as ventricular dilation and wall thinning, are associated with impaired LV function. Also, it is known that the increase of LV mass in individuals without HF, can predict the development of both systolic and diastolic HF, making it an independent risk factor (Nauta et al., 2020). Despite the above described importance of LV remodeling in HF, it has traditionally been classified based on left ventricular ejection fraction (LVEF) rather than LV geometry (Ponikowski et al., 2014). However, recently, there has been a strong emphasis on the significance of both conventional and innovative (i.e. linked to structure and shape) echocardiographic parameters in HF assessment (La Canna and Scarfo', 2020).

The evidence from animal studies showed that adverse effects associated with chemical exposure are often mediated through common mechanisms related to mitochondrial function and oxidative stress (Zolkipli-Cunningham and Falk, 2017). Mitochondrial dysfunction, in particular, has been implicated in the development of heart failure. The heart relies heavily on oxidative metabolism in mitochondria as its primary energy source, and the inability to generate and transfer energy has long been recognized as a primary mechanism linking mitochondrial dysfunction to contractile failure (Zhou and Tian, 2018). Both in vitro and in vivo studies have shown that overexposure or chronic exposure to environmental chemicals can lead to myocardial cell death and direct injury to the myocardium (Casarett and Doull, 2008). Mitochondrial dysfunction in cardiomyocytes has been identified as a central mechanism underlying cardiac remodeling (Werbner et al., 2023), and it may significantly contribute to the development of left ventricular dysfunction (LVD). Additionally, in vitro toxicity studies have supported the hypothesis that various environmental chemicals, including pesticides, flame retardants, polycyclic aromatic hydrocarbons (PAHs), plasticizers, ambient air pollution, and metals such as arsenic, cadmium, and lead, have the potential to contribute to adverse cardiovascular outcomes (Krishna et al., 2021). Considered collectively, relevant LVD markers (echocardiographic abnormalities) of asymptomatic HF might be (1) measured concurrently in healthy subjects without precedent CVD history and (2) determined by environmental factors other than those traditionally associated with CVD. These hypotheses are, however,

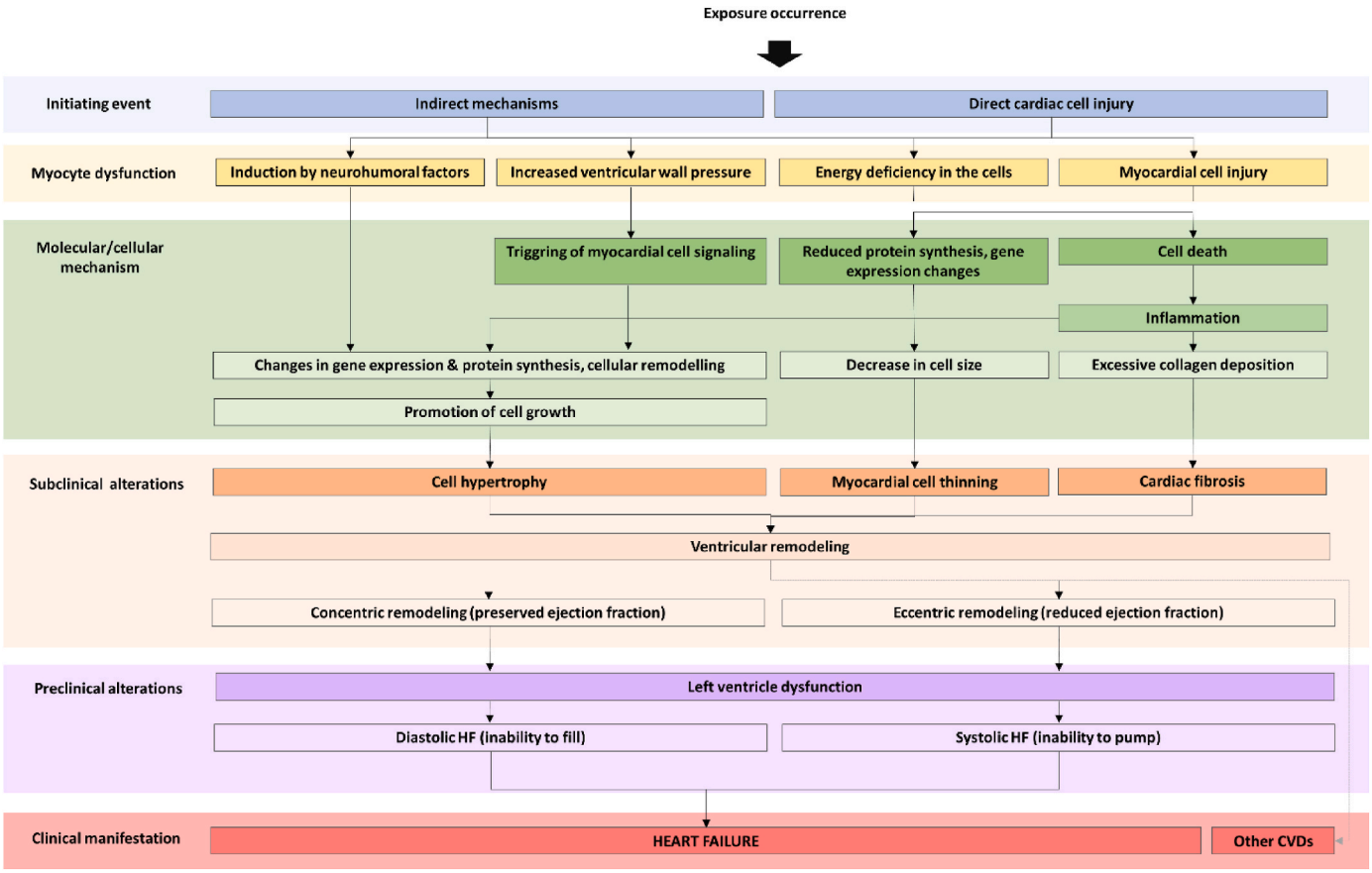

Fig. 1. A comprehensive framework is proposed to characterize the impact of environmental factors on the progression of heart failure (HF) once they enter the body. This framework illustrates the pathways through which chemical agents' effects interact with myocardial tissue, initiating signaling cascades and physiological responses. These processes eventually lead to subclinical and preclinical pathological changes that precede the onset of clinical HF.

unclear based on the literature assessing incidence of HF referring to ICD-10 code I50 for Heart failure as listed by WHO under the range of diseases of the circulatory system. It is possible that cardiac compensatory mechanisms revert the manifestation of HF and early signs of cardiac toxicity are incompletely reported, contributing to hindering the relevance of environmental chemicals on cardiovascular health.

1.2. Aims and objectives

We conducted a comprehensive systematic review and subsequent meta-analysis with the primary aim of exploring the impact of environmental pollutant exposure on the occurrence of LVD. Our investigation was guided by the following PECOS question framework, which encompasses Population, Exposure, Comparator, Outcome, and Study design:

- Population (P): We focused on humans, including particularly susceptible groups such as children and the elderly.
- Exposure (E): We analysed the effects of occupational and residential exposure to environmental pollutants such as particulate matter, heavy metals and pesticides.
- Comparator (C): Our analysis involved comparisons to non-exposure or low-exposure scenarios.
- Outcome (O): The central outcome of interest was LVD.
- Study Design (S): Our review encompassed observational and ecological studies.

To achieve a specific focus, we selected studies that met the following criteria: they reported echocardiographic measurements conducted on healthy individuals, examining the potential relationships between exposure to environmental pollutants and LVD. These exposures were assessed within various settings, both occupational and residential in nature.

2. Methods

This systematic review and meta-analysis was based on a review protocol accessible online including the full search strategy, data sources, eligibility and exclusion criteria (Linzalone et al., 2022).

2.1. Data extraction

We gathered all observational studies (including cohort, case-control, cross-sectional, time-series, and case-crossover designs) that explored the connection between environmental exposure and cardiovascular diseases leading to heart failure (HF). Conversely, we excluded randomized clinical trials, reviews, systematic reviews, editorials, commentaries, other non-original reports, as well as in vivo and in vitro studies involving cells, tissues, and animals. Furthermore, studies investigating effects on vulnerable groups (those with pre-existing CVDs and/or documented lifestyle risk factors) and hospital readmissions were also omitted.

For each study meeting the eligibility criteria, we compiled comprehensive details. These included the last name of the primary author and publication year, geographic location of the study area, study design, population characteristics (sample size, age, sex), environmental risk factor, exposure unit or comparator, exposure timing, echocardiographic abnormalities categorized as LVSD, LVDD, Structure, and

Geometry, risk estimations, along with confidence intervals and p-values for both adjusted and unadjusted statistical models for each measurement within individual studies. This encompassed the reported confounders as well. The entire dataset is presented in Table S1.

2.2. Assessment of quality

The quality of the studies by applying a risk of bias (RoB) tool at the study- and item-level using a modified version of the ROBINS-I instrument tailored for non-randomized studies (NRS) addressing environmental exposures and further described in the validated protocol (Morgan et al., 2019).

2.3. Statistical analysis

We conducted a meta-analysis to pool the effect sizes estimated in studies that measured the levels of environmental pollutants on a quantitative scale. In particular, for air pollutants (PM2.5, PM10, NO2), we considered seven studies (Dominguez-Rodriguez et al., 2013; Aung et al., 2018; Yang et al., 2017a; Van Hee et al., 2009; Hu et al., 2023; Zheng et al., 2023; Ohlwein et al., 2016) on which the exposure was reported as a quantitative measure derived from monitor stations or prediction models. Studies that used proxies as the distance from major roads (Van Hee et al., 2009; Weaver et al., 2016) or self-reported questionnaire (Burroughs Peña et al., 2017, 2018a, 2020), were not included in the meta-analysis. A similar approach was used for evaluating the exposure to heavy metals (arsenic and leads); in the meta-analysis we included five out of six studies that used quantitative methods to evaluate metal concentrations: two studies that assessed the exposure by analysing of blood lead levels (Tepper et al., 2001; Taheri et al., 2012) and three studies that evaluated the presence of lead, arsenic and cadmium in biological samples (Pichler et al., 2019; Osorio-Yáñez et al., 2015; Yang et al., 2017b). We did not include in the meta-analysis one studies that measured the exposure to heavy metals using self-reported questionnaires (Burroughs Peña et al., 2020).

For each of the outcomes considered (left Ventricular structure, left ventricular systolic function, left ventricular diastolic function), we considered the environmental pollutants (PM2.5, PM10, NO2, arsenic and lead) for which there were at least five estimates of the effect size. An adequate number of estimates (greater than five) allows for accurate estimates of the between-study variance and the pooled effect size (Kontopantelis et al., 2013).

The choice of considering only studies on which the exposure was measured in a quantitative scale allows us to use methods to harmonise the different effect size measures used to represent the association between environmental exposures and the outcomes. As shown in Appendix A, these procedures allow the transformation of the diverse effect size measures (regression coefficients, mean differences, odds ratios) presented in the different studies into a unique effect size estimate, namely a standardised regression coefficient (see Appendix A). Importantly, these methods require that the exposure variable is a quantitative variable, as they used some descriptive statistics of the exposure like the mean and the standard deviation. For each outcome and pollutant combination, we used a random-effects meta-analysis employing the Residual Maximum Likelihood (REML) method to compute the aggregate estimate, along with 95% confidence intervals. The I^2 statistic was employed to evaluate the heterogeneity among studies incorporated into the meta-analysis, and values of 25%, 50%, and 75% were classified as low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). As part of a sensitivity analysis, we contemplated the potential lack of independence among estimates presented within the same article by conducting a multilevel meta-analysis (Sera et al., 2019). All meta-analyses were executed using the mixmeta package in R (Sera et al., 2019). Given the inclusion of fewer than ten studies, an assessment of publication bias was not conducted. (Sutton et al., 2000).

3. Results

3.1. Study selection

The literature search initially found 3200 articles. After removing 1546 duplicates, we screened the titles and abstracts of 1654 articles and excluded 1457 of them. We evaluated the inclusion of the remaining 197 articles through a full-text assessment and after this screening process we included 12 articles in the systematic review. We also included 5 additional articles by citation searching, obtaining a total of 17 articles to be included in the systematic review. Fig. 2 depicts the number of records identified and the screening process, also including the reasons for exclusion in the last phase of the screening process.

3.2. Study characteristics

The flow diagram of the process of article selection is shown in Fig. 2, which resulted in the inclusion of 17 articles. Sixteen of these articles were cross-sectional and one cohort study. All of them were population-based. Table 1 shows the main characteristics. Nine studies measured the concentrations of pollutants in the environment (air or water) of which two used direct and indirect measures and one only a proxy based on the distance (Weaver et al., 2016). The sample size ranged from 353 to 25983 with an overall total of 43358. Six studies measured the concentrations of metals in blood or urinary samples (Burroughs Peña et al., 2020; Tepper et al., 2001; Taheri et al., 2012; Pichler et al., 2019; Osorio-Yáñez et al., 2015; Yang et al., 2017b) and one measured the serum concentrations of PCB congeners (Sjöberg Lind et al., 2013) and the sample size ranged from 114 to 1337 with an overall total of 2973. Three studies addressing a plethora of different toxics compounds (Burroughs Peña et al., 2017, 2018a, 2020), used an indirect recording of the exposure with a self-administered questionnaire and the sample size ranged from 782 to 1069 with an overall total of 2038.

3.2.1. Structural and/or functional cardiac abnormality

Structural and functional cardiac parameters were determined by echocardiography in all included studies. We classified them in three categories: structure/geometry, systolic function and diastolic function. Among the structural/geometrical parameters, the most investigated was the LV mass, expressed both in grams and grams per square meter. Overall, LV mass was considered by 12 out of 17 studies. Regarding systolic and diastolic function, LVEF and E/A ratio, expressed as %, and dimensionless ratio, were examined by 14 and 8 studies respectively. Nine studies among those reviewed, simultaneously measured at minimum the cardiac alterations representative of the three categories structure/geometry, systolic function and diastolic function (Aung et al., 2018; Yang et al., 2017a, 2017b; Burroughs Peña et al., 2017, 2018a, 2020; Taheri et al., 2012; Pichler et al., 2019). Overall, we found 407 estimates of the association between environmental pollutants exposure and structural and functional cardiac parameters. Of these, 167 were reported as significant associations with pollutants exposures. All estimates can be found in the full data matrix (Table S1).

3.2.2. Quality assessment

We identified several areas of concern in the studies reviewed, including residual confounding, selection bias, measurement bias, and departure from intended exposure (Dominguez-Rodriguez et al., 2013; Van Hee et al., 2009; Hu et al., 2023; Zheng et al., 2023; Weaver et al., 2016; Burroughs Peña et al., 2017, 2018a, 2020; Tepper et al., 2001; Osorio-Yáñez et al., 2015). Overall, two out of seven items resulted in a critical risk of bias attributable to the measurement of exposure and departures from exposure. When evaluating each single item (columns of Table 2), the confounding bias and measurement of exposure and departures from exposure items were reported as a serious risk. All the other items were classified as moderate or low risk. At the study level, nine out of seventeen studies have a moderate risk of bias, while five

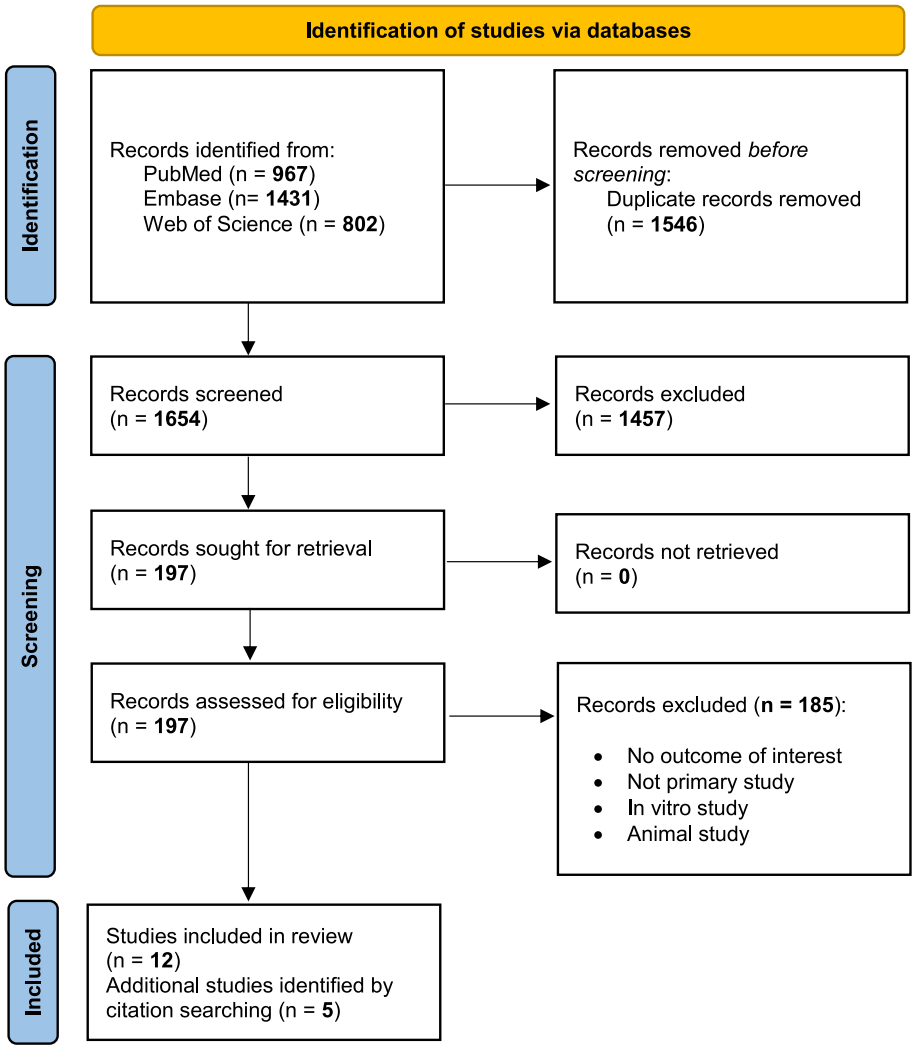

Fig. 2. PRISMA flow diagram All studies adjusted for age and gender, and most studies adjusted for cardiac risk factors (addressing high blood pressure, cholesterol and diabetes) and/or medications (n = 13), body mass index (n = 12), smoking status (n = 11), physical activity (n = 8), alcohol consumption (n = 5). However, fewer studies adjusted for confounding factors, including educational level (n = 6) or socioeconomic status (n = 4), ethnicity (n = 3), income or occupation (n = 3). The exposure levels and the effect measures in the included studies are shown in Table S1.

have a serious risk and three have a critical risk. No studies were classified as low risk of bias (see Table 2).

3.2.3. *Exposure to air pollution*

Eleven out of seventeen cross-sectional studies reported in Table 1 assessed the relationship between the exposure to air pollution and cardiac structure and/or function parameters (Dominguez-Rodriguez et al., 2013; Aung et al., 2018; Yang et al., 2017a; Van Hee et al., 2009; Hu et al., 2023; Zheng et al., 2023; Ohlwein et al., 2016; Weaver et al., 2016; Burroughs Peña et al., 2017, 2018a, 2020). A variety of methods of exposure measurement were used in the included studies. Regarding methods that assessed the exposure in a quantitative scale, most of them used prediction models (Aung et al., 2018; Yang et al., 2017a; Van Hee et al., 2009; Hu et al., 2023; Zheng et al., 2023; Ohlwein et al., 2016), while one study obtained air pollutants measures from an urban background monitoring station (Dominguez-Rodriguez et al., 2013). The remaining studies used residential proximity to traffic as a proxy measure for exposure to air pollution (Van Hee et al., 2009; Weaver et al., 2016) or self-reported questionnaires (Burroughs Peña et al., 2017, 2018b, 2020). As shown in Table 2, we attributed different quality judgments based on the methods used to assess exposure, assigning moderate risk of bias to those studies that used predictive models. On the other hand, lower ratings were assigned to the remaining studies by attributing a serious risk and a critical risk of bias to studies which used proxy measures (Van Hee et al., 2009; Weaver et al., 2016) and questionnaires (Burroughs Peña et al., 2017, 2018b, 2020) respectively.

3.2.4. *Exposure to heavy metals*

Six studies examined the effect of metal exposure on cardiac structure and/or functional parameters (Burroughs Peña et al., 2020; Tepper et al., 2001; Taheri et al., 2012; Pichler et al., 2019; Osorio-Yáñez et al., 2015; Yang et al., 2017b). Five out of six studies used quantitative methods to evaluate metal concentrations. The two earliest studies (Tepper et al., 2001; Taheri et al., 2012) were conducted in occupational settings and assessed the exposure by analysing of blood lead levels. The most recent studies (Pichler et al., 2019; Osorio-Yáñez et al., 2015; Yang et al., 2017b) have also quantitatively evaluated the presence of lead, arsenic and cadmium in biological samples. Only one study, which was not included in the systematic review, assessed exposure using self-reported questionnaires (Burroughs Peña et al., 2020).

3.2.5. *Exposure to synthetic organic chemicals compounds*

Two studies examined the effect of synthetic organic chemicals compounds exposure on cardiac structure and/or functional parameters

Table 1
Characteristics of all included studies.

Pollutant category	Exposure type	Study design	Population (age)	Study area	Sample size (N)	Exposure assessment	Pollutants	Endpoints/unit	Covariates	First author
air pollution	Residential	cohort	adults (45.78 and 43.26 - mean ages of males and females respectively)	China	N = 3145	satellite-based spatial-temporal models	PM1, PM2.5, PM10, NO2, O3	Interventricular septal thickness at diastole (cm), LV internal dimension-diastole (cm), LV internal dimension-systole (cm), LV posterior wall dimensions (cm), end-diastolic volume (ml), end- systolic volume (ml), LV EF (%), stroke volume (%), E pressure gradient (mmHg), E velocity (cm/s)	gender, body mass index (BMI), activities, marital status, highest education attained, urbanicity	Hu et al. (2023)
air pollution	Residential	cross-sectional	adults (50.4 years - mean age)	China	N = 25983	chemical data assimilation system (ChemDAS)	PM10, PM2.5, NO2	Abnormal LV diastolic function	age, gender, areas, habitation altitude, ethnicity, education, smoke, drinking, family history of CVD, obesity, hypertension, hyperlipidemia, diabetes, medical therapy, solid heating fuels, passive smoke, indoor, ventilation and cookstove ventilation	Zheng et al. (2023)
air pollution	Residential	cross-sectional	adults (61.7 years - mean age) UK Biobank	UK	N = 3920	land use regression models	PM10, PM2.5, PMcoarse, NOx and NO2, traffic intensity	LV end-diastolic volume (ml), LV end-systolic volume (ml), LV EF (%), LV mass (g), LA maximal volume (ml), LA EF (%), Concentric remodeling, Eccentric hypertrophy, Concentric hypertrophy	age, gender, body mass index, physical activity, socioeconomic factors, cardiac risk factors, medications, ethnicity, height	Aung et al. (2018)
air pollution	Residential	cross-sectional	adults (50.4 years - mean age) Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO)	Belgium	N = 671	high resolution spatiotemporal interpolation method	PM10, PM2.5, black carbon, NO2	LV mass index (g/m2), end-diastolic diameter (cm), relative wall thickness, LV EF (%), longitudinal strain (%), longitudinal strain rate (s-1), radial strain (%), radial strain rate (s-1), LA volume index (ml/m2), E peak (cm/s), A peak (cm/s), E/A ratio, e' (cm/s), a' (cm/s), E/e' ratio	age, gender, body mass index, smoking status, socioeconomic status, heart rate, antihypertensive treatment (by drug class), mean arterial pressure, fasting plasma glucose, total-to-HDL cholesterol ratio, serum creatinine, g-glutamyltransferase, use of the lipid-lowering drug	Yang et al. (2017a)
air pollution	Residential	cross-sectional	adults (69 years - mean age)	Spain	N = 353	urban monitoring station	PM10, PM2.5, PM1, CO, SO2, NO2, O3	LV EF (%)	age, gender, hypertension, LV EF, PM10	Dominguez-Rodriguez et al. (2013)
air pollution	Residential	cross-sectional	elderly women (aged 69–79 years) SALIA cohort study	Dortmund, Duisburg, Essen, Gelsenkirchen, Herne, Borken and Dülmen (Germany)	N = 402	land use regression models	PM2.5, PM2.5absorbance, PM10, PMcoarse, NOx, NO2 distance to major roadways	LA volume index (mL/kg2), E/E′ ratio	body mass index, physical activity smoking status, alcohol consumption, socioeconomic status, low-density lipoprotein, high-density lipoprotein and intake of statins	Ohlwein et al. (2016)
air pollution	Residential	cross-sectional	adults (aged 54–59 years) Jackson Heart Study cohort	Jackson, Mississippi (U.S.)	N = 4866	residential proximity to traffic	distance to major roadways	LV EF (%), E-wave velocity (m/s), isovolumic relaxation time, LA diameter index (mm/m2), and pulmonary artery systolic pressure.	age, gender, body mass index, physical activity, smoking status, alcohol consumption, socioeconomic status, educational level, occupation	Weaver et al. (2016)

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Table 1 (*continued*)

Pollutant category	Exposure type	Study design	Population (age)	Study area	Sample size (N)	Exposure assessment	Pollutants	Endpoints/unit	Covariates	First author
air pollution	Residential	cross-sectional	adults (aged 45–84 years) multi-ethnic longitudinal epidemiologic study	Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota (U.S.)	N = 3827	interpolation method and residential proximity to traffic	distance to major roadways	LV mass index (g/m2), and LV EF (%)	age, gender, physical activity, smoking status and history, alcohol consumption, hours per week of second-hand smoke exposure, educational level, ethnicity, household income, antihypertensive medication use, low-density lipoprotein and high-density lipoprotein cholesterol, lipid-lowering medication use, diabetes status by fasting blood glucose criteria, and use of diabetes medications	Van Hee et al. (2009)
air pollution	Residential	cross-sectional	adults (aged 45–74 years)	Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California (U.S.)	N = 1069	self-report questionnaire	household second-hand smoke	LV mass index (gm/m2), LV end-systolic volume (mL), LV end-diastolic volume (mL), LV EF (%), LV stroke volume (mL), LV longitudinal strain (4-chamber) (%), LV longitudinal strain (2-chamber) (%), LV longitudinal strain (average) (%), Medial E′ velocity (cm/s), Lateral E′ velocity (cm/s), E/E′ ratio, E/A ratio, Isovolumic relaxation time (s), LA volume index (mL/m2)	age, gender, physical activity, alcohol consumption, educational level, study site,	Burroughs Peña et al. (2018a)
air pollution	Residential	cross-sectional	adults (aged ≥35 years) CRONICAS longitudinal cohort study	Puno, Peru	N = 187	self-report questionnaire	daily biomass fuel use	LV internal diameter, diastole (cm), LV internal diameter, systole (cm), LV diastolic volume (mL), LV systolic volume (mL), LV EF (%), LV mass (g), LA diameter (cm), LV area 4-chamber (cm2), LV area 2-chamber (cm2), E/A ratio, lateral E' (cm/s), lateral A' (cm/s), lateral S' (cm/s), septal E' (cm/s), septal A' (cm/s), septal S' (cm/s), diastolic dysfunction grade, LA strain (2-chamber), LA strain (4-chamber) (%), LV strain (global longitudinal) (%), LV strain (4-chamber) (%), LV strain (3-chamber) (%), LV strain (2-chamber) (%)	age, gender, body mass index, height, physical activity, smoking status, diabetes	Burroughs Peña et al. (2017)
metals	Occupational	cross-sectional	adult males (aged 25–55 years)	Isfahan (Iran)	N = 142	biomonitoring	blood lead	LV end-diastolic dimension (mm), interventricular septal (mm), posterior wall thickness (mm), LA diameter (mm), aortic diameter (mm),	age, body mass index, physical activity, smoking status, systolic and diastolic blood pressure	Taheri et al. (2012)

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Table 1 (*continued*)

Pollutant category	Exposure type	Study design	Population (age)	Study area	Sample size (N)	Exposure assessment	Pollutants	Endpoints/unit	Covariates	First author
								LVEF (%), LV mass (g), LV mass index, E/A ratio.		
metals	Occupational	cross-sectional	adult males (aged 36–73 years)	The U.S.	N = 114	biomonitoring	blood lead	LV Mass (g/m2)	age, gender, body mass index, and family history of hypertension.	Tepper et al. (2001)
metals	Residential	cross-sectional	adults (39.1 years - mean age) Cadmium in Belgium (CadmiBel) study	10 districts in northeastern Belgium	N = 191	biomonitoring	blood lead, urinary cadmium	LV mass index (g/m2), end-diastolic diameter (cm), relative wall thickness, LV EF (%), global longitudinal strain (%), regional longitudinal strain (%), regional longitudinal strain rate (s-1), regional radial strain (%), and regional radial strain rate (s-1), E peak (cm/s), E/A ratio, e' peak (cm/s), E/e' ratio	age, gender mean arterial pressure, heart rate, body mass index, smoking status, fasting plasma glucose, total-to-HDL cholesterol ratio, serum creatinine, c-glutamyltransferase, antihypertensive treatment (by drug class), corrected for dilution bias	Yang et al. (2017b)
metals	Residential	cross-sectional	children (aged 3–8 years)	Zimapan, Mexico	N = 191	biomonitoring/ environmental monitoring	urinary arsenic and arsenic in drinking water	LV mass (g), LV EF (%), shortening fraction (%), aortic root diameter (mm), LA diameter (mm)	age, gender, body mass index, systolic blood pressure, NOx,	Osorio-Yáñez et al. (2015)
metals	Residential	cohort	young adults (mean age 30.7 years) Strong Heart Study	Arizona, Oklahoma, North Dakota, and South Dakota (U.S.)	N = 1337	biomonitoring	urinary arsenic	LV mass index (g/m2), LA systolic diameter (cm), LV internal diameter (cm), interventricular septum (cm), LV posterior wall thickness (cm), relative wall thickness (dmls), heart rate (bpm), stroke volume (mL), LV EF (%), mitral E-velocity (cm/s), mitral A-velocity (cm/s), E/A ratio, atrial filling fraction, deceleration time (ms), Isovolumic relaxation time (ms)	age, gender, body mass index (continuous), smoking status, region, dyslipidemia (no/yes), fasting glucose level (continuous), estimated glomerular filtration rate (continuous), systolic blood pressure (continuous), and blood pressure treatment (no/yes).	Pichler et al. (2019)
mixed	Occupational	cross-sectional	Adults (52.9 years - mean age) Hispanic Community Health Study/Study of Latinos	Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California. (U.S.)	N = 782	self-report questionnaire	burning wood, vehicle exhaust, solvents, pesticides, metals (lead, manganese, mercury)	LV mass index (g/m2), LV mass index (g/m2.7), LV end-diastolic volume (mL), LV end-systolic volume (mL), LV EF (%), LV stroke volume (mL), LV longitudinal strain (4-chamber) (%), LV longitudinal strain (2-chamber) (%), LV longitudinal strain (average) (%), Medial E′ velocity (cm/s), Lateral E′ velocity (cm/s), E/E′ ratio, E/A ratio, Isovolumic relaxation time (s), LA volume index (mL/m2)	age, gender, physical activity, smoking status, alcohol consumption, educational level, study site	Burroughs Peña et al. (2020)
POPs	Residential	cross-sectional	Elderly (aged 70 years) Prospective Investigation of the	Uppsala, Sweden	N = 998 elderly	biomonitoring	serum concentrations of PCB congeners 74, 99, 105, 118, 196, 138, 153,	LV EF (%), E/A ratio, Isovolumic relaxation time (ms)	gender, body mass index, smoking, systolic blood pressure, antihypertensive medication,	Sjöberg Lind et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Pollutant category	Exposure type	Study design	Population (age)	Study area	Sample size (N)	Exposure assessment	Pollutants	Endpoints/unit	Covariates	First author
			Vasculature in Uppsala Seniors (PIVUS) study				156, 157, 169, 170, 180, 189, 194, 206, 209 and OCDD, HCB, TNC, p, p'-DDE, BDE 47		diabetes and LV hypertrophy at ultrasound	

(Burroughs Peña et al., 2020; Sjöberg Lind et al., 2013). The first one studied 23 persistent organic pollutants (POPs), including 16 polychlorinated biphenyls (PCBs), one brominated biphenyl ether (BDE), one octachlorodibenzo-p-dioxin (OCDD) and three organochlorine pesticides (OC), that are hexachlorobenzene (HCB), trans-nonachlor (TNC) and p,p'-DDE (2,2-bis(4-chlorophenyl)-1,1-dichloroethene) (Sjöberg Lind et al., 2013). The other one studied the occupational exposure to solvents and pesticides (Burroughs Peña et al., 2020).

3.3. Association analyses using meta-analysis

Our meta-analysis quantified the pooled effect of an exposure to a pollutant confirming only some associations with the early markers of HF (see **Figs. 3 and 4**). For synthetic organic chemicals it was not possible to conduct a meta-analysis due to the limited number of studies. The comprehensive analysis reported the effect sizes (ES) and 95% confidence intervals (CI) for each pollutant in relation to LV structure geometry, LV systolic function, and LV diastolic function.

3.3.1. Impact of air pollution on cardiac health

The relationship between residential exposure to fine particulate matter (PM2.5), coarse particulate matter (PM10), nitrogen dioxide (NO2), and various cardiac parameters was examined. Data were collected from groups of individuals exposed to varying levels of air pollutants. Regarding LV structure or geometry, the findings did not show any association with PM2.5. The analysis showed for PM2.5 exposure an estimated effect size (ES) of 0.002, with a confidence interval (95% CI) ranging from −0.022 to 0.026. The level of heterogeneity was 69.96%, indicating a somewhat consistent effect on LV structure and geometry across the exposed population. Similarly, PM10 exposure displayed a comparable ES of 0.000, with a slightly wider confidence interval (95% CI: −0.017 to 0.017) and a level of heterogeneity of 65.34%. On the other hand, NO2 exposure demonstrated an ES of 0.001, with a narrow confidence interval (95% CI: −0.130 to 0.014) and a level of heterogeneity of 60.11%, suggesting a rather weak effect on LV structure and geometry. Moving on to LV systolic function, the results revealed negative associations with all three pollutants. For PM2.5 exposure, the ES was −0.069, and the confidence interval (95% CI) ranged from −0.104 to −0.033. The data showed a level of heterogeneity of 70.90%, suggesting some variability in the impact on LV systolic function among individuals. As for PM10 exposure, the ES was −0.055, with a confidence interval (95% CI) from −0.087 to −0.022, and a level of heterogeneity of 80.27%, indicating more significant variability in responses. NO2 exposure demonstrated an ES of −0.042, and the confidence interval (95% CI) ranged from −0.071 to −0.013, with a level of heterogeneity of 61.46%. These findings suggest that exposure to these pollutants might impair the ability of the left ventricle to contract and pump blood effectively. Regarding LV diastolic function, the associations were also negative for all pollutants. PM2.5 had the strongest impact, the ES was −0.044, with a confidence interval (95% CI) from −0.062 to −0.025, and a relatively high level of heterogeneity (72.09%), indicating varied responses among individuals. For PM10 exposure, the ES was −0.030, with a confidence interval (95% CI) ranging from −0.050 to −0.010, and a significantly higher level of heterogeneity (90.77%), highlighting substantial variability. Finally, NO2 exposure displayed an ES of −0.021, with a confidence interval (95% CI) from −0.037 to −0.004, and a level of heterogeneity of 87.02%. These results suggest that residential exposure to these pollutants might lead to impaired LV relaxation and filling. The data indicated that residential exposure to PM2.5, PM10, and NO2 might have adverse effects on LV structure, systolic function, and diastolic function, with some variations among individuals. The negative associations observed for LV systolic and diastolic functions and positive observed for structure and geometry raise concerns about the impact of these environmental pollutants on heart health.

3.3.2. Impact of lead and arsenic poisoning on cardiac health

The data gathered from a diverse group of individuals who had been exposed to varying levels of lead and arsenic were analysed. It was found that lead exposure had a minimal impact on **LV structure and geometry**, with an estimated effect size (ES) of 0.006 and a confidence interval (95% CI) ranging from −0.028 to 0.040. However, it was worth noting that the data showed a moderate level of heterogeneity (I2 = 37.0%) and that residential and occupational data were considered to compute the effect measures. On the other hand, arsenic exposure displayed a slightly higher ES of 0.034, with a narrower confidence interval (95% CI: 0.015 to 0.053) and a higher level of heterogeneity (I2 = 87.1%). This indicated a more substantial effect on LV structure and geometry due to arsenic exposure, compared to lead. Moving on to the critical aspects of LV function, the impact of lead and arsenic poisoning on both systolic and diastolic functions was estimated. Lead exposure was associated with a significant reduction in LV systolic function, with an ES of −0.033 and a confidence interval (95% CI) ranging from −0.051 to −0.016. The data also showed no heterogeneity (I2 = 0.00%), signifying a consistent effect across the exposed population. Conversely, arsenic exposure yielded a similar ES of −0.033 for LV systolic function, but the confidence interval (95% CI: −0.119 to 0.053) was notably wider, indicating greater uncertainty about its true impact. Moreover, the level of heterogeneity was substantially higher (I2 = 97.3%), suggesting that arsenic's effect on LV systolic function varied significantly among individuals.

Regarding LV diastolic function, both lead and arsenic exposure had adverse effects. Lead exposure demonstrated a relatively minor impact, with an ES of −0.003 and a confidence interval (95% CI) from −0.017 to 0.012. The heterogeneity was moderate (I2 = 27.9%), indicating varying responses in different individuals. On the other hand, arsenic exposure displayed a more pronounced negative impact on LV diastolic function, with an ES of −0.009 and a narrower confidence interval (95% CI: −0.017 to −0.001). Surprisingly, there was no heterogeneity (I2 = 0.00%) in this case, suggesting a consistent effect across the population.

The data clearly indicated that both lead and arsenic poisoning could affect various cardiac parameters, potentially leading to serious cardiovascular issues.

4. Discussion

CVDs are the leading cause of death globally. Nearly a decade ago, there was a significant demand for a thorough comprehension of the role of heavy metal toxicity in the development of CVDs. which included a requirement for large-scale prospective studies that followed the general population over time and utilized appropriate cardiovascular biomarkers and endpoints (Alissa and Ferns, 2011). However, to the best of our knowledge, this is the first systematic review and metanalysis focusing on human epidemiological studies found in the literature that showed how environmental pollutants -including heavy metals - may induce the development of LVD based on asymptomatic population data. Most of the studies focusing on echocardiographic measures (~82%) were published in the last decade (2013–2023), indicating the growing interest in investigating the effects of exposure to environmental chemicals on cardiac morpho-functional parameters such as left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), and E/A ratio as prognostic biomarkers for CVDs in both general and occupational populations. Our systematic review contributed to strengthening the existing addressed evidence by combining studies within the same pollutant group to summarize risk associations. However, the association between exposure to environmental chemicals and LVD remained at some level unclear due to the limited number of available studies, which primarily employed a cross-sectional design and analysed different age groups and types of exposure. To address this gap, a meta-analysis was conducted on seven studies examining air pollutants and five studies investigating heavy metals, involving a total of 271/131 effect measures of LVD from 14,172/1975 subjects in the general population. Additionally, two subgroups, elderly women exposed to air pollution and young/children exposed to metals, were investigated. The main findings of the meta-analysis are summarized in Figs. 3 and 4. The meta-analysis results revealed a statistically significant negative association between exposure to PM2.5, PM10, and NO2 and systolic function (−0.069, 95% CI: −0.104, −0.033; −0.055, 95% CI: −0.087, −0.022; −0.042, 95% CI: −0.071, −0.013) as well as diastolic function (−0.044, 95% CI: −0.062, −0.025; −0.030, 95% CI: −0.050, −0.010; −0.021, 95% CI: −0.037, −0.004). In the case of lead exposure, there was a negative association with systolic function (−0.033, 95% CI: −0.051, −0.016). As for arsenic exposure, a positive association with left ventricular structure (0.034; 95% CI: 0.015–0.053) and a negative association with left ventricular diastolic function (−0.009; 95% CI: −0.017 to −0.001) were observed. However, the associations for metals were not confirmed in a sensitivity analysis. It is important to note that the findings were based on a limited number of observations, and larger sample investigations are needed to confirm the results. Also, the interpretation of these results should consider that the estimates of effect showed by the different authors may be influenced by uncontrolled residual confounders, such as individual susceptibility and exposure misclassification. Hence, our systematic review has offered compelling evidence that is highly relevant to humans, yet a certain level of uncertainty persists. To overcome this limitation and reach conclusions regarding the existence of causal relationships between chemical exposure and health outcomes, it is recommended to utilize faster methodologies, such as the use of New Approach Methodologies (NAMs), than longitudinal studies (Schaffert et al., 2023). NAMs are alternative methods to animal testing that use human-based data and models to assess the safety and efficacy of substances (Kim et al., 2022). NAMs can help to collect all available evidence and establish links between observed disease phenotypes in studied populations and the mechanisms of action and molecular initiators of AOPs. These pathways serve as useful constructs for organizing existing information in a sequential manner, developing linear causal networks of biological pathways composed of interlinked essential components (Key Events) that lead to adverse outcomes relevant to regulatory decisions (Perkins et al., 2022). For example, NAMs can be used to identify the molecular targets of air pollutants and heavy metals that trigger oxidative stress and inflammation in cardiac cells, leading to LVD and CVDs. Adopting a collaborative approach is essential for gathering knowledge from various sources of evidence, including mechanistic, toxicological, and epidemiological data (Svingen et al., 2021). This innovative approach aims to establish plausible connections between exposure-health associations and maintain a link to individual organism- and population-level risks through biomarkers of effect (Bajard et al., 2023).

4.1. Proposed comprehensive framework

The studies analysed in this review employed a diagnostic approach that extended beyond solely considering the ejection fraction in classifying phenotypic presentations of HF. They are consistent with the considerations of some authors who recently validated this approach based on the consideration that abnormalities in heart shape and function are related features of cardiac remodeling that lead to heart failure (Nauta et al., 2020; Triposkiadis et al., 2019). Most studies that we analysed include the simultaneous measurement of multiple HF early markers, including mass (by weight or surface area), ejection fraction (measurement % of normal), and E/A ratio (ratio of times, dimensionless). Our study proposes a framework of the mechanisms leading to HF which include echocardiographic markers significantly associated with exposures (Fig. 5).

Including the three parameters mentioned above provides a minimum indication of the overall impairment in heart shape and function (Aung et al., 2018; Yang et al., 2017a, 2017b; Burroughs Peña et al., 2017, 2018a, 2020; Taheri et al., 2012; Pichler et al., 2019). Besides the LVEF parameter, Weaver and colleagues (Weaver et al., 2016) used

Table 2
Risk of bias matrix.

First author, year	Confounding	Selection	Measurement of exposure	Departures from exposure	Missing data	Measurement of outcomes	Reported results	Study-level judgment
[24]	M	L	C	C	L	L	L	C
[26]	M	L	L	M	L	L	L	M
[33]	M	L	M	M	L	L	L	M
[32]	M	L	C	C	L	L	L	C
[31]	M	M	C	C	L	L	L	C
[29]	M	L	L	M	L	L	L	M
[34]	M	L	M	M	L	L	L	M
[23]	M	L	S	S	L	L	L	S
[37]	M	M	M	M	L	L	L	M
[25]	S	L	L	L	L	L	L	S
[30]	M	L	M	M	L	M	L	M
[35]	S	M	C	C	M	L	L	C
[27]	M	L	L	L	L	L	L	M
[36]	M	L	S	S	L	L	L	S
[28]	S	M	L	L	M	L	L	S
Item level judgment	S	M	C	C	M	M	L	

Low (L)	Moderate (M)	Serious (S)	Critical (C)

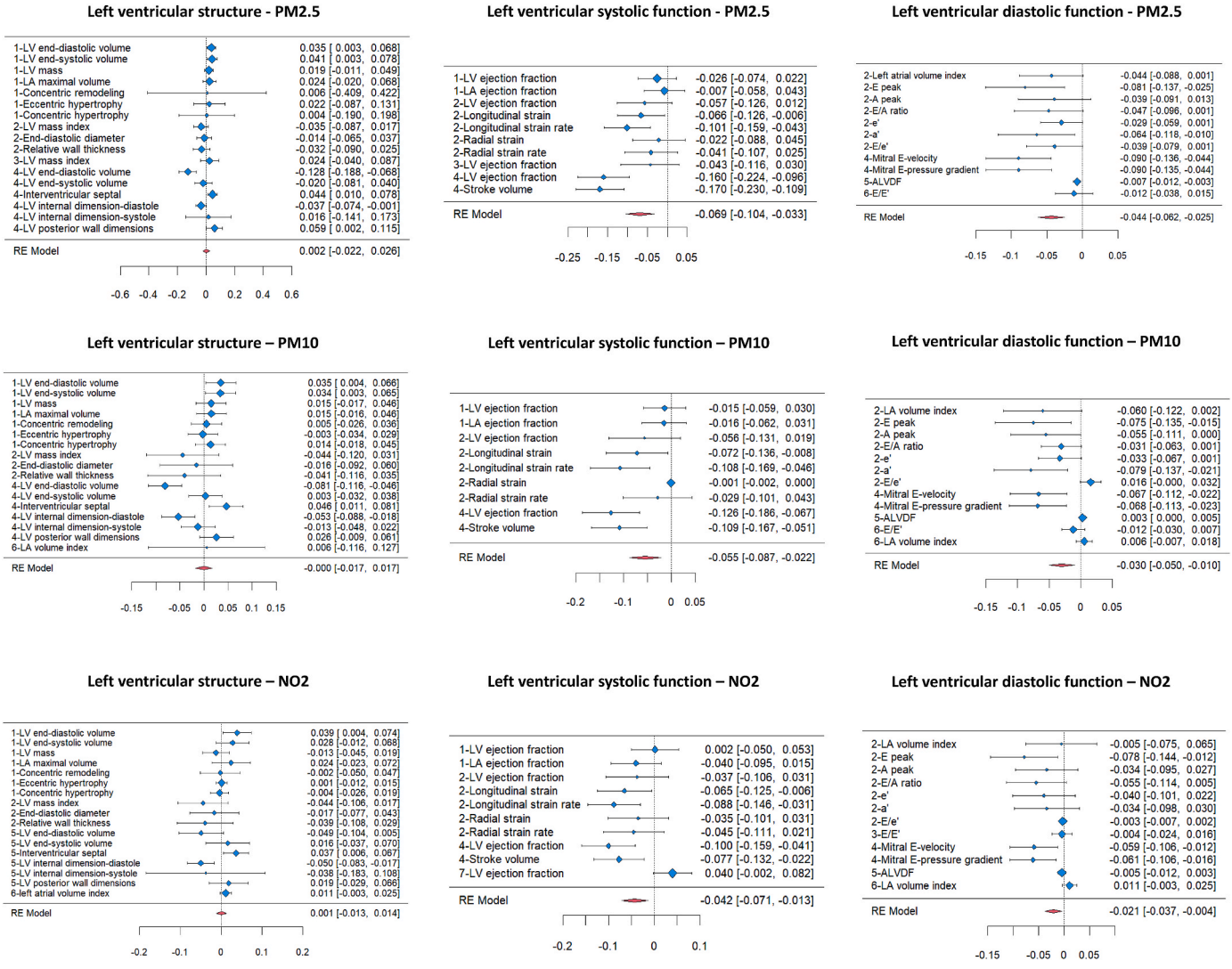

Fig. 3. Forest plot (random-effects model) displaying effect measures and their corresponding 95% confidence intervals (CIs) for the association between residential exposure to air pollutants and the risk of LVD at the endpoint level. Each effect measure is linked to the reference study. 1-[29], 2-[30], 3-[31] 4-[32], 5-[33], 6-[34], 7-[28].

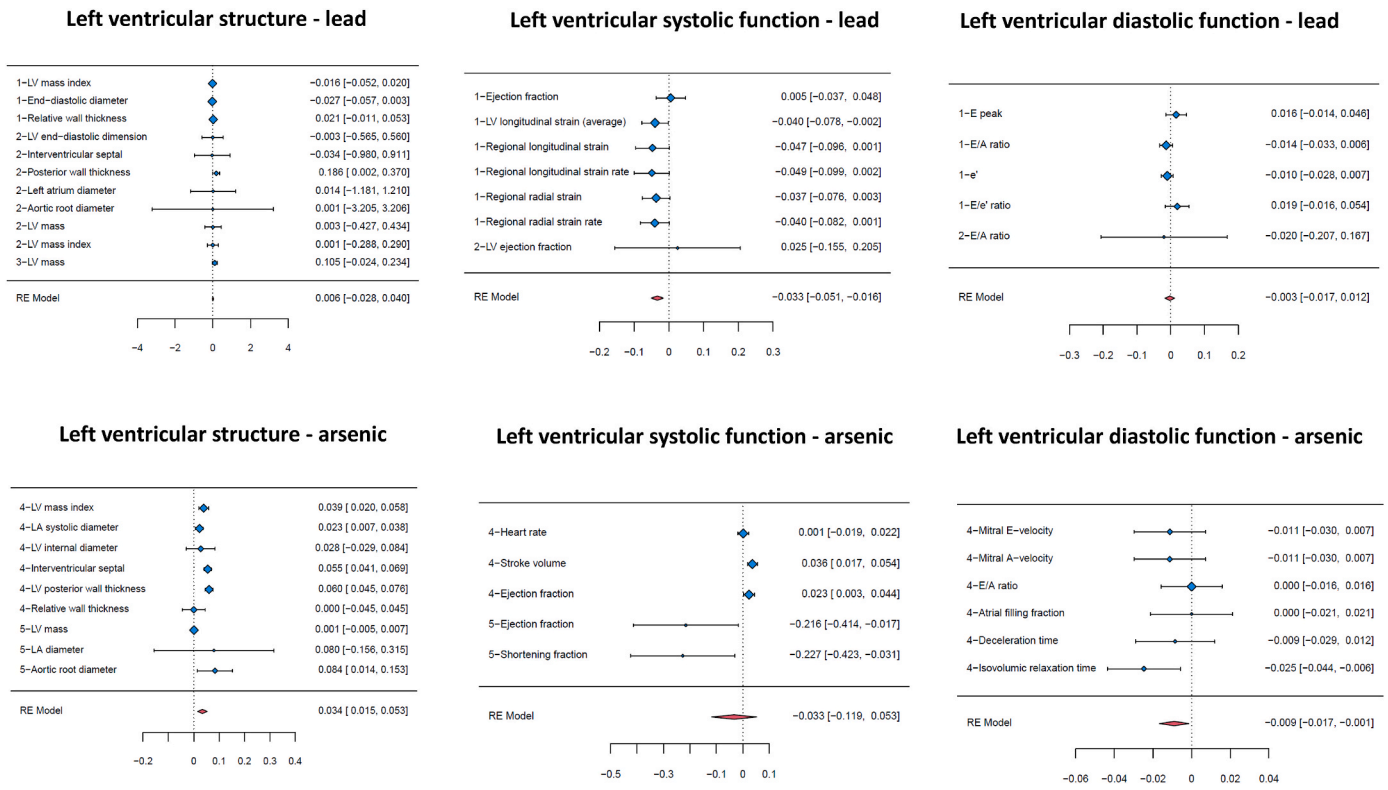

Fig. 4. Forest plot (random-effects model) displaying effect measures and their corresponding 95% confidence intervals (CIs) for the association between exposure to heavy metals and the risk of LVD at the endpoint level. Each effect measure is linked to the reference study. 1-[43], 2-[40], 3-[39], 4-[41], 5-[42].

E-wave velocity (m/s) and isovolumic relaxation time to define the systolic functionality and the LA diameter index (mm/m2) to monitor the alteration of the geometry. Dominguez-Rodriguez and colleagues (Dominguez-Rodriguez et al., 2013) took a minimal approach by measuring only systolic function with the ejection fraction. Ohlwein and colleagues (Ohlwein et al., 2016) focused only on diastolic function impairments, contrary to Osorio-Yáñez and colleagues (Osorio-Yáñez et al., 2015) which disregarded measuring diastolic function. Van Hee and colleagues (Van Hee et al., 2009) combined the systolic function with the evaluation of the structure contractility, opposing Lind and colleagues (Sjöberg Lind et al., 2013) who did not consider the structure and geometry. In the older study, the structure was measured through the mass indicator alone (Tepper et al., 2001). In each of the three studies, Burroughs Peña and colleagues (Burroughs Peña et al., 2017, 2018a, 2020) presented a large wealth of parameters collected simultaneously for each of the categories. However, the confidence in the results from Burroughs Pena and colleagues was limited as information on exposure came from questionnaire interviews. Different studies have used different echocardiographic parameters to define systolic and diastolic functionality and monitor the alteration of the geometry of the heart. However, high heterogeneity among parameters is undesirable in a dataset for meta-analysis. Therefore, we suggest that future studies should define a minimal set of relevant echocardiographic parameters as early markers of asymptomatic HF.

Consistency across evidence streams increases confidence in the overall assessment provided that bias and exposure from different studies meet the minimum criteria for triangulation in aetiological epidemiology (Lawlor et al., 2016). The concept of consistency, that Austin Bradford Hill defines as results repeatedly observed by different researchers, in different places, populations, circumstances and times has some characteristics in common with triangulation (Hill, 2015). Results in our meta-analysis are consistent, although low-risk coefficients are reported, when compared with different lines of evidence addressing the same underlying causal question.

4.1.1. Air pollution

In previous studies, air pollution exposure was positively associated with numerous adverse CVDs events, such as myocardial infarction, cerebrovascular disease, hypertension, and HF (Azzouz et al., 2022), thereby addressing the large CVD's group based on the international classification. By the way, cardiac muscle abnormalities in failing hearts are strongly related to an adaptative mechanism of the form to function, contributing to left ventricular systolic and diastolic dysfunction (Katz and Rolett, 2016). Accordingly, our results were consistent with the literature, as most of the studies included in the systematic review reported numerous associations with chronic air pollution exposures. These exposures were connected to changes in cardiac structure and systolic and diastolic functions in individuals without pre-existing CVDs, which are used as markers of asymptomatic HF (Dominguez-Rodriguez et al., 2013; Aung et al., 2018; Yang et al., 2017a; Van Hee et al., 2009; Ohlwein et al., 2016; Burroughs Peña et al., 2017, 2018a, 2020). Both short-term (acute) and long-term (chronic) exposure to fine particulate matter air pollution are responsible for triggering HF. Long-term exposure to fine particulate matter air pollution was associated with an increase in hospital procedures in heart failure patients (Catalano et al., 2023). Also, experimental and animal studies confirmed that a cardiac phenotype is consistent with incipient heart failure after long-term exposure to environmentally relevant concentrations of PM2.5. In this process, chemicals and metals attached to PM, which is a mixture of heterogenous components including anthropogenic sources, are considered activators of underlying mechanisms inducive of direct myocyte damage (Ain and Qamar, 2021).

PM is considered to be a key contributor to cardiac toxicity based on evidence of increased production of reactive oxygen species (ROS) and subsequent oxidative stress (Brook et al., 2010; Burns et al., 2019; Lederer et al., 2021b; Yang et al., 2019). Elevated ROS levels have been shown to trigger cardiomyocyte apoptosis or dysfunction, resulting in cardiac hypertrophy, myocardial ischemia-reperfusion, and ultimately heart failure (D'Oria et al., 2020). Nonetheless, the underlying

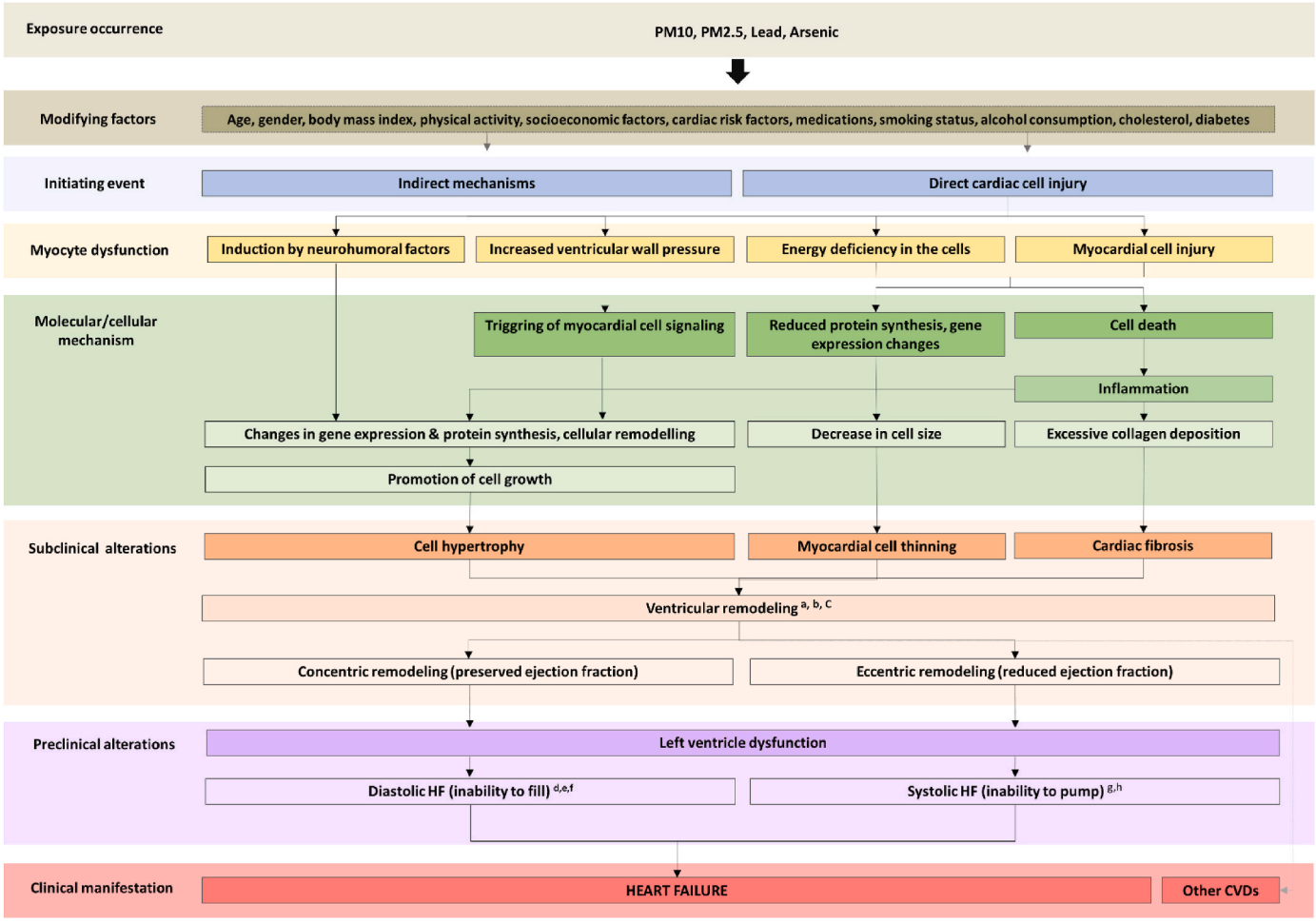

Fig. 5. A comprehensive framework which incorporates the findings of various studies included in this systematic review. a) PM10 - PM2.5 - LV mass index, LA maximal volume, RWT, LV end-systolic and diastolic volume, concentric hypertrophy, concentric remodeling; b) LEAD: LV mass index, LA systolic diameter, RWT, PWT, AR diameter, LV end-systolic and diastolic volume; c) ARSENIC: LV mass index, LA systolic diameter, RWT, PWT, AR diameter, IVS, LV internal diameter; d) PM10 - PM2.5: E/A ratio, E peak, e', E/e' ratio, a', A peak, LA volume index; e) LEAD: E/A ratio, E peak, e', E/e' ratio; f) Arsenic: E/A ratio, E-velocity, Atrial filling fraction, Deceleration time, IRT; g) PM10 - PM2.5 - Lead: LV EF, LA EF, Longitudinal strain rate; h) Arsenic: LV EF, shortening fraction, heart rate, LV stroke volume.

biomolecular mechanisms contributing to the cardiotoxic effects remain not fully understood. Even though health effects have been reported also in relation to the metal components of airborne particulate matter (PM), no specific component can be definitively excluded from this association. Available animal and human studies reveal similar toxicity pathways for these metals and include ROS generation, weakening of the antioxidant defence, enzyme inactivation, and oxidative stress (Balali-Mood et al., 2021). However, there is scarce epidemiological and toxicological literature investigating long-term exposure compared to short-term exposure (Wyzga and Rohr, 2015).

4.1.2. Heavy metals

Mercury, lead, chromium, cadmium, and arsenic have been the most common heavy metals that induced human poisonings. Within this review, six studies (Burroughs Peña et al., 2020; Tepper et al., 2001; Taheri et al., 2012; Pichler et al., 2019; Osorio-Yáñez et al., 2015; Yang et al., 2017b) examined the presence of arsenic, cadmium, and lead, which are known for their high degree of toxicity and significant public health implications (Tchounwou et al., 2012).

4.1.3. Arsenic

The two studies investigating the effect of environmental arsenic exposure showed associations with structural and functional cardiac indices (Pichler et al., 2019; Osorio-Yáñez et al., 2015). High arsenic exposure has been linked to clinical CV endpoints such as coronary heart disease and peripheral arterial disease (Moon et al., 2012). The meta-analysis confirmed an association between arsenic exposure and cardiac structure and diastolic function. Studies conducted in rodent models have provided additional information on the effects of arsenic exposure on the heart. These investigations have shown associations between arsenic exposure and outcomes such as LV mass, LV interventricular system, concentric hypertrophy, cardiomyocyte damage, and cardiac contractility (Phan et al., 2014; Sanchez-Soria et al., 2012). Several underlying mechanisms have been proposed to explain the potential cardiotoxic effects of arsenic. These mechanisms include the formation of reactive oxygen species (ROS) and the accumulation of arsenic in cardiomyocytes. The plausibility of these cardiotoxic effects is supported by previous research findings (Ellinsworth, 2015; Zhao et al., 2008).

4.1.4. Lead

Blood lead levels were measured in three occupational studies and one residential study (Burroughs Peña et al., 2020; Tepper et al., 2001; Taheri et al., 2012; Yang et al., 2017b). No association with LV endpoints was highlighted in two investigations involving 128 subjects on average (Tepper et al., 2001; Taheri et al., 2012). According to the quality score, the study by Tepper and colleagues (Tepper et al., 2001) got a serious risk of bias due to unavailable information regarding

relevant confounding like smoking habits, physical activity or body mass index. On the other hand, the study conclusion by Taheri and colleagues (Taheri et al., 2012) was quite well supported by the available information from a minimum set of LVD relevant endpoints and covariates, including smoking status and systolic and diastolic blood pressure, which allowed to achieve a moderate level of bias. Opposite findings were reported by Yang and colleagues (Yang et al., 2017b) in a residential biomonitoring surveillance study regarding 191 adults. The exposure (lead, cadmium, or both), which was generally lower than in an occupational setting, displayed a risk factor for systolic LVD, after adjustment for antihypertensive drug use. The study quality was judged moderate due to the departure from the exposure item. Our meta-analysis showed an association between systolic dysfunction and lead exposure based on two studies (Taheri et al., 2012; Yang et al., 2017b), and confirmation is needed from future studies providing additional measures. Also, Burroughs Peña and colleagues found numerous associations with structural and functional cardiac parameters in a larger (four-fold) sample of workers from different study sites and assessed numerous relevant markers of LVD. The location was included in the adjusted model and some proxy of socioeconomic status but not the hypertensive history. However, due to the misleading exposure attribution with interviews, the risk of bias was critical, and the studies were improper for the meta-analysis.

Lead exposure was reported to play an important role in the occurrence and development of HF (Chen et al., 2021) and blood lead levels are associated with the risk of hypertension in the general population (Tsoi et al., 2021). However, the inconsistency of findings related to LV structure and function demonstrates that there is still insufficient evidence to confirm an association (Navas-Acien et al., 2007). For this pollutant, our meta-analysis results showed only an association with systolic function, which deserves further investigation. These associations could be supported by experimental studies in rats, which showed depressed myocardial contractility due to exposure to lead and cadmium (Kopp et al., 1980; Prentice and Kopp, 1985; Protsenko et al., 2020). As for the arsenic associations, we have to interpret results on lead with caution due to the limited number of studies.

4.1.5. Pesticides

Only two studies included in the systematic review examined the effects of pesticides, specifically persistent POPs, on LV structure and systolic and diastolic dysfunction (Burroughs Peña et al., 2020; Sjöberg Lind et al., 2013). POPs are synthetic chemicals widely used in various industries and consumer products, known for their ability to persist in the environment, resist degradation, and accumulate in living organisms (Fitzgerald et al., 2014). They have been associated with toxicity, carcinogenicity, and endocrine-disrupting effects (Bonefeld-Jørgensen et al., 2014). POPs cause a variety of adverse health effects (Guo et al., 2019) and some authors recently suggested a potential association between historical exposure to POPs and increased risk of CVDs (Henríquez-Hernández et al., 2017). The findings showed by Burroughs Peña and colleagues and Lind and colleagues, who reported some associations between exposure to pesticides and structural and functional cardiac parameters, suggest that more investigation of their role in causing LVD is still needed (Burroughs Peña et al., 2020; Sjöberg Lind et al., 2013). In fact, Lind and colleagues investigated only 3 functional parameters, LV EF, E/A ratio, IVRT, not taking into consideration structural parameters. Moreover, Peña and colleagues showed a critical risk of bias in exposure assessment, implying low confidence in the results. For these toxic chemicals, it was not possible to perform a meta-analysis due to the insufficient number of effect size estimates.

4.2. Strengths and limitations

Strengths of this review include a specific and well-defined search strategy, a larger sample size of LVD cases, and being the first systematic review examining the relationship between multiple parameters of LVD and environmental contaminants. However, some studies have limitations as not all potential confounding factors were measured, possibly introducing bias and affecting the meta-analysis results.

The review provides a quantification of the relationship between chemical substances and the risk of HF based on a large number of samples from population-based studies. However, detailed subgroup analyses for specific groups like the elderly and children were not feasible. Additionally, the study confirms a statistically significant association between outcome-pollutants effect estimates that meet a minimum number of similar measures. Further focused studies could potentially provide confirmations for other outcome-pollutant pairs, including unexplored compounds.

Specifically, two studies evaluating air pollution exposure and two studies evaluating heavy metals exposure were found to have a serious or critical risk of bias due to the absence of socioeconomic status information and no use of geocoded home addresses. This limitation hinders our ability to observe risks with sufficient confidence and stratify the observations in groups of sensitive subjects, limiting our understanding of the risk associations between environmental exposures and LVD.

For instance, the absence of adjustment for socioeconomic status in some studies may limit understanding associations between environmental exposures and LVD. Specifically, of the included studies, two studies evaluating air pollution exposure and two studies evaluating heavy metals exposure were found to have a serious or critical risk of bias. As for air pollution, the absence of socioeconomic status information and no use of geocoded home address lowered the confidence for Dominguez-Rodriguez and colleagues (Dominguez-Rodriguez et al., 2013) and Van Hee and colleagues (Van Hee et al., 2009). Regarding heavy metals, no information on socio-economic status confounding was included by Tepper and colleagues (Tepper et al., 2001) and Osorio-Yáñez and colleagues (Osorio-Yáñez et al., 2015). Therefore, a serious limitation to improving our knowledge of the risk associations between environmental exposures and LVD is the lack of effect to observe the risks with sufficient confidence and stratify the observations in groups of sensitive subjects.

Governmental authorities have recently recognized the value of using epidemiological data in risk assessment and have recommended incorporating human epidemiological data in the risk assessment process (Burns et al., 2019). To investigate the progression from subclinical cardiac dysfunction to incident clinical HF, longitudinal studies and case-control studies (Sjöberg Lind et al., 2013) focusing on the effect of environmental exposure to chemicals and mixtures on markers of LVD in the human population are needed in the future. Although the current conclusions of the review have been cautious in suggesting potential risks, more studies in this research area may uncover more significant risks associated with pollutants, and this expectation is supported by the extensive amount of toxicological data available.

5. Conclusion

This review explores the relationship between environmental contaminants and LVD, a major risk factor for HF. It identifies associations between pollutants like air pollution and heavy metals with increased LVD risk. Meta-analysis confirms an increased risk with exposure to PM10, PM2.5, NO2, lead, and arsenic. Nonetheless, the evidence concerning metal exposure has limited confidence due to residual biases and the limited number of consistent studies. Further research, standardized methodologies, and considering susceptible populations are urged including the elderly. Longitudinal studies with objective exposure quantification are recommended to confirm some unclear associations. Also, NAMs are suggested to deepen the knowledge on causality links and support the development of AOPs. Preventing heart failure and improving cardiovascular health through early risk identification and upstream interventions is proposed as effective cardiovascular health mitigation strategy. Overall, the review underscores the importance of

addressing environmental risk factors for better cardiovascular well-being.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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