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Left ventricular diastolic dysfunction and cardiovascular disease in different ambient air pollution conditions: A prospective cohort study

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Left Ventricular Diastolic Dysfunction and Cardiovascular Disease in Different Ambient Air

Pollution conditions: A prospective cohort study

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Abstract

Although previous studies indicated that the left ventricular diastolic dysfunction (LVDD) is associated with cardiovascular disease (CVD), it remains unclear whether effects would be enhanced or accelerated by long-term air pollution exposure. During 4.65 years (107,726 person-years) of follow-up, 942 cases of CVD events incident were identified among 23,143 participants from the China Hypertension Survey (CHS). Grading diastolic dysfunction was based on Recommendations for the evaluation of left ventricular diastolic function by echocardiography (2009). The annual average $PM_{2.5}$, PM_{10} and NO_2 concentrations were obtained by the chemical data assimilation system. Cox proportional hazards models were employed to estimate hazard ratios (HRs) for CVD in relation to LVDD. At baseline, the participants' mean age was 55.7 years, 46.8% were male. Compared to normal group, the HR (95% CI) of LVDD was 1.27 (1.07-1.50) after adjusting for all covariates. When stratified by ambient air pollution, we found that in middle and worst third $PM_{2.5}$ areas, increased CVD risk was associated with increasing LVDD grade, both *P* for trend < 0.05; The HRs (95% CI) of the CVD incidence were 1.52 (0.66-3.47), 4.97 (1.76-14.03) and 4.07 (1.44-11.49) for severe LVDD in the best, middle and worst third $PM_{2.5}$ areas, respectively. Similar results were also presented for PM_{10} and NO_2. In conclusion, our study highlights a stronger detectable adverse association between LVDD with CVD in worse ambient air quality assessed by any of the three primary ambient air pollutants ($PM_{2.5}$, PM_{10} and NO_2). Our study calls for appropriate interventions to reduce air pollution, which may promote great benefits to public health potentially by providing protection against the adverse CVD events.

Key Words: Air pollution; cardiac function; cardiovascular disease; prospective cohort study; population

1. INTRODUCTION

Air pollution is a growing public health concern of global significance, and almost 90% of the world's population estimated to currently live in places where air quality levels exceed World Health Organization (WHO) guidelines (WHO, 2018). Globally, air pollution was the 4th highest ranking risk factor for mortality, with just less attributable deaths than high systolic blood pressure, tobacco and dietary risks (Brauer et al., 2021). Previous data well indicated that the global mortality and morbidity burden of cardiovascular disease (CVD) associated with fine and coarse particles and nitrogen dioxide (NO$_2$; Lee et al., 2014; Pranata et al., 2020) , which are dramatically greater than what has been thought up to now (Hoek et al., 2013; Mannucci et al., 2019), especially in middle-income or low-income countries (Cohen et al., 2017; Yusuf et al., 2020). Moreover, the urgency to combat air pollution is not diminished, but instead heightened in the context of the COVID-19 pandemic.

Left ventricular diastolic dysfunction (LVDD), an early sign of cardiac dysfunction, is a predictor of fatal and/or nonfatal cardiovascular events (Kuznetsova et al., 2014; Sharp et al., 2010). It was reported that even in asymptomatic patients, mild or moderate diastolic dysfunction was associated with a higher mortality in comparison with normal ones (Nagueh et al., 2009; Redfield et al., 2003). Although air pollution has been demonstrated a close association with heart failure (Bai et al., 2019; Beggs et al., 2019) or cardiac dysfunction (Aung et al., 2018; Golshahi et al., 2016), little was known about whether the effects of LVDD on CVD incidence would be changed by air pollution. Similarly, Afoakwah et al. (2020) has reported that acute exposure to pollution increases readmissions to hospitals and was more evident among those suffering from heart failure in Queensland.

In the current study, a large-scale prospective cohort from the China Hypertension Survey (CHS), we investigated the relationship between LVDD with CVD in different ambient air pollution conditions.
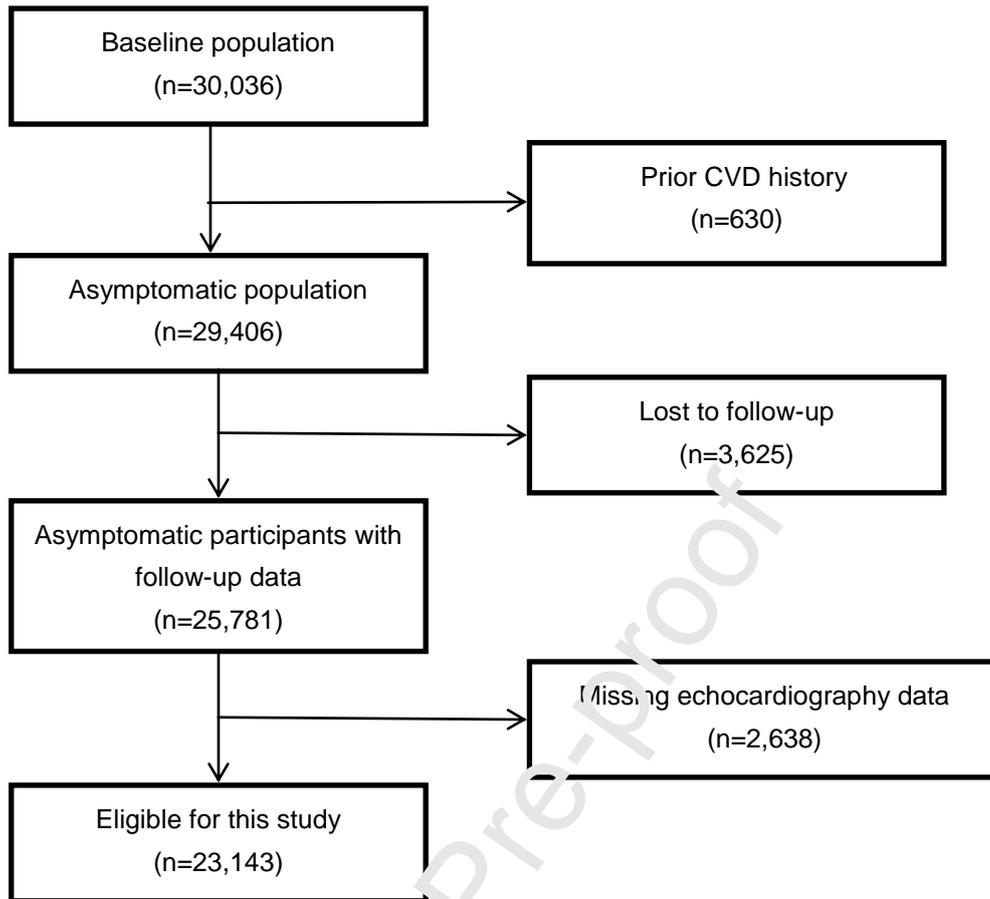
We hypothesized that individuals with LVDD have a higher risk of serious fatal/unfatal CVD events in worse ambient air quality compared with those in better conditions.

2. MATERIALS & METHODS

2.1 Study design and population

Baseline data was from the CHS a national representative large scale cross-sectional study, and the detailed description of the study has been published previously (Wang et al., 2018a; Wang et al., 2018b). In brief, the CHS employed 4-stage stratified multistage random sampling method to obtain nationwide aged ≥ 35 years subjects from 14 provinces in 2012-15. And a recent follow-up survey about 5-year CVD and all-cause mortality was conducted from 2018-19. The written informed consent was obtained from each participant. The Ethics Committee of Fuwai Hospital (Beijing, China) approved the study.

After excluding 630 participants with prior CVD history at baseline, 3,625 without follow-up results, and 2,638 participants with missing echocardiography data, finally, 23,143 participants from 14 provinces and 30 districts were included for the finally analysis (Fig. 1).

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┌─────────────────────────┐
│   Baseline population    │
│      (n=30,036)          │
└─────────────────────────┘
              │              ┌─────────────────────────┐
              ├─────────────▶│    Prior CVD history     │
              │              │       (n=630)            │
              ▼              └─────────────────────────┘
┌─────────────────────────┐
│  Asymptomatic population │
│      (n=29,406)          │
└─────────────────────────┘
              │              ┌─────────────────────────┐
              ├─────────────▶│   Lost to follow-up      │
              │              │      (n=3,625)           │
              ▼              └─────────────────────────┘
┌─────────────────────────┐
│ Asymptomatic participants│
│     with follow-up data  │
│      (n=25,781)          │
└─────────────────────────┘
              │              ┌─────────────────────────┐
              ├─────────────▶│ Missing echocardiography │
              │              │   data (n=2,638)         │
              ▼              └─────────────────────────┘
┌─────────────────────────┐
│  Eligible for this study │
│      (n=23,143)          │
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Fig. 1. Flow diagram of participants recruitment. CVD, cardiovascular diseases.

2.2 CVD Ascertainment

CVD was defined as fatal or nonfatal coronary heart disease (CHD) and stroke in this study. Acute myocardial infarction (MI) was identified as a change in biochemical markers of myocardial necrosis accompanied by ischemic symptoms, pathological Q waves, ST-segment elevation or depression, or coronary intervention. CHD included MI, percutaneous transluminal coronary angioplasty (PTCA), stent implantation and coronary artery bypass grafting (CABG). CHD death included all fatal events resulting from MI or other coronary deaths. Stroke included clinical signs and symptoms of subarachnoid or intracerebral hemorrhage or cerebral infarction, which were rapidly developing signs of focal (or global) disturbances in cerebral function lasting >24 hours without an apparent nonvascular cause.

2.3 Baseline LVDD assessment

The clinical evaluation of left ventricular function was conducted in baseline survey field, which was based on echocardiography, and the collection data of cardiac ultrasound examination in the questionnaire included M-mode and two-dimensional measurements, heart value structure, Doppler flow parameters. All experienced echocardiographers were trained using the protocol. And the difficult-to-diagnose special cases were discussed with the experts from the coordination center.

Grading diastolic dysfunction was based on Recommendations for the evaluation of left ventricular diastolic function (LVDF) by echocardiography (2009) (Nagueh et al., 2009). The grading scheme is mild/grade I (impaired relaxation pattern), moderate/grade II (pseudo normal), and severe/grade III (restrictive filling) or grade III. Abnormal LV diastolic function group included grade I- III totally.

2.4 Ambient and indoor air pollution exposure assessment

The annual average $PM_{2.5}$, PM_{10} and NO_2 concentrations were obtained from a high-resolution air quality reanalysis dataset over china from 2013 to 2018 (Kong et al., 2021) which was produced by the chemical data assimilation system (ChemDAS) developed by the Institute of Atmospheric Physics, Chinese Academy of Sciences. This dataset has high spatial (15 Km) and temporal (1 hour) resolutions, and the qualities of which have been assessed by the cross-validation method and independent datasets, suggesting a high accuracy. The above air quality reanalysis data were interpolated to each subject of current study according to his/her residential address via the bilinear interpolation method. In the current study, we explored the effect of air pollutants annual average concentrations of the baseline survey year for each participant; except for 317 participants who were registered in December 2012, their exposure data estimated by the annual average concentrations of 2013.

Each participant was asked to provide detailed information about indoor air pollution exposure

related to solid heating fuels and passive smoke. Participants who used heating in winter were asked additional questions about the primary fuel type used, which included central heating (a system generating heat in a centralized location distant from residential areas and distributing the heat to individual households via underground hot water or steam pipes) (Yu et al., 2018), gas, coal, wood/charcoal, crop straw and other unspecified fuels. Coal, wood /charcoal, crop straw was considered "solid fuels," while gas and central heating were considered "clean fuels" because they tended to generate much less air pollution than solid fuels (Wang and Luo 2018). Nonsmokers were asked "Are you exposed to second-hand smoke usually?", "How many days per week are you exposed to second-hand smoke usually?" Those who answered 'None' were categorized as non-exposed to second-hand smoke and all others were categorized as exposed to second-hand smoke.

2.5 Baseline covariates

At baseline survey, trained workers administered a standardized electronic questionnaire to collect information on demographic characteristics (age, sex, ethnicity, area, habitation altitude and education level), lifestyle behaviors (smoking and alcohol consumption), indoor air pollution and family CVD history. Habitation altitude of each survey sites were estimated from 2400 homogenized surface stations (Hu et al., 2017). Blood pressure was measured with the OMRON HBP-1300 Professional Portable Blood Pressure Monitor (OMRON, Kyoto, Japan) three times, and the average of the three readings was used for analysis. Body weight was obtained using OMRON body fat and weight measurement device (V-body HBF-371; Omron, Kyoto, Japan). Laboratory analyses were performed by a central core laboratory (Beijing Adicon Clinical Laboratories, INC, Beijing, China) using standardized techniques. All blood samples were obtained in the morning after at least 8 hours overnight fast.

2.6 Statistical Analysis

Baseline characteristics of the study population were described by gender, using numbers with the corresponding percentages for categorical variables and means with the standard deviation for continuous variables, group differences were assessed by χ^2 test, respectively.

The survival (free of CVD events incidence) status was estimated using the Kaplan-Meier method and the comparison between different survival curves was made by the Log-rank test (Goel et al. 2010). Cox proportional hazards models (Bradburn et al., 2003) were employed to estimate hazard ratios (HRs) and 95% CIs for CVD in relation to LVDD or grade I- III LVDD in Table2. Fully-adjusted multivariable model (Model 5 in Table2) included the following covariates: age, sex, areas (urban, rural), habitation altitude (<1500m, 1500-3500m, >3500m), ethnicity (Han, minority), education (primary, middle, high), smoke (current, former, never), drinking, family history of CVD, obesity (normal, overweight, obesity), hypertension, hyperlipidemia, diabetes, three ambient pollutants ($PM_{2.5}$, PM_{10} and NO_2) and indoor air pollution (solid heating fuels and passive smoke). We substituted all primary air pollutants ($PM_{2.5}$, PM_{10} and NO_2) by a composite latent variable (a linear combination of all air pollutants) through principal component analysis (PCA) which is an excellent approach to cope with collinearity among air pollutants, and then included this latent variable in the model (Stafoggia et al., 2017).

Cox regression models were stratified by 3-level (best, middle, and worst third) ambient air pollution ($PM_{2.5}$, PM_{10} and NO_2) exposure conditions in Table3.The three pollutants level were categorized into 3 groups according to the tertiles of the value, and the best middle and worst third $PM_{2.5}$ group were <51.96, 51.96~67.93 and >67.93μg/m³, for PM_{10} were <79.59, 79.59~96.57 and >96.57μg/m³, and for NO_2 were <22.76, 22.76~31.4 and >31.4μg/m³.

All the analyses were carried out using SAS version 9.3 (SAS institute, Cary, NC, USA), and the figures were completed though Python. The two-sided P values <0.05 were considered statistically significant.

3. RESULTS

3.1 Summary statistics and the population characteristics

23,143 participants were considered for this study after exclusion (Fig. 1). During 4.65 years (107,726 person-years) of follow-up, 942 cases of CVD events incident were identified in total. Of the total number of CVD cases, 66.14% (n=623) were stroke, 31.42% (n=296) were CHD, and 2.44% (n=23) were both stroke and CHD.

The baseline demographic characteristics of the participants were presented in Table 1. At baseline, the mean age of participants was 56.7 years, 46.8% were male, the crude prevalence of GradeI~III LVDD were 47.32%, 1.49% and 1.25%. The annual average ambient $PM_{2.5}$, PM_{10} and NO_2 concentration of the baseline survey year were 61.66, 92.52 and 28.93μg/m^3. 26.88% participants reported solid fuel use at baseline and 9.56% reported exposure to secondhand smoke. And male subjects tended to have higher blood pressure, triglycerides, fasting plasma glucose, and higher prevalence of LVDD and lower indoor pollutants exposure level.

3.2 LVDD and CVD

The CVD incidence was 4.21 per 1000 person-year and 13.32 per 1000 person-year for normal LVDF and LVDD group, P<0.001; 13.41, 10.63 and 12.87 per 1000 person-year for participants with the mild, moderate, and severe LVDD, respectively.

The relationships of LVDD with CVD events in the crude and multivariate models were displayed in

Table 2. Compared to normal LVDF group, the hazard ratio (95% CI) of LVDD was 3.15 (2.71-3.66)

before adjusting for any covariates; and 3.17 (2.72-3.68), 2.56 (1.56-4.18) and 3.22 (1.94-5.34) for

mild, moderate, and severe LVDD, respectively (P_{trend} <0.001). After adjusting for various

confounders, a significant association was observed among those with LVDD in full adjusted model

(HR,95%CI: 1.27,1.07-1.50); and an elevated risk of CVD was found with increasingly grade of

LVDD (P_{trend} =0.034).

3.3 LVDD and CVD stratified by ambient air pollution

The cumulative survival probability of different grades of LVDD with CVD in the population by

different levels of ambient $PM_{2.5}$ were presented in Figure .' (all Log-rank P＜0.001), which illustrated

the prevalence of CVD for severe LVDD group was higher in the middle (B) and worst(C) third $PM_{2.5}$

group compared to the best $PM_{2.5}$ conditions (A)

Similar results were found in PM_{10} (Fig. S1) and NO_2 (Fig. S2).
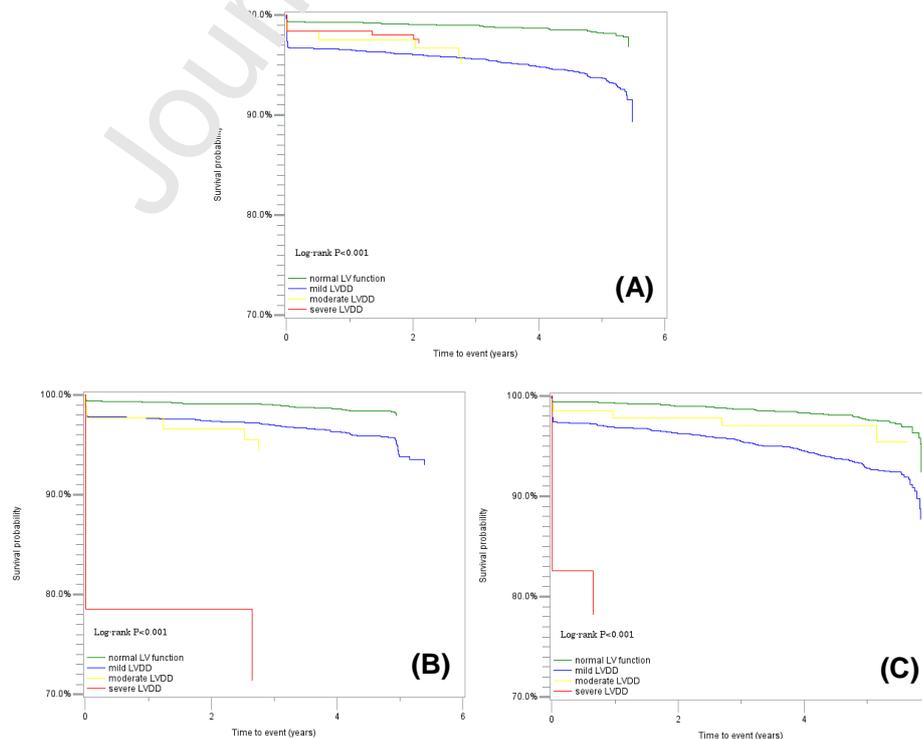
Figure 2. Kaplan-Meier CVD survival curves for participants with normal vs. mild ormoderate or severe diastolic function in different ambient PM$_{2.5}$ condition exposure. Best (A), middle (B) and worst(C) third PM$_{2.5}$ group.

Multivariate-adjusted HRs for the associations of LVDD with the CVD incidence risk by ambient air pollution were presented in Table 3. Only in middle and worst third PM$_{2.5}$ areas, increased CVD risk was associated with increasing LVDD grade, both *P* for trend <0.05. The HRs (95% CI) of the CVD incidence were 1.52 (0.68-3.44), 4.97 (1.76-14.03) and 4.07 (1.44-11.49) for severe LVDD in the best, middle and worst third PM$_{2.5}$ areas, respectively. And for those exposure to the middle and worst third PM$_{10}$ or NO$_2$, severe LVDD was also significantly associated with greater increased CVD incidence. Similar results were found among male (Table S1.) and female (Table S2.) participants.

4. DISCUSSION

To our knowledge, this is the first large-scale nationwide prospective cohort study evaluating the relationship between LVDD and CVD in different ambient air pollution conditions. It was demonstrated a significant association between LVDD with an increase risk in cardiovascular mobility and mortality. And those with severe LVDD grade seemed to carry greater risk on CVD in the worse ambient air pollution conditions assessed by any of the three primary ambient air pollutants (PM$_{2.5}$, PM$_{10}$ and NO$_2$). Our results suggested that ambient air pollution might be a potential effect modifier which could increase the long-term CVD incidence caused by LVDD.

Our results were consistent with prior studies suggesting that LVDD was the causation of fatal and nonfatal CVD. For all our participants, the risk of 5-year CVD was increased with LVDD (HR=1.27) and the increasing LVDD grade (*P* trend =0.034). In accordance, Sharp et al. (2010) performed

Conventional and tissue Doppler echocardiography on 980 hypertensive participants in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and investigated that the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E') was the strongest predictor of first cardiac events, and a unit rise in the E/E' ratio was associated with a 17% increment in risk of a cardiac event (HR=1.17, CI:1.05-1.29; P = 0.003). And E/E' ratio has been extensively used both clinically and in multidisciplinary clinical research as a noninvasive surrogate for left ventricular filling pressure and LVDD (Sharifov et al., 2016). The previously published analysis of a cross-sectional survey of 2,042 randomly selected residents of Olmsted County, Minnesota, aged 45 years or older showed that in multivariate analysis, controlling for age, sex, and EF, mild diastolic dysfunction (HR, 8.31 [95% CI, 3.00-23.1], $P<.001$) and moderate or severe diastolic dysfunction (HR, 10.17 [95% CI, 3.28-31.0], $P<.001$) were predictive of all-cause mortality (Redfield et al., 2003).

Although air pollution has been demonstrated a close association with heart failure (Bai et al., 2019; Beggs et al., 2019) or cardiac dysfunction (Aung et al., 2018; Golshahi et al., 2016), in the current study, we firstly found that worse ambient air exposure would approximately increase 3-5-fold the significantly association between severe LVDD and CVD incidence according to the stats in Table 3. Similar to our results, Afoakwah et al. (2020) found that acute exposure to pollution increases readmissions to hospitals within 3-12 months after discharge and is more evident among those suffering from heart failure; furthermore, they also found that exposure to extreme levels of pollution increases the use of health services among heart diseases and the study also estimated that air pollution accounts for a significant amount of healthcare expenditure in Queensland.

The possible explanation and mechanisms: i) for general population: $PM_{2.5}$-induced detrimental effects through multiple mechanisms, including endothelial injury, an enhanced inflammatory response,

oxidative stress, autonomic dysfunction, and mitochondria damage as well as genotoxic effects. These effects can lead to a series of physiopathological changes including coronary artery atherosclerosis, hypertension, an imbalance between energy supply and demand to heart tissue, and a systemic hypercoagulable state (Meng et al., 2016; Nogueira, 2009). PM_{10} had an acute pathogenic effect on the incidence of CVD, particularly arrhythmia (Zhang et al., 2021). The mechanisms by which PM_{10} affect the health of the circulatory system remains to be elucidated, and some studies have reported that ambient PM_{10} usually combine with $PM_{2.5}$ can trigger cardiovascular events by affecting blood viscosity, vascular fibrinogen and C-reactive protein (Donaldson et al., 2001). Exposures to NO_2 cause airway inflammation, effects on blood cells, and increased susceptibility of airway epithelial cells to injury from respiratory viruses which increase the burden and damage circulatory system (Frampton et al., 1989; Goldstein et al., 1973). In previous study Frampton MW and his colleagues found that NO_2 effect was unlikely to be of clinical significance for healthy subjects, however, individuals with underlying chronic disease may be more susceptible to such effects (Frampton et al., 2002). ii) However, it has been still unclear whether there were different mechanisms for the impact of the three specific pollutants among different grades LVDD group. In this study, we found that air pollution could enhance or accelerate the effect of serious LVDD leading to CVD, most probably because people with LVDD (especially for serious grade), appear to be more vulnerable which may be due to a combination the above-mentioned air pollution effect and other factors including comorbidities (e.g., metabolic syndrome), socioeconomic status, lifestyle, and treatment adherence (de las Fuentes et al., 2007; Rahman et al., 2015).

5. STRENGTH & LIMITATIONS

The current study firstly reported the effect of long-term exposures to ambient air pollutants on

LVDD burden. The strengths of this study include a large well-representative sample size of prospective follow-up results, high accuracy estimation of ambient air pollution and various covariates in baseline survey which were the potential confounding factors in the adjusted model. Moreover, indoor pollution which was an independent CVD risk factors (Cao et al., 2021), has been considered in the full-adjusted model to make up for the deficiency/limitation of the most of the previous studies about ambient pollutants and CVD events.

However, several limitations should be noted in this study. First, the follow-up period of our cohort was only around 5 years and some potential outcomes (fatal/nonfatal CHD and stroke event) could not be observed which might underestimate the HRs in the current study. Additionally, less than 3% our free-living participants were diagnosed as moderate (the rude prevalence of Grade II was 1.49%) or Severe (Grade III was 1.23%) LVDD, which reduced the statistical power of the analysis about the separate three LVDD grades. Third, we did not have data on some important covariates, such as dietary habit, so we could not take them into account in the all-adjusted model. Finally, we defined and evaluated the LV diastolic function according to the 2009 American Society of Echocardiography (ASE) guidelines, not the latest 2016 version, because the protocol was developed in 2012 to 2014, which may decrease the specificity for the older population.

6. CONCLUSIONS

LVDD was significantly associated with an increase risk in cardiovascular mobility and mortality, and those with severe LVDD grade seemed to carry greater risk on CVD in the worse ambient air pollution conditions assessed by any of the three primary ambient air pollutants ($PM_{2.5}$, PM_{10} and NO_2). Confirmatory studies and randomized clinical trials would further strengthen our findings. The current

study provided a reference that the effect of LVDD leading to CVD would probably be enhanced or accelerated by long-term air pollution exposure. Thus, for those with cardiac dysfunction, other modifiable cardiovascular disease risk factors control should be much stricter, and adequate personal protective equipment of air pollution should be more necessary when they exposure to a certain concentration of air pollutants. Furthermore, appropriate government interventions to reduce air pollution may promote great benefits to public health potentially by providing protection against the adverse CVD events.

Disclosures

None declared.

Table 1. Baseline characteristics of the study participants

	Total (n=23,143)	Male (n=10,838)	Female (n=12,305)	P value
Demographics				
Age (years)	56.7±13.1	57.5±13.2	56.0±12.9	<0.001
Rural (%)	13,159(56.86)	6,049(55.81)	7,110(57.78)	0.003
Habitation altitude	445.30±693.40	435.20±691.38	454.20±695.06	0.038
Education (≥Middle school)	10,916（47.17）	5,989（55.26）	4,927（40.04）	<0.001
Clinical characteristics				
Smoking (%)				
Current	5,845（25.25）	5,414（49.95）	431（3.50）	<0.001
Former	1,401（6.05）	1,301（12.00）	100（0.81）	
Never	15,897（68.69）	4,123（38.04）	11,774（95.68）	
Alcohol drinking (%)	6,475(27.98)	5,611(51.77)	864(7.02)	<0.001
Family history of CVD (%)	2,750 (11.88)	1,221(11.27)	1,529(12.43)	0.007
SBP (mmHg)	132.64±20.41	133.37±19.48	132.00±21.17	<0.001
DBP (mmHg)	77.33±11.10	79.27±11.18	75.62±10.75	<0.001
BMI (Kg/m^2)	24.56±3.49	24.47±3.37	24.73±3.59	<0.001
Total cholesterol (mmol/L)	4.79±0.99	4.70±0.96	4.87±1.02	<0.001
HDL-cholesterol (mmol/L)	1.36±0.34	1.32±0.35	1.40±0.34	<0.001
LDL-cholesterol (mmol/L)	2.81±0.82	2.75±0.70	2.86±0.84	<0.001
Triglycerides (mmol/L)	1.45±1.02	1.49±1.13	1.42±0.92	<0.001

FPG (mmol/L)	5.63±1.55	5.68±1.58	5.58±1.52	<0.001
Medical therapy (%)				
Anti-hypertensive drug	4,613(19.93)	2,102(19.39)	2,511(20.40)	>0.05
Hypoglycaemic drug	1,124(4.86)	511(4.71)	613(4.98)	>0.05
Statin	820(3.54)	368(3.40)	452(3.67)	>0.05
LVDD (%)				
Mild (Grade I)	10,952（47.32）	5,438（50.18）	5,514（44.81）	<0.001
Moderate (Grade II)	345（1.49）	188（1.73）	157（1.28）	
Severe (Grade III)	285（1.23）	146（1.33）	139（1.13）	
Annual average ambient pollutants				
$PM_{2.5}$ (μg/m³)	61.66±23.11	61.40±22.90	61.88±23.29	>0.05
PM_{10} (μg/m³)	92.52±41.14	92.42±40.78	92.60±41.45	>0.05
NO_2 (μg/m³)	28.93±12.93	29.02±12.84	28.85±13.10	>0.05
Indoor Pollutants				
Solid heating fuels (%)	6,221(26.88)	2,830(26.11)	3,391(27.56)	0.013
Secondhand smoke (%)	2,213(9.56)	495(4.57)	1,718(13.96)	<0.001

Numbers are mean±SD or no.(%). BMI, indicates body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; LVDD, left ventricular diastolic dysfunction, included impaired relaxation pattern (Grade I), pseudo normal (Grade II), and restrictive filling (Grade III).

Table 2. CVD Hazard ratio (95% CI) in relation to LVDD

Characteristics	LVDD	Three-level LVDD			P_{trend}
		Mild	Moderate	Severe	
Person years	53,611.59	50,768.69	1,599.54	1,243.36	--
No of cases	714	681	17	16	--
Incidence rate[†]	13.32	13.41	10.63	12.87	--
Cox regression					
Crude model	3.15 (2.71-3.66)	3.17 (2.72-3.68)	2.56 (1.56-4.18)	3.22 (1.94-5.34)	<0.001
Adjusted Model 1[a]	1.45 (1.23-1.71)	1.46 (1.24-1.72)	1.40 (0.86-2.31)	1.55 (0.93-2.58)	<0.001
Adjusted Model 2[b]	1.43 (1.21-1.68)	1.43 (1.21-1.68)	1.34 (0.82-2.20)	1.48 (0.89-2.48)	<0.001
Adjusted Model 3[c]	1.29 (1.09-1.53)	1.29 (1.09-1.53)	1.30 (0.79-2.13)	1.32 (0.78-2.13)	0.028
Adjusted Model 4[d]	1.30 (1.10-1.53)	1.29 (1.09-1.53)	1.30 (0.79-2.14)	1.34 (0.79-2.28)	0.025
Adjusted Model 5[e]	1.28 (1.08-1.52)	1.28 (1.08-1.51)	1.28 (0.78-2.11)	1.53 (0.90-2.60)	0.030

†Incident rate per 1000 person years.

a Model 1: Crude model + adjusted for age and sex.

b Model 2: Model 1+ adjusted for areas, habitation altitude, ethnicity, education, smoke, drinking and family history of CVD.

c Model 3: Model 2 + obesity, hypertension, hyperlipidemia, diabetes.

d Model 4: Model 3 + adjusted for ambient $PM_{2.5}$, PM_{10} and NO_2.

e Model 5: Model 4 + adjusted for indoor air pollution (solid heating fuels and passive smoke).

LVDD, left ventricular diastolic dysfunction.

Table 3. Hazard ratio (95% CI) of LVDD associated with CVD in stratified analysis by ambient air pollution

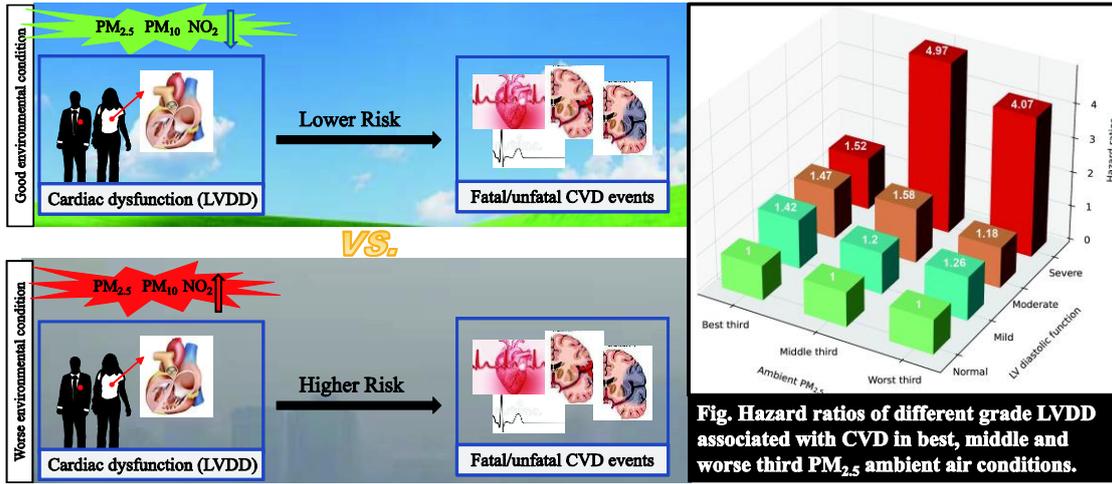| LV diastolic function	Ambient $PM_{2.5}$			Ambient PM_{10}			Ambient NO_2		
	Best third ($<51.96\mu g/m^3$)	Middle third ($51.96\sim67.93\mu g/m^3$)	Worst third ($>67.93\mu g/m^3$)	Best third ($<79.59\mu g/m^3$)	Middle third ($79.59\sim96.57\mu g/m^3$)	Worst third ($>96.57\mu g/m^3$)	Best third ($<22.76\mu g/m^3$)	Middle third ($22.76\sim31.4\mu g/m^3$)	Worst third ($>31.4\mu g/m^3$)
Normal	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Mild	1.42 (1.05-1.92)	1.20 (0.86-1.67)	1.26 (0.96-1.65)	1.42 (1.05-1.92)	1.15 (0.86-1.54)	1.44 (1.05-1.98)	0.99 (0.72-1.36)	1.29 (0.97-1.71)	1.48 (1.10-1.99)
Moderate	1.47 (0.63-3.40)	1.58 (0.63-3.97)	1.18 (0.51-2.74)	1.46 (0.63-3.83)	1.56 (0.71-3.40)	1.14 (0.4-3.19)	1.70 (0.61-4.70)	1.79 (0.89-3.61)	0.82 (0.29-2.26)
Severe	1.52 (0.68-3.44)	4.97 (1.76-14.03)	4.07 (1.44-11.49)	1.52 (0.68-3.44)	4.24 (1.68-10.71)	4.76 (1.4-15.75)	1.34 (0.67-2.68)	6.52 (1.53-27.69)	4.35 (1.33-14.28)
P_{trend}	>0.05	0.021	0.045	>0.05	0.018	0.022	>0.05	0.024	0.010

All models were adjusted age, sex, areas, habitation altitude, ethnicity, education, smoke, drinking, family history of CVD, obesity, hypertension, hyperlipidemia, diabetes, and indoor air pollution (solid heating fuels and passive smoke). LV, left ventricular.

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Graphical Abstract

Fig. Hazard ratios of different grade LVDD associated with CVD in best, middle and worse third PM$_{2.5}$ ambient air conditions.

Highlights

What is new?

- Although previous studies indicated that the left ventricular diastolic dysfunction (LVDD) associated with cardiovascular disease (CVD), it remains unclear whether effects would be enhanced or accelerated by long-term air pollution exposure.

- This is a large well-representative sample size prospective cohort study with high accuracy estimation of various ambient air pollutants and household air pollution.

- A stronger detectable adverse association between LVDD with CVD in worse ambient air quality assessed by anyone of the three primary ambient air pollutants ($PM_{2.5}$, PM_{10} and NO_2).

What are the clinical implications?

- For those with cardiac dysfunction, other modifiable risk factors control should be much stricter and adequate personal protective equipment of air pollution should be more necessary when they are exposure to a certain concentration of air pollutants.

- Appropriate interventions to reduce air pollution may promote great benefits to public health potentially by providing protection against the adverse CVD events.

Disclosures

None declared.

Author Contributions Statement

Zengwu Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Zengwu Wang, Congyi Zheng.

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