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ORIGINAL RESEARCH ARTICLE

A case-crossover study on the effect of short-term exposure to moderate levels of air pollution on the risk of heart failure

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Abstract

Aims Exposure to high levels of air pollution in industrialized urban areas is associated with an increased risk of heart failure (HF). On most days, the majority of European cities are only moderately affected by air pollution. The aim of this study was to evaluate the association between short-term exposure to moderate levels of air pollution with the risk of HF in a city with good air quality.

Methods and results We recruited 576 patients (median age 82 years; 58.2% men) admitted to a large university hospital in Central Germany for HF to participate in a hospital-based, bidirectional, case-crossover study. Diagnosis of HF and symptom onset were verified individually. The effect of short-term exposure to nitrogen dioxide (NO_2), particulate matter (PM_{10}), and ozone (O_3) on the risk of HF was estimated using linear and non-linear (categorized) multivariate analyses for three different lag times (1, 2, and 3 days before HF onset). Air pollution variables were adjusted to the date of HF symptom onset. During the study period, the average daily concentration of air pollutants was only moderate and reflects the average European background air pollution. In particular, the concentration of air pollutants ranged from 2 to 63.39 $\mu g/m^3$ (median = 17.46 $\mu g/m^3$) for NO_2, from 2 to 125.88 $\mu g/m^3$ (median = 44.61 $\mu g/m^3$) for O_3, and from 2.21 to 166.79 $\mu g/m^3$ (median = 18.67 $\mu g/m^3$) for PM_{10}. We did not find a linear or non-linear association between short-term exposure to NO_2, O_3, or PM_{10} and risk for HF at all lag times in the overall population and subgroups.

Conclusions In an area with only moderate air pollution, short-term exposure to major air pollutants does not increase the risk for HF. Future studies should focus on a potential threshold effect of air pollution on HF risk as a basis for evidence-based development of statutory limits in highly polluted areas.

Keywords Heart failure; Air pollution; Pollutants; Nitrogen dioxide; Particulate matter; Ozone

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Introduction

Heart failure (HF) is a common, yet complex, clinical syndrome that affects 26 million people globally.[1] Especially, patients suffering from cardiac and non-cardiac co-morbidities, such as hypertension, coronary heart disease, diabetes, or chronic kidney disease, are more likely to develop HF.[2] With estimated annual costs of $108 billion,[3] HF is not only a burden on global public health care systems and societies, but it also adversely affects each patient who may experience severe symptoms, such as shortness of breath, fluid retention, or poor exercise tolerance.[4]

In addition to classical pathophysiological concepts, it has been suggested that short-term exposure to major air

pollutants might trigger the development and acute exacerbation of HF,[5–12] although results regarding the magnitude of the association and the specific air pollutant responsible for HF risk increases vary, and not all studies could consistently show a significant association.[13,14] For instance, a study undertaken in 26 large Chinese cities with particularly low air quality found a significant correlation between hospitalization for HF and concentrations of the major air pollutants of nitrogen dioxide (NO_2), carbon dioxide (CO_2), and particulate matter with diameters < 10 μm (PM_{10}).[7] A study involving seven large US cities, including New York, Chicago, and Los Angeles, showed an association between increasing levels of ambient carbon monoxide (CO) and admissions for HF, but results for other air pollutants were not significant.[6]

Although the effect of air pollution on the risk to develop HF has been characterized for dense urban areas with high levels of air pollution, less is known about this association in areas with good-to-moderate ambient air quality. For example, in a comprehensive and detailed meta-analysis on the global association of air pollution and HF,[15] average air pollution concentrations were two to three times higher than average concentrations found in urban areas in Germany.[16] Furthermore, several methodological issues in previous studies prevent generalization of the results. For example, most studies available[5–8,11,13,14] selected patients on the basis of their International Classification of Diseases (ICD) diagnostic codes, potentially leading to a misclassification bias caused by coding and/or diagnostic errors.[17] All available studies but one[12] have regarded the day of hospital admission as the day of HF onset.[5–11,13,14] However, HF symptoms often develop ≥1 day before hospital admission,[18] and allocation of the air pollution variables with the respective HF patient can be significantly biased.

To overcome these limitations, we thought that it would be useful to determine the influence of short-term exposure to major air pollutants on the risk of developing HF in an urban area with only moderate air pollution. Identifying a potential link between moderate air pollution and HF might help to enhance statutory limits of air pollution even in areas with presumably good ambient air and to achieve greater public health protection. We hypothesized that the short-term concentrations of the major ambient air pollutants, NO_2, PM_{10}, and O_3, would be associated with HF risk 1 to 3 days before the symptoms of HF develop. We used a case-crossover approach[19] to estimate the air pollution-dependent HF risk in a cohort of patients with a verified diagnosis and known onset of HF symptoms. Our study used a multivariable statistical model that also considers weather as a significant confounder.

Methods

Study design

This retrospective, hospital-based, case-crossover study was carried out at the Jena University Hospital in Central Germany after approval by the local Ethics Committee. The study area, Jena, is a city with 100 000 inhabitants in the centre of Europe and is a model region for studying the acute effects of environmental factors on human health, including air pollution and cardiovascular health.[20–23] Jena has a temperate climate with moderately cool winters and mild summers.[24]

The study period was from 1 January 2010 until 30 September 2015. Patient discharge data from patients ≥ 18 years of age living <10 km from Jena University Hospital (filtered by postal codes) were drawn from the hospital's patient data management system using the ICD, 10th revision codes for left ventricular failure (I50.1X) in the primary diagnostic position. Patient health records and all medical reports, including emergency records, together with echocardiography and laboratory results, were individually screened to verify the diagnosis of HF according to the 2016 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[25] and to determine the date regarding onset or exacerbation of HF-related symptoms, such as breathlessness or orthopnoea. Regular meetings were held during the study period to ensure consistent classification procedures. In the case of multiple admissions of a single patient during the study period, only the first admission was considered.

To identify subgroups at risk, cases were classified in patients suffering from HF with preserved (HFpEF), mid-range (HFmEF), and reduced ejection fraction (HFrEF) following the 2016 ESC guidelines.[25] Usually, patients with suspected HF receive basic laboratory diagnostic tests as well as an assessment of heart structure and left ventricular ejection fraction (LVEF) by echocardiography. Those with HFrEF showed a diminished LVEF of ≤40%; patients with HFmEF had an LVEF between 40% and 49%, elevated levels of brain natriuretic peptide (BNP ≥ 35 pg/mL), and a structural heart disease, such as left ventricular hypertrophy (LVH) or left atrial enlargement (LAE). Finally, patients with HFpEF had an LVEF ≥ 50%, elevated natriuretic markers, and LVH or LAE. Patients were not classified when LVEF was visually estimated and not quantified.

Exclusion criteria

Patients were excluded if (i) the admission was for another reason than HF or the diagnosis of HF could not be verified after screening the patient file, (ii) we were unable to

retrospectively determine the onset of HF symptoms or the onset was outside the study catchment area, or (iii) ≥5 days had passed between the onset or exacerbation of HF symptoms and hospital admission.

Environmental data

Air pollution data containing NO_2, O_3, and PM_{10} were provided by the Thuringian State Environmental Agency in Jena (longitude 11°35′E/latitude 50°56′N/altitude 140 m). Meteorological data, including ambient temperature, relative air humidity, and atmospheric pressure, were provided by the Meteorological Monitoring Station of the Jena University of Applied Sciences (longitude 11°34′E/latitude 50°55′N/altitude 215 m).

Statistical methods

Air pollution-dependent HF risk was determined by using a bidirectional case-crossover analysis. The case-crossover approach had previously been developed to determine a change in risk associated with a short and transient exposure to a potential risk factor[19]; it is similar to the case–control design with the difference being that each patient serves as his or her own control. Individual risks, such as age, sex, socio-economic status, or seasonal influences that do not change over a short time period, are controlled for by design. Inference in this study was based on within-person comparisons of the potentially health-influencing air pollutant concentrations shortly before HF symptoms onset (hazard period) with the same concentrations that prevailed in the previous and following week (bidirectional control period to control for time trends[26]). Based on a predecessor study,[27] intervals of 1, 2, and 3 days before onset of HF symptoms were chosen as appropriate hazard intervals, and respective days in the previous and proximate week were regarded as control intervals. The number of days between exposure to the air pollutant and onset of HF symptoms is referred to as lag time. Three different hazard intervals were used to consider a potential delay before the effect of the specific air pollutant exposure on HF risk. Air pollutants were analysed as absolute values in two different statistical models. Model 1 assumed a linear association between exposure to air pollution and risk of HF. In this model, air pollutants were evaluated as continuous variables. In Model 2, considering a potential non-linear relationship between air pollution and risk of HF, air pollutants were analysed as categorized variables in four categories compared with one reference category. Categories were chosen after visual inspection of the respective distribution curve. For cut-off values, see *Figure 1*. Data were analysed in the overall population and in the following subgroups: sex (male/female), age (<65 years = young/≥65 years = old), and HF classification (HFrEF, HFmEF, or HFpEF). Generalized linear mixed models (GLMMs) were fitted by using the odds ratio (OR) and corresponding 95% confidence interval (95% CI) to quantify the association between environmental data and risk of HF.[27,28] GLMMs extend the generalized linear model, allowing the linear predictor to contain fixed as well as random effects. In this study, air pollutants together with corresponding meteorological parameters (ambient air temperature, relative air humidity, and atmospheric pressure) were regarded as fixed effects and the single patient as a random effect. Because a number of air pollutants are known to be correlated with meteorological factors[29] and patients are likely to be exposed to both environmental components, we used this multivariable approach combining air pollution and weather in one statistical model. The statistical software R (V. 3. 2. 3, package 'lme4', function 'glmer'; The R Project for Statistical Computing, https://www.r-project.org/about.html) was used for all calculations. To reduce possible bias associated with multiple testing, air pollutants, meteorological variables, hazard, and CIs, the outcome groups and statistical tests performed were chosen prior to examination of the data. Given that HF is a relatively rare disease with a lifetime prevalence of <10%, we interpreted ORs as relative risks.[30]

Results

Study population

In total, 1093 datasets of patients with HF in the primary diagnostic position were retrieved from the hospital's data management system. Of the 1093 datasets, 183 (17%) were excluded because the HF diagnosis could not be confirmed (e.g. patients admitted for scheduled HF diagnostic or optimization of medication, incorrect coding of HF diagnosis, and suspected but not confirmed HF). Another 233 (21%) datasets were excluded because we were unable to retrospectively determine the date of onset of HF symptoms or the patients were outside the study catchment area at the date of symptoms onset. Finally, to rule out a potential recall bias, 101 (9%) datasets were excluded because the time between symptoms onset and admission was >5 days. The remaining 576 datasets were the basis of this case-crossover study. There were 428 (74%) patients admitted on the day of HF symptoms onset, 59 (10%) 1 day after onset, and 89 (16%) 2 to 5 days after onset. The patient characteristics are presented in *Table 1*, and the patient selection process is visualized in *Figure 2*.

Environmental parameters

During the study period, average daily concentrations ranged from 2 to 63.39 $\mu g/m^3$ (median: 17.46 $\mu g/m^3$) for NO_2, from 2 to 125.88 $\mu g/m^3$ (median: 44.61 $\mu g/m^3$) for O_3, and from 2.21

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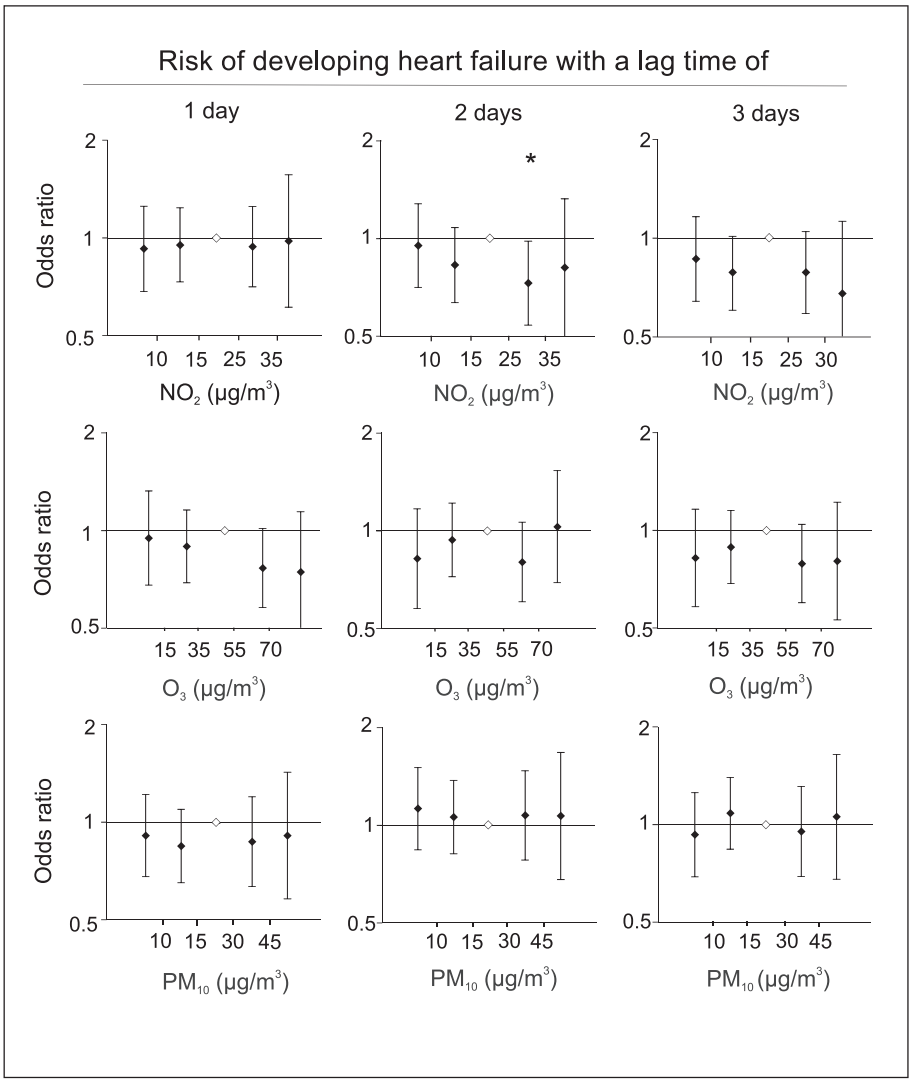
Figure 1 Association of air pollutants and risk of developing heart failure. Odds ratios for the association of nitrogen dioxide (NO_2), ozone (O_3), and particulate matter with a diameter < 10 μm (PM_{10}) with heart failure for different cut-off points and lag times in the overall study population. Bars indicate 95% confidence interval. * indicates odds ratio with confidence interval not including 1.00. White boxes represent the reference category.



to 166.79 μg/m^3 (median: 18.67 μg/m^3) for PM_{10}. *Table 2* summarizes the distribution of mean daily values of air pollutants.

Risk of heart failure associated with exposure to air pollution

Model 1: Linear analysis

In the overall population and all subgroups, exposure to NO_2, O_3, or PM_{10} analysed as a continuous variable was not associated with a risk for HF at all lag times.

Model 2: Non-linear analysis

Figure 1 shows the association between HF risk and exposure to NO_2, O_3, or PM_{10} analysed as a categorized variable. In the overall population, HF risk decreased 2 days after exposure to comparably high concentrations of NO_2 (category 20–35μg/m^3; OR: 0.73; 95% CI: 0.52–0.98, Figure 1). However, this result could not be reproduced in subgroups or at other lag times, nor did ORs in other categories show a similar pattern, which suggested that the statistical significance was by chance rather than because of a clinically relevant result. In the overall population and in all subgroups, exposure to O_3 or PM_{10} was not associated with HF risk at all lag times.

Discussion

This case-crossover study investigated the influence of short-term exposure to moderate concentrations of air

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Table 1 Patient characteristics

	No.	(%)
Total number of patients	576	(100)
Age in years (median)	82	
Young (<65)	52	(9)
Old (≥65)	529	(91)
Sex		
Male	241	(41.8)
Female	335	(58.2)
Heart failure classification		
HFrEF	65	(11.3)
HFmEF	38	(6.6)
HFpEF	146	(25.3)
Not classified	327	(56.7)
Left ventricular ejection fraction		
≤40%	92	(16)
41–49%	59	(10.2)
≥50%	214	(37.6)
Not quantified	211	(36.6)
Structural abnormalities in left atrium or ventricle		
Yes	306	(53.1)
No	270	(46.9)
BNP		
BNP > 35 pg/mL	473	(82.1)
BNP < 35 pg/mL	4	(0.7)
Not determined	99	(17.2)
Atrial fibrillation (paroxysmal/persistent)		
Yes	315	(54.7)
No	261	(45.3)
Arterial hypertension		
Yes	447	(77.6)
No	129	(22.4)
Coronary heart disease		
Yes	209	(36.3)
No	367	(63.7)
Diabetes mellitus		
Yes	257	(44.6)
No	319	(55.4)
Chronic kidney disease		
Yes	276	(47.9)
No	300	(52.1)
Chronic obstructive pulmonary disease/Asthma		
Yes	136	(23.6)
No	440	(76.4)

BNP, brain natriuretic peptide; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Characteristics of the study cohort.

Table 2 Distribution of average daily air pollutant concentrations

	Percentiles						
Air pollutant	Min	10th	25th	Median	75th	90th	Max
NO_2, μg/m^3	2	8.7	12.21	17.46	24.04	30.42	63.39
O_3, μg/m^3	2	13.46	27.75	44.61	58.3	68.87	125.88
PM_{10}, μg/m^3	2.21	9.08	12.58	18.67	27.42	39.21	166.79

NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with a diameter < 10 μm.
Distribution of average daily air pollutant concentrations over the study period 1 January 2010 until 30 September 2015.

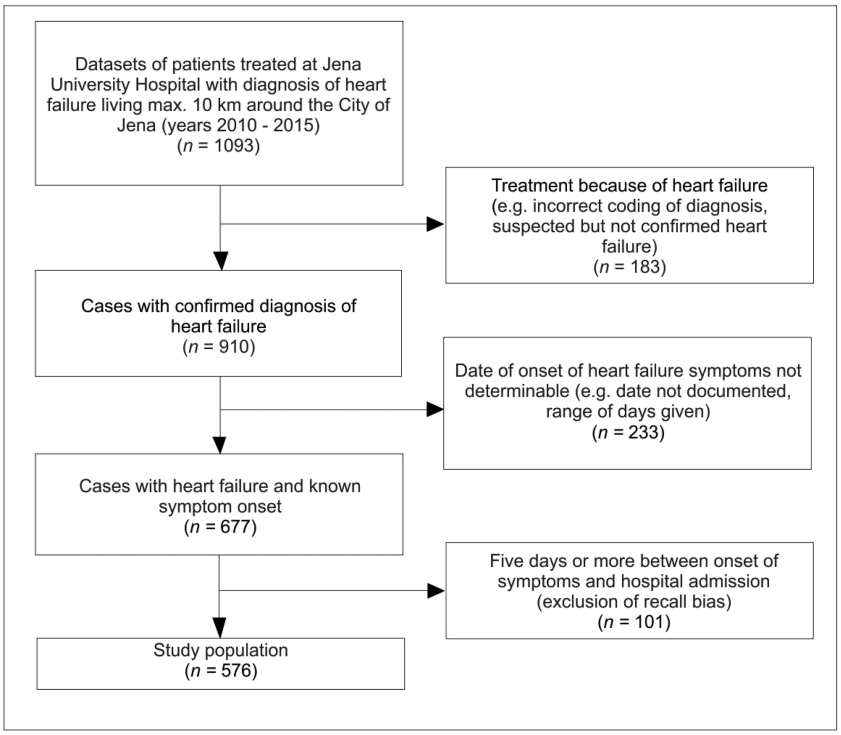
pollution on the risk for HF in a well-defined set of patients with verified HF diagnosis and known symptoms onset. The comprehensive multivariate statistical model comprising linear and non-linear data analyses in this study indicated that short-term exposure to moderate concentrations of major air pollutants did not affect the risk of HF.

The case-crossover study design used in this study had previously been developed to study the association between transient exposure and risk factors for development of an acute and rare event.[19] Because of its self-matching structure, the advantage of this efficient variation of a case–control study is that by design, it controls for individual risk factors, such as sex, age, long-term medication, or seasonal influences, that do not change over a short period of time. Additionally, by choosing a bidirectional control interval in this case-only study, we minimized the effect of time trends in exposure on HF risk estimates.[26] Further, we controlled for circadian confounders, such as weekday,[31] by applying a 7 day control interval.

To estimate the air pollution-dependent risk of HF, we conducted a multivariable analysis that also takes meteorological data into account. This approach considers the known interactions between air pollution and weather, such as between PM_{10} and temperature[29] or between NO_2 and basic meteorological parameters,[32] as well as interactions between the single pollutants. To detect a potential non-linear association between air pollution and risk for HF, our statistical approach included analysis of continuous and categorized air pollution data. However, we could observe neither a linear nor non-linear association between air pollution and risk for HF.

Our results are in contrast to those of a number of studies from different geographical regions that reported an association between short-term exposure to major air pollutants and risk for HF.[5–10,12,15] However, the majority of these studies investigated the impact of air pollution on HF in dense urban or industrialized areas with high levels of gaseous and particulate pollutants. Compared with these studies, the air quality in the city of Jena is good and generally reflects the average European background air pollution. For example, the study from Liu *et al*. performed in 26 of China's largest cities[7] reported two to four times higher annual concentrations of NO_2 (44.1 vs. 17.5 μg/m^3) and PM_{10} (106.8 vs. 18.7 μg/m^3) than concentrations that prevailed in Jena during the study period (*Table 2*). The good air quality in Jena is also reflected by the low numbers of days during which the concentration of air pollutants exceeds the daily air quality limit values.[33] Nevertheless, air pollution in Jena was still high enough to increase the risk for other cardiovascular diseases, such as acute myocardial infarction, in a similar predecessor study.[22] Thus, the negative results in the present study may be indicative of a threshold concentration for an air pollution-dependent HF risk that has not been reached in Jena but was reached in studies in areas with higher air pollution.[15,34] Another explanation for the contrasting results could be the patient selection process that was improved in three major aspects relative to those of previous studies. First, we considered the date of the start or exacerbation of

Figure 2 Patient data selection process.



HF symptoms as an appropriate case period, whereas others used the day of hospital admission in their analyses.[5–10] The rationale behind our approach was based on a previous observation that not every patient gets admitted to the hospital on the day of onset of HF symptoms. A study by Evangelista *et al*. conducted in Los Angeles in the USA reported a delay of 2.93 ± 0.68 days by persons who experienced HF in seeking treatment after symptoms onset.[18] Indeed, in our study, >25% of the patients were not admitted on the day the HF symptoms began. This finding suggests that in previous studies, a significant proportion of HF patients were not matched correctly with their corresponding air pollution variables, which most likely resulted in a substantial bias. This was consistent with the findings of a small epidemiological study on the association of fine particulate matter with a diameter of <2.5 μg and exacerbation of previously diagnosed congestive HF showing that the associations became non-significant when the day of admission instead of the start of HF symptoms was analysed.[12] Second, we retrospectively verified the diagnosis of HF for every patient by applying the 2016 ESC guidelines for HF. All patients showed symptoms of HF mostly along with elevated BNP levels and echocardiography pathologies. Most available studies have relied on administrative data and ICD codes to identify patients suffering from HF.[5–7,13,14] However, it is known that the validity of administrative data on HF varies highly, with positive predictive values ranging from 12% to 100%.[17] Consistent with the difficulty in establishing validity, we had to exclude 17% of all patients because the diagnosis of HF could not be verified. Third, this study did not include patients with isolated right ventricular failure to minimize the confounding influence of restrictive and obstructive pulmonary diseases, such as asthma, chronic obstructive pulmonary disease, or pulmonary hypertension, which can be aggravated by short-term exposure to air pollution.[35,36] Aggravation of these pulmonary diseases is known to lead to impaired functioning of the right ventricle.[37,38]

This study has some limitations that should be considered. When using the case-crossover approach to estimate HF risk, the time point of onset of HF symptoms needs to be determined to correctly match the air pollution variables with their respective patients. Even though we were able to retrospectively determine the date of manifestation of HF symptoms in 79% of the patients, especially those with less severe symptoms (usually patients with HFpEF), determination of symptoms onset was rather complex. HFpEF symptoms are often mild because the condition tends to progress slowly.[39,40] Furthermore, in Germany, patients with mild HF symptoms are more likely to be treated in an ambulatory setting. Therefore, we cannot exclude that in our hospital-based study, the proportion of cases with HFpEF was underrepresented. However, we do not regard this selection bias as significant for the overall results. Even in patients with HFpEF and reliably determined symptoms onset, no association

between HF risk and air pollution was detected. Additionally, the time point of onset of HF symptoms is retrospectively determined from patient self-reports, which are known to be prone to varying degrees of recall bias. We minimized this bias by excluding patients with HF symptoms onset $>$ 5 days before hospital admission. Moreover, our data did not include information on air pollution exposure at the individual level. Instead, air pollution data were provided by the official Thuringian State Environmental Agency-run monitoring station at a city-wide level. However, the monitoring station is located within the geographical centre of Jena and classified as an urban background station. As such, its location ensures that measured pollution levels are representative of the general urban population's exposure. To further reduce the influence of the potential variance in the data on pollution exposure, our study comprised only patients who lived within 10 km of Jena University Hospital. Owing to the retrospective study design, we were not able to control for short-term cessation of long-term HF treatment.

Conclusions

In this study, we tried to overcome the methodological shortcomings of previous studies on an air pollution-dependent HF risk by individual application of diagnostic criteria of HF and exact determination of HF onset. In this well-defined population, we could not prove an association between short-term exposure to moderate concentrations of NO_2, O_3 and PM_{10} and the risk of HF.

Future studies should focus on a potential threshold effect of air pollution on HF risk. Defining a threshold for an air pollution-dependent HF risk would help to define evidence-based statutory limits for air pollution in areas with low air quality.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017; **3**: 7–11.
2. Roe AT, Sjaastad I, Louch WE. Heart failure with preserved ejection fraction. *Tidsskr Nor Laegeforen* 2017; **137**: 3.
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014; **171**: 368–376.
4. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368–378.
5. Huynh QL, Blizzard CL, Marwick TH, Negishi K. Association of ambient particulate matter with heart failure incidence and all-cause readmissions in Tasmania: an observational study. *BMJ Open* 2018; **8**: e021798.
6. Morris RD, Naumova EN, Munasinghe RL. Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. *Am J Public Health* 1995; **85**: 1361–1365.
7. Liu H, Tian Y, Song J, Cao Y, Xiang X, Huang C, Li M, Hu Y. Effect of ambient air pollution on hospitalization for heart failure in 26 of China's largest cities. *Am J Cardiol* 2018; **121**: 628–633.
8. Lee I-M, Tsai S-S, Ho C-K, Chiu H-F, Yang CY. Air pollution and hospital admissions for congestive heart failure in a tropical city: Kaohsiung, Taiwan. *Inhal Toxicol* 2007; **19**: 899–904.
9. Yang C, Chen A, Chen R, Qi Y, Ye J, Li S, Li W, Liang Z, Liang Q, Guo D. Acute effect of ambient air pollution on heart failure in Guangzhou, China. *Int J Cardiol* 2014; **177**: 436–441.
10. Morris RD, Naumova EN. Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. *Environ Health Perspect* 1998; **106**: 649–653.
11. Barnett AG, Williams GM, Schwartz J, Best TL, Neller AH, Petroeschevsky AL, Simpson RW. The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. *Environ Health Perspect* 2006; **114**: 1018–1023.
12. Symons J, Wang L, Guallar E, Howell E, Dominici F, Schwab M, Ange B, Samet J, Ondov J, Harrison D. A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. *Am J Epidemiol* 2006; **164**: 421–433.
13. Poloniecki JD, Atkinson RW, de Leon AP, Anderson HR. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. *Occup Environ Med* 1997; **54**: 535–540.
14. Vanasse A, Talbot D, Chebana F, Bélanger D, Blais C, Gamache P, Giroux J-X, Dault R, Gosselin P. Effects of climate and fine particulate matter on hospitalizations and deaths for heart failure in elderly: a population-based cohort study. *Environ Int* 2017; **106**: 257–266.
15. Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013; **382**: 1039–1048.
16. Schultz MG, Klemp D, Wahner A. Luftqualität. In *Klimawandel in Deutschland*. Springer; 2017. p 127–136.
17. Quach S, Blais C, Quan H. Administrative data have high variation in validity for recording heart failure. *Can J Cardiol* 2010; **26**: e306–e312.
18. Evangelista LS, Dracup K, Doering LV. Treatment-seeking delays in heart failure patients. *J Heart Lung Transplant* 2000; **19**: 932–938.

19. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991; **133**: 144–153.
20. Rakers F, Schiffner R, Rupprecht S, Brandstädt A, Witte OW, Walther M, Schlattmann P, Schwab M. Rapid weather changes are associated with increased ischemic stroke risk: a case-crossover study. *Eur J Epidemiol* 2016; **31**: 137–146.
21. Rakers F, Walther M, Schiffner R, Rupprecht S, Rasche M, Kockler M, Witte OW, Schlattmann P, Schwab M. Weather as a risk factor for epileptic seizures: a case-crossover study. *Epilepsia* 2017; **58**: 1287–1295.
22. Rasche M, Walther M, Schiffner R, Kroegel N, Rupprecht S, Schlattmann P, Schulze PC, Franzke P, Witte OW, Schwab M. Rapid increases in nitrogen oxides are associated with acute myocardial infarction: a case-crossover study. *Eur J Prev Cardiol* 2018; **25**: 1707–1716.
23. Franzke P, Bitsch A, Walther M, Schiffner R, Rupprecht S, Rasche M, Volk GF, Witte OW, Schlattmann P, Guntinas-Lichius O. Weather, weather changes and the risk of Bell's palsy: a multicenter case-crossover study. *Neuroepidemiology* 2018; **51**: 207–215.
24. Peel MC, Finlayson BL, McMahon TA. Updated world map of the Köppen-Geiger climate classification. *Hydrol Earth Syst Sci Discuss* 2007; **4**: 439–473.
25. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
26. Navidi W. Bidirectional case-crossover designs for exposures with time trends. *Biometrics* 1998; **54**: 596–605.
27. Rasche M, Walther M, Schiffner R, Kroegel N, Rupprecht S, Schlattmann P, Schulze PC, Franzke P, Witte OW, Schwab M, Rakers F. Rapid increases in nitrogen oxides are associated with acute myocardial infarction: a case-crossover study. *Eur J Prev Cardiol* 2018; **25**: 1707–1716.
28. Szyszkowicz M. Use of generalized linear mixed models to examine the association between air pollution and health outcomes. *Int J Occup Med Environ Health* 2006; **19**: 224–227.
29. Olivares G, Johansson C, Ström J, Hansson H-C. The role of ambient temperature for particle number concentrations in a street canyon. *Atmos Environ* 2007; **41**: 2145–2155.
30. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. *Am J Epidemiol* 2003; **157**: 940–943.
31. Allegra JR, Cochrane DG, Biglow R. Monthly, weekly, and daily patterns in the incidence of congestive heart failure. *Acad Emerg Med* 2001; **8**: 682–685.
32. Gardner M, Dorling S. Neural network modelling and prediction of hourly NO*x* and NO_2 concentrations in urban air in London. *Atmos Environ* 1999; **33**: 709–719.
33. Guerreiro CBB, Foltescu V, de Leeuw F. Air quality status and trends in Europe. *Atmos Environ* 2014; **98**: 376–384.
34. Brauer M, Brumm J, Vedal S, Petkau AJ. Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects. *Risk Anal* 2002; **22**: 1183–1193.
35. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. *PLoS ONE* 2017; **12**: e0174050.
36. Zhang S, Li G, Tian L, Guo Q, Pan X. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: a systematic review and meta-analysis. *Environ Res* 2016; **148**: 15–23.
37. D'Souza JC, Kawut SM, Elkayam LR, Sheppard L, Thorne PS, Jacobs DR Jr, Bluemke DA, Lima JAC, Kaufman JD, Larson TV, Adar SD. Ambient coarse particulate matter and the right ventricle: the multi-ethnic study of atherosclerosis. *Environ Health Perspect* 2017; **125**: 077019.
38. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB, National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation* 2006; **114**: 1883–1891.
39. Aizawa Y, Sakata Y, Mano T, Takeda Y, Ohtani T, Tamaki S, Omori Y, Tsukamoto Y, Hirayama A, Komuro I. Transition from asymptomatic diastolic dysfunction to heart failure with preserved ejection fraction. *Circ J* 2011; **75**: 596–602.
40. Lekavich CL, Barksdale DJ, Neelon V, Wu J-R. Heart failure preserved ejection fraction (HFpEF): an integrated and strategic review. *Heart Fail Rev* 2015; **20**: 643–653.