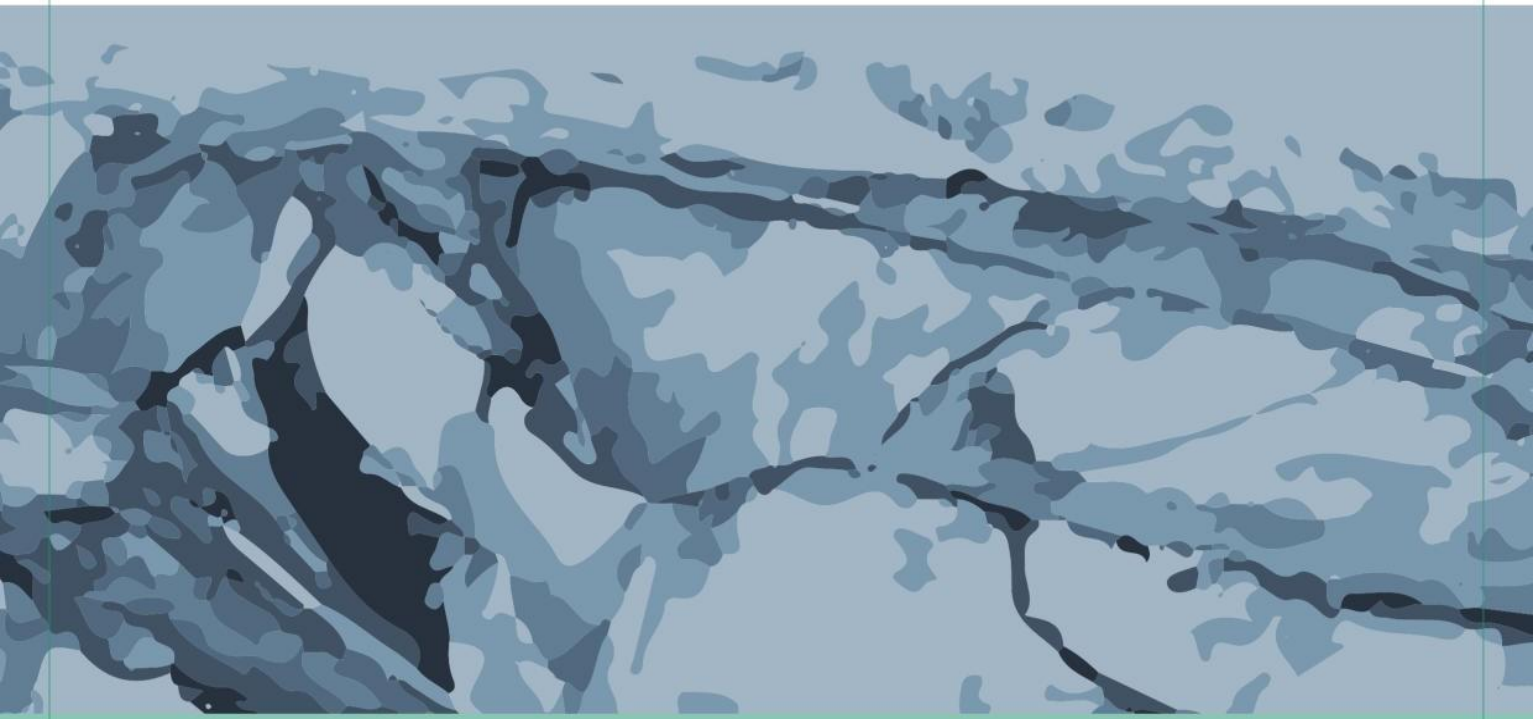
Project review 4

ChiNorBC

HUMAN HEALTH EFFECT OF BLACK CARBON IN AIR POLLUTION



Chinese-Norwegian Project on Emission, Impact, and Control Policy for Black Carbon and its Co-benefits in Northern China

CAEP CICERO CRAES Norwegian Environment Agency NIPH

Chinese-Norwegian Project on Emission, Impact, and Control Policy for Black Carbon and its Co-benefits in Northern China

About this report

This report is part of a series of outputs produced under the Chinese-Norwegian Project on Emission, Impact, and Control Policy for Black Carbon and its Co-benefits in Northern China (ChiNorBC). The project is jointly implemented by the Chinese Research Academy of Environmental Sciences (CRAES) and the Norwegian Environment Agency (NEA), in partnership with the Chinese Academy of Environmental Planning (CAEP), the Norwegian Institute of Public Health (NIPH) and CICERO Center for International Climate Research, with financial support from the Norwegian Ministry of Foreign Affairs.

There is no internationally agreed definition of black carbon (BC) and organic carbon (OC). BC is the light-absorbing component of fine particles and is produced by incomplete combustion of fossil fuel, biofuel and biomass. BC is always co-emitted with OC. Emissions of BC and OC affects the climate and have adverse health effects. Reductions of BC and OC will have co-benefits for climate, air quality and health.

ChiNorBC will develop improved emission inventories for BC- and OC- emissions in China using the most recent, best available national statistics and measurements obtained in the project. Based on this, new estimates of effects of BC/OC on climate, air quality, and health will be provided. The project will further raise scientific, governmental, and public awareness and enhance the understanding of the positive impacts of BC/OC emissions reductions. Ultimately the ChiNorBC will provide Chinese policy makers with policy solutions for reducing BC/OC emissions in China which maximizes the co-benefits.

The project has six outputs. This report is a result of Output 4, Review of human health effect of black carbon in air pollution. For a more comprehensive description of the project, and to get access to all the project reports, please visit the project web site http://chinorbc.net/.

Acknowledgements

In addition to the authors highlighted above, we would like to acknowledge the guidance and insights of a number of people.

Findings and opinions expressed in this paper are not necessarily shared by those contributing to the work, and any errors and omissions are the responsibility of the authors and partner institutions.

Date: September 2022

Published by the ChiNorBC-project

The cover design is non-figurative and created by Eilif Ursin Reed, Communication Advisor, Cicero, and is inspired by melting glaciers and polluted snow.

About the partner institutions in the ChiNorBC-project

Chinese Research Academy of Environmental Sciences

The Chinese Research Academy of Environmental Sciences (CRAES), founded in 1978, is a leading institute in environment-related studies in China, including studies on short-lived climate pollutants and its impacts. There are more than 1000 employees whose backgrounds cover all important areas of environmental sciences, including atmospheric science. One of the main responsibilities of CRAES is to provide technical and scientific support for decision making of Ministry of Ecology and Environment (MEE).

Norwegian Environment Agency (NEA)

The Norwegian Environment Agency (NEA) is an advisory and executive body under the Ministry of Climate and Environment (MCE), fully funded by the Norwegian Government. It has about 700 employees in Trondheim and Oslo as well as in local offices throughout the country. NEA was established 1st July 2013 after a merge of the former Directorate for Nature Management (est. 1965) and the Climate and Pollution Directorate (est. 1974). The Norwegian Nature Inspectorate (SNO) is organized as a department within NEA. The primary tasks of NEA are to reduce greenhouse gas emissions, manage Norwegian nature, and prevent pollution.

Chinese Academy of Environmental Planning (CAEP) is a public institution with independent legal status founded in 2001. Its missions are: Carrying out strategic research on national ecological civilization, green development and beautiful China, and undertaking technical support for the preparation and implementation of national medium and long-term ecological environment planning, key river basins and regions planning, and environmental planning in key fields, so as to meet the major needs of the country.

The Norwegian Institute of Public Health (NIPH) is a Norwegian government agency and research institute and is Norway's national public health institute. NIPH acts as a national competence institution placed directly under the Ministry of Health and Care Services, with approximately 1400 employees in Oslo and Bergen. It is responsible for knowledge production and systematic reviews for the health sector and provides knowledge about the health status in the population, influencing factors and how it can be improved.

CICERO Center for International Climate Research (CICERO) is a private foundation that for over thirty years has delivered interdisciplinary research of high scientific quality on climate science, economics, and policy. CICERO's mission is to conduct research and provide reports, information and expert advice about issues related to global climate change and international climate policy with the aim of acquiring knowledge that can help mitigate the climate problem and enhance international climate cooperation. CICERO has approximately 80 employees situated in the Oslo Science Park.

4. Human health effect of black carbon in air pollution

Decades ago, Europe began to pay attention to air pollution from combustion. And they used “black smoke (BS)” as a measurement index to assess air quality. In the initial epidemiological studies, BS was often used as one of the indexes of air pollution to study whether there was an association between mortality and air pollution. However, as technology and measurement methods have improved, new scientific evidence has led to a recognition of the significant role of black particles (black carbon-BC) as one of the short-lived climate forces. BC has also been found to have significant impacts on health (see Figure 4-1). These include impacts on cardiovascular system, respiratory and nervous systems. Evidence on the health impacts from BC is still developing.

The development of air pollution standards ideally involves the integration of data from the disciplines of epidemiology, controlled clinical studies, and animal toxicology. Epidemiological studies show statistical associations between health outcomes and exposure; they cannot establish a definite cause-effect relationship. The utility of toxicological studies is to establish this relationship.

In this report, we review all evidence so far on the health impacts from BC in the literature using a systematic review process. We review the global literature on long-term / short-term epidemiological studies, experimental studies, and practice statements from the WHO. This gives us a good overview of the literature that we can then use to develop further experimental studies in the project.

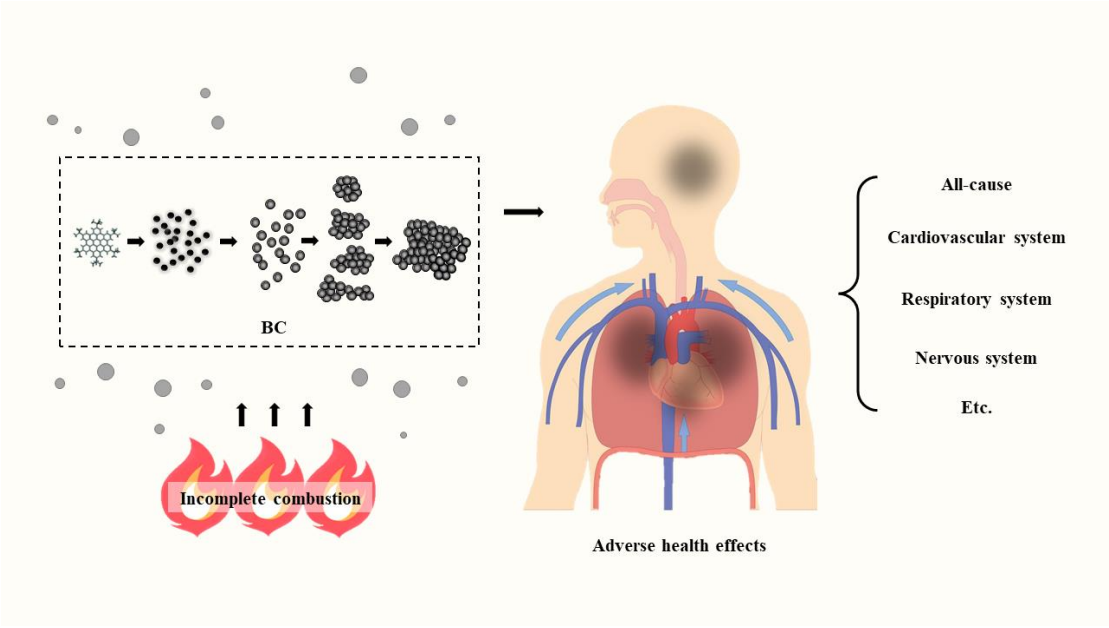


Figure 4-1 Impacts of BC on human health

4.1 Health effects in epidemiological studies

We present the results from a systematic review that we conducted. Exposure to BC in a short or long

term, people will have varying degrees of adverse effects, especially on the respiratory system, cardiovascular system, and even the nervous system. We identify the need for a systematic quantitative review of the evidence.

The major exposure of BC is inhaled by human body through the respiratory tract. BC in the indoor environment mainly comes from outdoor (Hong et al., 2005; Jia, 2014), and the concentrations of BC are usually lower than the outdoor (Tran et al., 2018). In this study, we mainly research all global articles related to BC in the outdoor environment.

4.1.1 Systematic analysis

Meta-analysis is an important systematic analysis method. It allows us to express quantitatively by summarizing the research results of scholars and using statistical methods.

According to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guide, four authoritative databases were searched for articles on epidemiology published from the establishment of the database to July 1, 2021. The databases were PubMed, Embase, The Cochrane Library and Web of Science. Searching words were focused on BC, air pollution, mortality and morbidity (searching process see Figure 4-2). Study design was based on an observational epidemiological study, including cohort, case-control, time-series, and case-crossover. We have included all studies on mortality or morbidity of heart and lung diseases, neurological diseases, and other diseases.

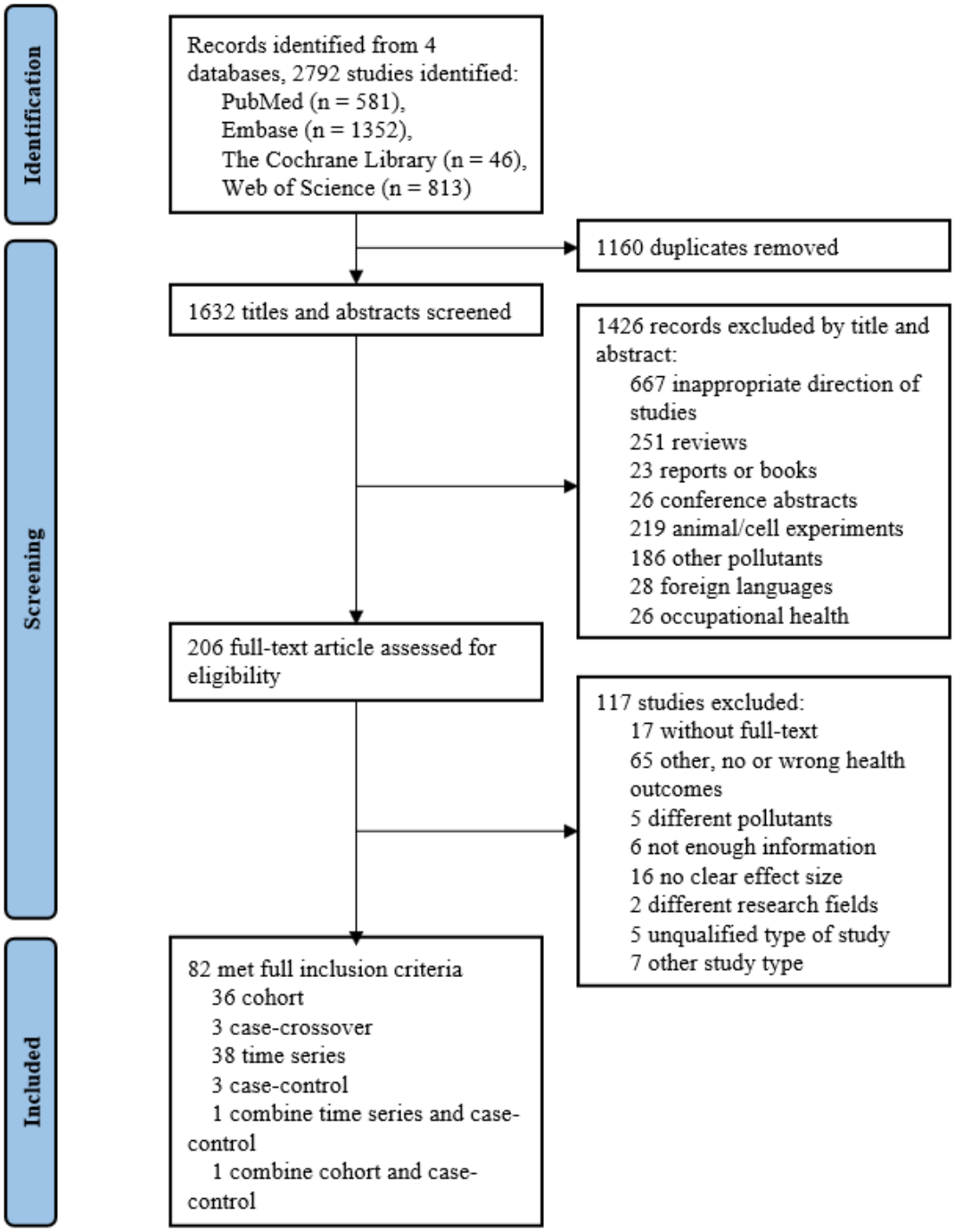


Figure 4-2 PRISMA 2020 flow diagram for this systematic analysis

The search results were 82 eligibility articles. Among them, there were 43 articles about short-term exposure and 40 articles about long-term exposure.

4.1.2 Short-term health effects

Through literature review, it is found that short-term exposure to BC affects the lung and

cardiorespiratory function of adults with complete immunity or relatively vulnerable children and the elderly, especially susceptible people with asthma, coronary heart disease or other diseases.

The search results of short-term exposure got 43 articles. Table 4-1 was the important information extracted, including study design, study region, study period, subject and sample size, pollutant, health outcome, effect size, international Classification of diseases (ICD), confounding factor, etc.

4.1.2.1 Study design and region

Studies of short-term health effects of BC usually use time series, case crossover, etc., which are common methods of observational epidemiological studies. The associations between short-term air pollution exposure (usually daily) and acute health effects can be established by these studies. Time series studies are usually based on stochastic process theory and mathematical and statistical methods to study the statistical patterns followed by random data series. Case crossover studies are a self-controlled approach.

The research areas covered Europe, Asia and South America. The highest number is in Europe with 27 studies. And the second is Asia with 8 articles on China, 3 of which are on northern China.

4.1.2.2 Air exposure assessment

Population exposure is assessed by measuring BC at one or more centrally located outdoor monitoring stations. The accuracy of estimates of the effects on health eventually depends on how well daily BC levels measured at the central outdoor monitoring site (ambient BC) reflect daily changes in personal exposure to BC (personal BC) in the study area. However, the accuracy of its response to personal exposure needs to be improved, otherwise to biased health effect estimates. Personal exposure data is most accurate and useful to assess air exposure. In recent years, more and more researchers pay attention to personal exposure, such as dressing vest which can real-time monitor of air pollutant concentrations, or filling in the daily behavior pattern table.

4.1.2.3 Statistical analysis

Poisson regression model and logistic regression model are used to analyze the association between pollutants and health outcomes in the short-term exposure. Logistical regression is used to deal with the regression problem in which the dependent variable is classified variable, such as binary variable and binomial distribution. Poisson regression is a regression method used for the count data. In addition, the impact of pollutants on human health might often have a lag effect. The short-term exposure studies the association between pollutant concentrations within a few days and human health effects. Therefore, the lag effect usually needs to be calculated. The lag effect time is usually calculated as the day of exposure (lag0), 1 day before exposure (lag1) to 3 days before exposure (lag3) and the period lags (lag01, lag02, lag03). For example, lag01 would be the 1-day moving average pollutant exposure (the average pollutant concentrations of the current day and 1 day). Air Pollutants often have strong correlation with each other. If they are all included in the model estimation, there may be strong collinearity impact results. Therefore, it is necessary to properly select single pollutant model, two-pollutant model or multi-pollutant model.

Before estimating the association between pollutants and health effects, it might be better calculated the

correlation among various pollutants. They usually have strong correlation, resulting in strong collinearity in the model and affecting the results. Therefore, it is necessary to properly select a single-pollutant model, double-pollutant model or multi-pollutant model. Furthermore, when estimating the association between pollutants and health effects in the model, it is important to control the impact of other factor on the result as much as possible. In short-term exposure studies, the confounding factors that often need to be controlled are age, gender, BMI, temperature, and relative humidity. Sometimes, educational levels, economic condition, workday, occupation, seasonality, smoking and cooking are also factors that need to be considered. However, it needs to distinguish the primary and secondary, and selects the suitable confounding factor to adjust the model according to the actual situation such as sample size.

4.1.2.4 Time-series studies of short-term exposure to BC and healthy outcomes

For the time-series studies, a meta-analysis was performed. Pooled random effects relative risk (RR) estimates were calculated for mortality (such as total mortality, cardiovascular mortality and respiratory mortality) for which estimates from at least three different studies were available for the same age group and for different cities. Summary random effects estimates were calculated using the "meta" package in R Studio. The standardized effect estimates were pooled using the random-effect model for there was substantial heterogeneity between the included studies. Heterogeneity among the included studies was evaluated by a Chi-square-based Cochrane Q statistic test and I-squared statistic.

In order to calculate pooled estimates and compare estimated effects for BC in each study, pooled effect estimates were expressed RR per 10 $\mu g/m^3$ and 95% confidence intervals (CIs). The short-term relationships between air pollution and health effects are characterized by the time lag (in days) between exposure and health events and investigators vary in which lags they study and report. This means that the use of any particular lag would result in the exclusion of many other studies. Therefore, if more than one lag measure was presented, this review selected one for meta-analysis according to the following algorithm: 1) the lag that the author focused on or stated a priori; 2) the lag that was the most statistically significant (positive or negative) and 3) the lag with the largest effect estimate (positive or negative).

There are 5 studies (Ballester et al., 1996; Ballester et al., 2002; Kim et al., 2015; Le Tertre et al., 2002; Sunyer et al., 1996) on total mortality, 9 studies (Ballester et al., 1996; Ballester et al., 2002; Cakmak et al., 2009a; Fischer et al., 2003; Kim et al., 2015; Le Tertre et al., 2002; Stanković et al., 2007; Yoo et al., 2019) on cardiovascular disease mortality, and 8 studies (Ballester et al., 1996; Ballester et al., 2002; Cakmak et al., 2009a; Dab et al., 1996; Kim et al., 2015; Le Tertre et al., 2002; Sunyer et al., 1996; Yoo et al., 2019) on respiratory disease mortality, all of which had complete information and the effect size was RR. The results of the meta-analysis showed a significant positive association of BC with both total mortality and respiratory disease mortality. The respiratory result has high heterogeneity.

Table 4-1 Extracted data of short-term exposure articles

Study design	Statistical model	Location	Period	Age	Number of events	lag	Outcome	Effect size	ICD	Confounding factors	Reference
time series	GAM (Generalized additive Poisson regression models)	Europe		all		lag0-1, lag0-5, lag3-30	CM, RM	Percent change	ICD-9 460-519, 390-459	seasonality, long-term trends, temperature, humidity, influenza epidemics, other unusual events, day of the week, and holidays	(Analitis et al., 2006)
time series	regression model	UK	1994.10-1996.12	all	2300000	lag0-1, lag0-2, lag0-3	ACM, CM, RM	Percent change	ICD-9 460-519, 390-459, 390-429, 410-414, 430-438, 493, 490-492, 494-496	long term time trends, seasonal patterns, influenza epidemics, day of the week, and temperature and humidity	(Anderson et al., 2001)
time series	GAM (Generalized additive Poisson regression models)	UK	2011-2012	all		lag1, lag2, lag0-6, lag1-30	CM, RM	Percent change	ICD-10 I00-I99, J00-J99	PM mass	(Atkinson et al., 2016)
time series	regression model	Spain	1991-1993	all	> 750000	lag0, lag1, lag2, lag3, lag4	CM, RM, TM（> 70years）	RR	ICD-9 390-459, 460-519	seasonality, temperature, humidity, long term trends, day of the week and holiday, influenza incidence	(Ballester et al., 1996)
time series	GAM (Generalized additive Poisson	Spain	1990-1996	all	8249790	lag0, lag1	CM, RM, TM	RR	ICD-9 001-799, 390-459, 460-519	temperature, humidity, long term trends, seasonality, incidence of flu, days of the	(Ballester et al., 2002)

	regression models)									week, holidays, unusual events	
time series	GLM（generalized linear (possion) model）	UK	1974-1998	≥50	≈1500000	lag0, lag1-6, lag7-12, lag13-18, lag19-24, lag25-30, lag0-30, lag0-40	ACM, CM, RM, LCM, other mortality	Percent change	ICD-9 410-414, 426-429, 434-440, 480-487, 490-496, 162	temperature	(Beverl et al., 2014)
time series	regression model	Scotland	1974-1988	35-64	15331	lag0-3, lag0-6, lag0-30	ACM, CM, RM	Percent change	ICD-9 410-414, 426-429, 434-440, 480-487, 490-496	potential confounding variables measured at baseline: smoking history, social class, BMI, marital status, systolic blood pressure, and total cholesterol	(Beverl et al., 2012)
time series	logistic regression	Netherland	1993-1995	50-70	327	lag0, lag1, lag2 and 5-days mean	RSP	OR	——	daily minimum temperature, linear, quadratic, and cubic time trend, and weekend/holidays	(Boezen et al., 2005)
time series	Poisson regression models	UK	1992-1994	all	≈7000000	lag0, lag1, lag2, lag3, lag0-1, lag0-2, lag0-3	ACM, CM, RM, all cancer mortality, all other causes mortality	Percent change	ICD-9 <800, 460-519, 490-96, 466, 480-486, 390-459, 410-414, 140-239	trend, seasonality, calendar, deaths from influenza, meteorology, and serial correlation	(Bremner et al., 1999)
time series	daily time-series analyses	Chile	1998-2006	all	≈498000	lag0, lag1, lag2	CM, RM, TM	RR	ICD-9 <800, ICD-9 390-459,	long term trends, day-of-the-week, and average humidex	(Cakmak et al.,

									ICD-9 460-519	on the day of death and the day prior to death Santiago de Chile	2009a)
time series	daily time-series analyses	Chile	2001-2006	all	2198000	lag0, lag1, lag2	total non-accidental morbidity, RM	RR	ICD-9 <800, ICD-9 460-519	long term trends, day of the week, and average humidex on the day of ED visit and the day prior to the visit	(Cakmak et al., 2009b)
time series	GLM (generalised linear (possion) model)	China	2004-2008	all	2700000	lag0, lag1, lag2, lag3	CM, RM, TM	Percent change	ICD-10 A00-R99, I00-I99, J00-J98, S00-T98	temporal trend, day of the week, temperature, relative humidity, SO_2, NO_2	(Cao et al., 2012)
time series	GLM (generalised linear (possion) model)	Scotland	1981-2001	all	≈1600000	lag0-40	ACM, CM, RM, non-cardiorespiratory causes mortality	Percent change	ICD-9 410-414, 426-429, 434-440, 480-487, 490-496	season and other long-term trend, day of week, black smoke (lag 0, 1 6, 7 12, 13 18, 19 24 and 25 30 days) and temperature (modelled as a double linear relationship, lagged 0, 1 6, 7 12, 13 18, 19 24 and 25 30 days).	(Carder et al., 2008)
time series	linear regression and autoregressive Poisson model	France	1987-1992	all	≈6140000	lag0, lag1, lag2 and cumulative lags over 4 days	RM, RA, AA, COPD admission	RR	ICD-9 460-519	long term trends, seasonal, weekly and daily patterns, meteorological factors, influenza epidemics, and holidays, a strike of medical residents and nurses in public hospitals	(Dab et al., 1996)

time series	GAM (Generalized additive Poisson regression models)	France	1988-1997	≥65, all	≈92000	lag0-1, lag0-5	NAM, CM, RM	Percent change	ICD-9 < 800, 460-519, 390-459	——	(Filleul et al., 2004)
time series	GAM (Generalized additive Poisson regression models)	Netherland	1986-1994	all	≈14800000	lag0-6	TM, CM, COPD mortality, PM	RR	ICD-9 480-486, 490-496, 390-448	long-term trends, seasonal trends, influenza epidemics, ambient temperature, ambient relative humidity, day of the week and holidays	(Fischer et al., 2003)
time series	DLM (distributed lag models)	China	2007.4.19-2008.12.31	all	≈7000000	maximum lag of 3 day	CM, RM, TM	Percent change	ICD-10 A00-R99, I00-I99, J00-J98	other pollutants	(Geng et al., 2013)
time series	logistic regression	USA	2014-2016	5-12	2488	——	AP	Percent change		SES, BMI, second hand smoking	(Gentile et al., 2020)
case-crossover	logistic regression	UK	1981-1996	all	14346	lag1-6, lag7-12, lag13-18, lag19-24, lag25-30, lag1-30	PM, community PM (community death from pneumonia), non-community PM	%RR change	ICD-9 480-487	subgroups defined by sex and age	(Gittins et al., 2013)
time series	GAM (Generalized additive Poisson regression models)	China	2006-2011	all		lag0, lag1, lag2, lag3, lag4, lag0-1, lag0-2, lag0-3, lag0-4	CM	%ER	ICD-10 I00-I99	subgroups defined by age, sex, educational attainment	(Gong et al., 2019)

time series	logistic regression	Netherland	1995.7.3-1995.10.6	18-55	60	lag0, lag1, lag2	respiratory symptoms (bronchodilator use, shortness of breath, woken up with breathing problems, pain on deep inspiration, cough and/or phlegm, nasal symptoms, inhaled steroids) and peak expiratory flow	RR	Global Initiative for Asthma	symptom prevalence and medication use, trends in mean morning and evening PEF, exposure to outdoor aeroallergens (data kindly provided by F.Th.M. Spieksma, Leiden, the Netherlands), exposure to environmental tobacco smoke, day of the week and daily maximum temperature (1 h average).	(Hiltermann et al., 1998)
time series	poisson time-series model	USA	2000-2006	≥40		lag0, lag1, lag3	CM, CVD hospitalization	%ER	ICD-9 402, 410, 414, 427, 428, 430-439, ICD-10 I11, I21-I22, I25, I48, I50, I60-I69	temporal and seasonal trends, temperature effects, and day of the week	(Ito et al., 2011)
time series	GAM (Generalized additive Poisson regression models)	USA	2003-2007	all		lag0, lag1, lag2, lag3, lag0-3	TM, CM, RM, IHD mortality, cancer mortality	RR	ICD-10 I00-I99, J00-J99, C00-C48	longer-term temporal trend, as time since the study began, day of week, and daily temperature and humidity	(Kim et al., 2015)
time series	Poisson time-series regression	France	1990-1995	all	≈11000000	lag0-1	TM, CM, RM	RR	ICD-9 390-459, 460-519	long-term trends, seasons, days of the week, holidays,	(Le Tertre et al.,

	model									influenza epidemics, temperature, and humidity	2002)
time series	Poisson regression models	USA	1995-1997	≥65		lag0, lag1, lag2, lag3, lag4	TM, CM	RR	ICD-9 390-448.9	day of the week with indicator variables, and time trends, temperature, and relative humidity with smoothing functions	(Mar et al., 2000)
time series	Poisson regression models	USA	2000-2003	>65		lag0, lag1, lag2, lag3	ACM, CM, RM	%ER	ICD-10 I00-I99	day of week, smoothing splines of one-day lags of average temperature and humidity [each with 3 degrees of freedom (df)], and a smoothing spline of time with 4 df per year of data	(Ostro et al., 2007)
time series	GEEs (Generalised estimating equations)	UK	1995.10-1997.10		94	lag1	FEV1, FVC, PEF, worsening symptoms (dyspnoea, sputum purulence or sputum amount, nasal discharge/congestion, wheeze or tight chest and upper respiratory symptoms)	OR		indoor temperature and time spent outdoors	(Peacock et al., 2011)

time series	Poisson log-linear model	UK	1981-1995	all	≈450000	lag0, lag1	CA, RA	Percent change	ICD-9 410-414, 426-429, 434-440, 480-487, 490-496	seasonal and weekday variation, daily temperature, and wind speed	(Prescott et al., 1998)
time series	generalized mixed model followed a poisson distribution linear mixed model	USA	2002-2005 spring	10-12	40	lag0, lag1	cough, wheeze, shortness of breath, total symptoms	RR	International Study of Asthma and Allergies in Childhood	——	(Spira-Cohen et al., 2011)
time series	GLM (generalised linear (possion) model)	Serbia	2001-2005	≥65	≈171000	lag0, lag0-3	daily CM	OR	ICD-10 I00-I99	——	(Stanković et al., 2007)
time series	Poisson time-series regression model	China	1998-2007	≥65	40150	lag0, lag1, lag2, lag3, lag0-1	emergency hospital admission for type 2 diabetes mellitus	%ER	ICD-9 250.X0, 250.X2, (X=0-9)	meteorological factors, time trends, public holiday, day of the week, and influenza epidemic	(Sun et al., 2016)
time series	Poisson regression models	Spain	1985-1991	≥70		lag0, lag1, lag3, lag5	TM, CM, RM	RR	ICD-9 390-459, 460-519	year, season, day of week, temperature, humidity, influenza, autocorrelation	(Sunyer et al., 1996)
case-crossover	logistic regression	Japan	2003.4-2007.12	≥65		lag0, lag1, lag2, lag3, lag0-1, lag0-3	ACM, CM, RM	%ER	ICD-10 I00-I99, J00-J99	ambient temperature, and relative humidity	(Ueda et al., 2016)

time series	GAM (Generalized additive Poisson regression models)	China	2014-2016		4186	lag0, lag1, lag2, lag0-1, lag0-2	daily hospitalizations for ischemic stroke	Percent change	ICD-10 I63	time, day of week, holidays, and weather conditions	(Wang et al., 2019)
case-crossover	Bidirectional time-stratified case-crossover analysis	USA	2006-2011	≥18	577	lag1, lag2, lag3, lag5, lag7	ICH among patients with a lobar but not deep ICH	OR	acute ICH (symptom onset within 1 day of presentation) confirmed by computed tomography scan.4 Lobar ICH was defined as selective involvement of cerebral cortex, underlying white matter, or both	barometric pressure (continuous), ambient temperature, and dew point temperature (natural cubic splines with 3 df).	(Wilker et al., 2018)
time series	generalized additive quasi-Poisson regression with polynomial distributed lag model (PDLM)	China	2011-2013	all		lag0, lag1, lag2, lag3, lag4, lag0-1, lag0-2, lag0-3, lag0-4	NAM, CM, RM, IHD mortality, stroke mortality, MI mortality, COPD mortality	Percent change	ICD-10 A00-R99, I00-I99, I60-I69, I20-I25, I21-I22, J00-J99, J40-J47	temperature and humidity	(Yang et al., 2020a)

time series	GAM (Generalized additive Poisson regression models)	Korea	2013-2015			——	NAM, CM, RM	RR	ICD-10 A00-R99, I00-I99, J00-J99	long-term temporal trend, day of the week, and meteorology	(Yoo et al., 2019)
time series	logistic regression using generalized estimating equations	USA	1995-2002, follow-up period 3.1 years	19-90	203	lag1, lag2, lag3, lag0-3	ventricular arrhythmic episode days	OR		season, temperature, relative humidity, day of the week, patient, and a recent prior arrhythmia	(Dockery et al., 2005)
time series	GLM (generalised linear (possion) model)	Korea	2003.3-2007.11			lag0, lag1, lag2, lag3	ACM, CM, RM	%ER	ICD-10 A00-R99, I00-I99, J00-J98, S00-T98	weather	(Heo et al., 2014)
time series	Time-series analysis using Poisson regression	China	2001-2010	all		lag0-7	NAM, diseases of the circulatory system mortality, hypertensive heart diseases mortality, IHD mortality, myocardial infarction mortality, heart	%ER	ICD-10 A00-R99, I00-I99, I10-I15, I20-I25, I21-I23, I500, I60-I69, J00-J99, J12-J18, J41-J44, K00-K93, N00-N99	co-constituent	(Sun et al., 2019)

							failure mortality, cerebrovascular diseases mortality, RM, PM, chronic obstructive pulmonary disease mortality, diseases of the digestive system mortality, diseases of the genitourinary system mortality				
time series	GAM (generalized additive models) and GLM (generalised linear model)	France	1990-1995	all		lag0, lag1, lag2, lag0-1, lag0-2	TM, CM, RM	Percent change	ICD-9 460-519, 390-459	temporal variations, temporal trends	(Zeghnoun et al., 2001)
time series	GAM (Generalized additive Poisson regression models)	China	2010-2016	all	2557	lag0, lag1, lag2, lag3, lag4, lag0-1, lag0-2, lag0-3, lag0-4	NAM, CM, RM	Percent change	ICD-10 A00-R99, I00-I99, J00-J99	long-term seasonal patterns	(Zhang et al., 2020)
time	distributed lag	USA	2002-			lag0, lag1,	ACM, CM, RM	%ER	ICD-10 A00-	time-varying covariates	(Zhou et

series	nonlinear model (DLNM) with Poisson		2004			lag2, lag3, lag0-2			R99, I01-I99, J00-J99		al., 2011)

TM means total mortality, DM means daily mortality, CM means cardiovascular mortality, TRM means total respiratory mortality, RM means respiratory mortality, ACM means all causes mortality, NAM means Non-accidental mortality, LCM means lung cancer mortality, LCI means lung cancer incidence, AP means asthma Prevalence, AI means asthma incidence, WP means wheezing prevalence, RSP means respiratory symptoms prevalence, PM means pneumonia mortality, NCM means Natural cause mortality, CRM means cardiorespiratory mortality, CCI means colon cancer incidence, ADC means Alzheimer's disease incidence, CA means Cardiovascular admissions, RA means Respiratory admissions , AA means asthma admissions , ACDA means all cause daily admission, LRS means lower respiratory tract, URS means upper respiratory tract, FEV1 means Forced Expiratory Volume In 1s, FVC means Forced Vital Capacity, PEF means Peak Expiratory Flow, IHD means Ischemic Heart Disease, COPD means Chronic Obstructive Pulmonary Disease, SES means socioeconomic status, BMI means body mass index, OR means odd ratio, RR means relative risk, ER means excess risk, HR means hazard ratio, ERR means excess relative risk, CI means confidence interval, IQR means interquartile range, ICD means International Classification Of Diseases, ETS means environmental tobacco smoke, USA means the United States of America, UK means the United Kingdom.

4.1.3 Long-term health effects

The search results of long-term exposure got 40 articles. See Table 4-2 for details. Through literature review, it found that long-term exposure to BC is prone to lung and cardiorespiratory adverse effects. Some studies showed that the cognitive function of the elderly and the newborns (due to exposure of the mother during the pregnancy) may be also affected, thus including neurological effects as a possible consequence of BC exposure.

4.1.3.1 Study design and country

The long-term health impact of BC is often followed up and investigated in the form of prospective cohort / retrospective cohort / ambispective cohort. The cohort study is a common observational study for long-term exposure without any intervention. And it has high reliability and can well reveal the objective causal association between air pollutants and human health effects. In addition, the case-control study is also one of common observational studies.

The research area involves Europe, Asia, North America, Oceanica and South America. The largest number of studies was in Europe, with 28. And the second was in Asia. Among it, there were 4 articles on China, but all of which are cities in South China.

4.1.3.2 Air exposure assessment

Land-use regression model (LUR) is often used to predict the BC concentrations in the environment and speculate the individual BC exposure concentrations in the epidemiological study. In the calculation of effect estimates in long-term epidemiological studies, contrasts in long-term exposure between persons are used. Consequently, the aim of exposure assessment is to accurately predict spatial variability in outdoor concentrations and further in personal exposure. For BC, within-city variability in concentrations is larger than for $PM_{2.5}$ owing to the considerable effect of local combustion sources, especially traffic, on concentrations (Hoek et al., 2002b; Nicole et al., 2008). Within-city variability may exceed between-city variability, which underlines the importance of considering small-scale variations in BC in epidemiological studies. Some epidemiological studies on the long-term effects of BC have relied on a crude estimation of exposure: BC concentrations measured at a single outdoor monitoring site have been assumed to reflect exposure within a city or even over a whole county. In others, the monitoring network has been dense enough to allow interpolation of exposures over an urban area. Neither method is able sufficiently to consider small-scale variations in BC concentrations, which may lead to an underestimation of the effects of BC. In contrast, LUR models have proved their efficiency in a number of recent studies (Jones et al., 2020; Tripathy et al., 2019). LUR models are stochastic models that typically use predictor variables obtained through geographic information systems. These rather simple regression models can explain similar proportions of variability in long-term outdoor concentrations as can dispersion models (Hoek et al., 2008).

4.1.3.3 Statistical analysis

Cohort study refers to the observation of people with some common characteristics for a certain period of time. It requires long-term observation and follow-up. And the Cox proportional hazards model is

often used for statistical analysis in most of cohort studies. This model is a kind of survival analysis model and is used to analyze the effects of exposure factors on two variables of survival outcome and survival time. It is suitable for the study of the impact of large samples on survival time and survival rate and is often used for multivariate analysis of cohort studies. Logistic regression is one of the most widely used analysis methods in the epidemiological studies. The binary data of mortality and prevalence (or morbidity) can still be used in the articles of long-term exposure types as dependent variables.

For the confounding factors of long-term exposure studies, age, sex, BMI are still important factors which need to be controlled. In addition, educational levels, economic condition, smoke and race are also usually controlled.

4.1.3.4 Cohort studies of long-term exposure to BC and healthy outcomes

For long-term exposure studies, the cohort study is one of the most commonly used study designs. And there was a meta-analysis about the cohort study of long-term exposure. Pooled random effects relative risk (RR) or hazard ratio (HR) estimates were calculated for mortality (such as cardiovascular mortality, respiratory mortality, and lung cancer mortality). For mortality, HR and RR can often be converted to each other.

There are 6 studies (Beelen et al., 2009; Dehbi et al., 2017; Elliott et al., 2007; Hansell et al., 2016; Hvidtfeldt et al., 2019; Yap et al., 2012) on cardiovascular disease mortality, 6 studies (Beelen et al., 2008; Chen et al., 2021; Elliott et al., 2007; Hvidtfeldt et al., 2019; Yang et al., 2018; Yap et al., 2012) on respiratory disease mortality, and 3 studies (Beelen et al., 2008; Elliott et al., 2007; Yap et al., 2012) on lung cancer mortality, all of which had complete information and the effect size was RR, HR or OR. The results of the meta-analysis showed only a significant positive association between BC and lung cancer mortality with low heterogeneity. The reason for the lack of significant association of other outcomes with BC may be related to the small number of relevant studies.

Table 4-2 Extracted data of long-term exposure articles

Study design	Statistical model	Location	Period	Age	Numb-er of events	Outcome	Effect size	ICD	Confounding factors	Refer-ence
cohort	GAM (Generalized additive Poisson regression models)	Netherland	1989-2006			CM, RM, TM	RR	ICD-10 I00-R99, J00-R99	potential confounding due to long-term trends, seasonal trends, influenza epidemics, ambient temperature, ambient air pressure, ambient relative humidity, day of the week and holidays	(Ischer et al., 2009)
cohort	Cox proportional hazard model	USA	2010-2015	≥18	41869	CeM, coronary heart disease mortality	HR	ICD-9 410.x, 36.x, 431.x, 434.x, 436.0 or ICD-10 I21.x-I22.x, 02.x, I60.x, I61.x, I63.x, I64.x	age, race, sex, BMI, NDI, smoking, baseline co-morbidities, medications, SES	(Alexeeff et al., 2018)
cohort	Cox proportional hazard model	Netherland	1987-1996	55-69	111816	NCM, CM, RM, LCM, other mortality	RR	ICD-9 all, <800, 400-440, 460-519, 162 or ICD-10 all, <V01, I10-I70, J00-J99, C33-C34	age, sex, smoke, socioeconomic status	(Beelen et al., 2008)
cohort	Cox proportional hazard model	Netherland	1987-1996	55-69	117528	CM, IHD mortality, CeM, heart failure mortality, cardiac dysrhythmia mortality	RR	ICD-9 400-440, 410-414, 430-438, 428, 427 or ICD-10 I10-I70, I20-I25, I60-I69, I50, I44-I49	age, sex, smoke, socioeconomic status	(Beelen et al., 2009)
case-control	Cox proportional hazard model	Scotland	1970-1979	35-64	15331	ACM, CM, RM	Percent change	ICD-9 410-414, 426-429, 434-440, 480-487, 490-496	seasonal effects and local air quality predictors including altitude (A), household density within a 250-m radius (HD), distance to nearest major	(Bevel et al., 2012)

									road (MR), and distance to an urban boundary (UB)	
cohort	multivariable logistic regression	Peru	2011-2014	9-19	484	rhinoconjunctivitis quality of life	OR		pediatric/adolescent survey, age, sex, socioeconomic status, Cole BMI classification (normal, overweight, obese), site (Pampas, Villa), baseline FEV1 percent predicted, temperature (˚C) and humidity (%)	(Bose et al., 2018)
cohort	Cox proportional hazard model	China	2006-2018	18-65 or ≥18	28793	NAM, RM, cardio-CeM, cancer mortality, other mortality	HR	ICD-10 A00-R99, I00-I99, C00-C97, J00-J99	age, sex, BMI, educational level, occupation, household income, smoke, drink, sports activity, history of chronic diseases	(Chen et al., 2021)
cohort	logistic regression	Canada	1994-1998, follow-up 1999-2002	45-85	380738	Incident diabetes	OR	ICD-9 250, ICD-10	age, sex, household income	(Clark et al., 2017)
cohort	Competing risk hazards regression models	UK	to 2014.12, to 201511	60-64; 40-69	3129+4400	CM	HR	ICD-9 390-459, ICD-10	age, sex, race, smoke, SES, regional poverty index, History of diagnosis of CD	(Dehbi et al., 2017)
cohort	logistic regression	Netherland	2006-2013 baseline, 2014-2017	18-93	132595 baseline, 65009 second	Prevalent chronic bronchitis and cough and sputum symptoms	OR	British Medical Research Council (MRC)	age, sex, educational level, BMI, smoke, smoke	(Doiron et al., 2021)

			second							
cohort	Poisson regression models	UK	1982.4-1986.3, 1994.4-1998.3	≥30	≈4919781	ACM, CM, RM, LCM, CRM other mortality,	ERR	ICD-9 390-519, 390-459, 460-59, 162	deprivation and urban/rural classification	(Elliott et al., 2007)
cohort	linear regression	Australia	2001-2004	≥70	4249	blood pressure, cholesterol, triglycerides, C-reactive protein, and total homocysteine	Percent change	ICD-9 390-434, 250 or ICD-10 AM I00-I78, AM E10-E14	age, smoking history (never-smokers, former-smokers who had quit 10 years, former-smokers who had quit <10years, current-smokers), smoking intensity among current smokers (# tobacco products /day), education level (completed university, completed high school, completed less than five years of high schools, and completed some primary school or never attended school), BMI, and history of CVD. socio-economic indicator score, prudence score, and treatment for either elevated blood pressure or cholesterol.	(Er Hoorn et al., 2021)
cohort	Cox proportional hazard model	France	1961-1971	25-59	14284	NAM, LCM, cardiopulmonary mortality	RR	ICD-9 < 800, 460-519, 390-459	sex, smoke, educational attainment, BMI, occupational exposure	(Filleul et al., 2005)
cohort	multivariable logistic regression	USA	1999-2002		2093	failed glucose challenge test /normal oral glucose tolerance test, impaired	OR		age, race, educational level, household income, previous pregnancy history of GDM, family history of diabetes,	(Fleisch et al., 2014)

						glucose tolerance, and GDM compared with normal glucose tolerance during pregnancy (prevalence)			smoke, Date of last menstruation, BMI, gestational weight	
cohort	Cox proportional hazard model	Canada	1994-1998, follow-up 1999-2002	45-85	467994	COPD mortality	RR	ICD-9 490-492, 496, ICD-10 J40-44	age, sex, Previous comorbidities, SES	(Gan et al., 2013)
cohort	Cox proportional hazard model	Canada	1994-1998, follow-up 1999-2002	45-85	452735	CHD mortality	RR	ICD-9 410-414, 429.2, ICD-10 I20-I25	age, sex, Previous comorbidities, SES	(Gan et al., 2011)
cohort	logistic regression	England and Wales	1971-2009	?	367658	CM, RM, ACM	OR	ICD	age, sex, social class of individual, area, population density, geographical region	(Hansell et al., 2016)
cohort	logistic regression	Sweden	1991-1994	45-64	6031	carotid plaques of prevalence	OR	B-scan ultrasonography	age, sex, education level, smoke score, apoB/apoA1 radio, use of lipid lowering drugs, living alone, cardiovascular heredity, diabetes mellitus, waist hip ratio, physical activity, alcohol consumption, median income level in residential area, systolic blood pressure, and being born	(Hasslöf et al., 2020)

									outside of Sweden	
cohort	logistic regression	China	2007-2014			mental and behavioral disorders mortality, nervous system diseases mortality, digestive system mortality, genitourinary system diseases mortality, cancer mortality, CM, RM	OR	ICD-10 F00-F99, G00-G99, K00-K93, N00-N99, C00-C97, I00-I99, J00-J99	age, sex, weekday/weekend and seasonal effects, and short-term impacts of air quality	(Ho et al., 2020)
cohort	Cox proportional hazard model	Netherland	1986-1994	55-69	4492	cardiopulmonary mortality, non-cardiopulmonary and non-lung cancer mortality, ACM	RR	ICD-9 <800, 400-440, 460-519, 162, not 400-440, not 162, not 460-519	age, sex, smoke, SES, adjustment for diet	(Hoek et al., 2002a)
cohort	GAM (Generalized additive Poisson regression models)	Netherland	1986-1994	all	≈2000000	CM, COPD mortality, pneumonia mortality	RR	ICD-9 480-486, 490-496, 390-448	long-term and seasonal trend, influenza morbidity counts, ambient temperature and relative humidity, and indicator variables for day of the week and holidays	(Hoek et al., 2000)
cohort	logistic regression	China	2016-2018		2326	gestational diabetes mellitus prevalence	OR	International Association of Diabetes and Pregnancy Study Groups	maternal age, BMI, income levels, city, relative humidity and temperature	(Hu et al., 2021)
cohort	Cox proportional hazard model		1985-2005	mean : 41.7-72.5	18963	LCI, adenocarcinomas incidence, squamous-cell carcinomas incidence	HR	ICD-9 162.2-162.9, ICD-10 C34, ICDO3 8140-8384, ICDO3 8050-8084	age, sex, calendar year, marital status, smoking, BMI, employment status, and neighborhood-level socio-economic status	(Hvidtfeldt et al., 2021)
cohort	Cox	Denmark	1993-	50-	49564	ACM, CM, RM	HR	ICD-10 I00-I99, J00-J99,	age, sex, educational attainment,	(Hvidt

	proportional hazard model		2015	64				C34	occupational status, marital status, smoking (status, intensity, and duration), ETS, alcohol consumption, BMI, waist circumference, fruit consumption, vegetable consumption, physical activity, neighborhood level SES, and road traffic noise at the residence	feldt et al., 2019)
cohort	Poisson log-linear model	Thailand	2010-2016		59605	CCI	RR	ICD-10		(Jenwitheesuk et al., 2020)
cohort	Cox proportional hazard model	Canada	2006.4.1-2014.3.31	<6	1130855	childhood AI	HR	ICD-10 J45	maternal age, child sex, proportion of visible minority in the dissemination area (as a proxy of race/ethnicity), dissemination area median family income (as a proxy of SES status), dissemination area percentage of female aged 25–64 years who completed postsecondary education (as a proxy of SES status), urban/rural status of place of residence and residential greenness exposure	(Lavigne et al., 2021)
cohort	Cox proportional hazard model	Europe	1992-2004		98058	COPD hospitalization	HR	ICD-9 490-492, 494-496, ICD-10 J40-J44	age, sex, sub-cohort, smoking duration, squared term, BMI, marital status, employment status, educational	(Liu et al., 2021)

									level, secondary school, area-level annual year income	
cohort	Cox proportional hazard model	Sweden	1990-2011		114758	stroke incidence, IHD incidence	HR	ICD-9 410-414, 431-436, ICD-10 I20-I25, I61-I65	sex, calendar year, subcohort (in Stockholm), smoking status (current, former, never smoker), alcohol consumption in Stockholm and Umeå (daily, weekly, seldom, never), physical activity (sedentary, moderate, intermediate, or vigorous in Gothenburg and Umeå and once a month or less/<1 h per week, about once a month/1 h per week, 3 times a week or more/>2 h per week in Stockholm), marital status (single, married or living with partner, no answer), socioeconomic index by occupation (blue-collar, low and intermediate white-collar and self-employed, high-level white-collar and selfemployed, professionals with academic degrees, no answer), education level (primary school or less, up to secondary school or equivalent, university degree or more, no answer), occupation status (gainfully employed, unemployed/not gainfully employed,	(Ljungman et al., 2019)

									retired, no answer), and mean neighborhood individual income in persons of working age	
cohort	linear mixed model	USA	2000-2011		1015	HRV	Percent change		age, BMI, fasting blood glucose, smoking history (current, former, or never), current use of anti-hypertensive medications (yes/no), room temperature at the time of electrocardiogram measurement, season (indicated using the sine and cosine of the date), mean arterial blood pressure, and moving averages of outdoor temperature corresponding to the pollutant exposure measurement interval of interest (using both a linear and quadratic term).	(Mordukhovich et al., 2015)
cohort	Cox proportional hazard model	France	1999-2001, follow-up 12 years	≥65	7066	All-cause dementia incidence, ADC, vascular or mixed dementia incidence	HR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition	age, sex, centre, education, APOE genotype, deprivation index, alcohol intake, and smoking habits.	(Mortamais et al., 2021)
cohort	Cox proportional hazard model	USA	2001-2007	30-80	101884	IHD mortality	HR	ICD-10 I00-I99, I20-I25, C34, J00-J98	age (divided into 2-year categories between 30 and 79 years of age, 3-year categories between 80 and 88 years, and one category for women ≥ 89 years); race [non-Hispanic white, other	(Ostro et al., 2015a)

									(African American, Hispanic, Asian, Pacific Islander, and Native American), or unknown]; marital status (married/living with partner, not married, and unknown); smoking status (never, former, and current smokers) and pack-years of smoking (continuous variable for former and current smokers); secondhand smoke exposure (none, household exposure, unknown); BMI (16–19, 20–24, 25–29, 30–39, 40–55 kg/m2); lifetime physical activity (tertiles, unknown); alcohol consumption [beer (no/yes/unknown), wine (no/yes/unknown), liquor (no/yes/unknown)]; average daily dietary intake of fat (tertiles, unknown), fiber (tertiles, unknown), and calories (tertiles, unknown); menopausal status and hormone replacement therapy use combined (premenopausal, peri/postmenopausal and no HT use, peri/postmenopausal and past HT use, peri/postmenopausal and current use of estrogen, peri/postmenopausal and	

									current use of estrogen plus progestin, and unknown menopausal status or HT use); family history of myocardial infarction (yes/no) or stroke (yes/no); and use of blood pressure medication (low, medium, high, unknown) or aspirin (low, medium, high, unknown).	
cohort	Cox proportional hazard model	USA	2002.6-2007.7	>30	9208	ACM, Cardiopulmonary mortality, IHD mortality, pulmonary mortality	HR	ICD-10 I00-I99, I20-I25, C34, J00-J98	smoking status, total pack-years, BMI, marital status, alcohol consumption, second-hand smoke exposure at home, dietary fat, dietary fiber, dietary calories, physical activity, menopausal status, hormone replacement therapy use, family history of myocardial infarction or stroke, blood pressure medication and aspirin use, and contextual variables (income, income inequality, education, population size, racial composition, unemployment).	(Ostro et al., 2010)
case-control	logistic regression	Denmark	1991-2015	1921-1985 30-85 years old		NCM, CM, RM, LCM	RR	ICD-8:000-799, ICD-10:A00-R99, ICD-8 390-459, 460-519, 162.1, ICD-10 I10-I99, J00-J99, C34	sex, age, and calendar time, by match; marital status, educational level, occupational status, income, country of origin, and number of children; car ownership, rented dwellings, unemployment, manual professions, education, income, one-parent	(Raasch hou-Nielsen et al., 2020)

									households, immigrants, and criminal records;	
cohort	Cox proportional hazard model	USA	1982-2004	≥30	445860	IHD mortality	HR	ICD-9 410-414, ICD-10 I20-I25		(Thurston et al., 2016)
cohort	Cox proportional hazard model	USA	1995-2005, followed up until 2005	28-105	3895	Acute Myocardial Infarction	HR		age (cubic), sex, hospital of admission, development of a Q-wave myocardial infarction (MI), occurrence of atrial fibrillation, cardiogenic shock, and heart failure during hospitalization and a medical history of stroke, heart failure, angina, diabetes, and previous MI	(Von Klot et al., 2009)
cohort	logistic regression	Japan	2005-2010	6-9	10069	AI	OR	American Society-Division of Lung Disease	sex; grade as a surrogate variable of age; BMI; respiratory symptoms, such as persistent cough, persistent phlegm, wheeze, and chest illness; presence of allergic disease, such as pollinosis; allergic reactions to food, such as egg, dairy products (milk), or other foods; feeding during the lactation period; past history of diseases or surgery, such as sinusitis, bronchitis, pneumonia, pertussis, otitis media, and tonsillectomy; smoker in the	(Yamazaki et al., 2014)

									household; siblings and first-born child; parents' past history of respiratory illnesses, such as asthma, atopy, or pollinosis; housing materials; cookware used at home; heating system installed; humidifier/dehumidifier use; presence of mold in house; flooring materials used in living room and own bedroom; presence of pets (cats, birds, dogs, hamsters, animals with and without fur); use of air cleaners; and use of clothes dryers. These variables were measured using a questionnaire	
cohort	Cox proportional hazard model	China	1998-2011	≥65	66820	ACM, CM, RM, IHD mortality, CeM, pneumonia mortality, COPD mortality	HR	ICD-10 A00-R99, I00-I99, I60-I69, I20-I25, J00-J47, J80-J99, J12-J18, J40-J44, I47	age at entry, sex, BMI, smoking status, physical activity, education level and monthly expenses; percentage of participants who are equal to or older than 65 years old, percentages of subjects whose educational level are higher than secondary school and average income per month within each Tertiary Planning Units (TPU) and percentage of smokers were also adjusted on district level	(Yang et al., 2018)
cohort	Cox	Scotland	1970-	45-	22011	ACM, CM, RM, IHD	HR	ICD-9 410-414, 426-429,	marital status, BMI, smoking,	(Yap et

	proportional hazard model		1976, follow-up until 1998	64		mortality, LCM		434-440, 786.5, 480-487, 490-496, 786.0, 786.2, 162	cholesterol, systolic blood pressure, social class	al., 2012)
cohort	Cox proportional hazard model and logistic regression	Netherland	2008-2015	≥30		NAM	HR			(Fischer et al., 2020)
cohort	logistic regression	Greece	1992-2013, follow-up until 2014		5057	LCM	RR	ICD-10 O3	age, sex, stage, place of residence, and smoking status	(Sifaki-Pistolla et al., 2017)

TM means total mortality, DM means daily mortality, CM means cardiovascular mortality, TRM means total respiratory mortality, RM means respiratory mortality, ACM means all cause mortality, NAM means Non-accidental mortality, LCM means lung cancer mortality, CeM means cerebrovascular disease mortality, LCI means lung cancer incidence, AP means asthma Prevalence, AI means asthma incidence, WP means wheezing prevalence, RSP means respiratory symptoms prevalence, PM means pneumonia mortality, NCM means Natural cause mortality, CRM means cardiorespiratory mortality, CCI means colon cancer incidence, ADC means Alzheimer's disease incidence, CA means Cardiovascular admissions, RA means Respiratory admissions , AA means asthma admissions , ACDA means all cause daily admission, LRS means lower respiratory tract, URS means upper respiratory tract, IHD means Ischemic Heart Disease, GDM means Gestational Diabetes Mellitus, COPD means Chronic Obstructive Pulmonary Disease, SES means socioeconomic status, BMI means body mass index, OR means odd ratio, RR means relative risk, ER means excess risk, HR means hazard ratio, ERR means excess relative risk, CI means confidence interval, IQR means interquartile range, ICD means International Classification Of Diseases, ETS means environmental tobacco smoke, USA means the United States of America, UK means the United Kingdom.

4.2

4.2 Experimental studies

The BC and substances adsorbed on the surface of BC are the main factors influencing the human health effect (Ni et al., 2014). In order to better determine the adverse effects of human exposure to BC, this study analyzed and summarized three aspects with toxicological mechanisms, animal experimental studies and human clinical studies. Among them, animal experiments and human clinical studies were compared with exposure groups and control groups from aspects of BC, DEP and soot in order to better understand the adverse effects of BC and the possible influence mechanism.

4.2.1 The formation of black carbon and toxicity

In the combustion process, BC is formed by nucleation after carbon atoms form aromatic rings at high temperature, and then gradually form small particles, which then polymerize into clusters to form larger particles (see Figure 4-3) (Ali et al., 2020). Ultra-fine particles could migrate deep into the alveolar area (Shrestha et al., 2010) and they usually carry highly toxic and even carcinogenic substances, such as polycyclic aromatic hydrocarbons (PAHs) (Koelmans et al., 2006). Particles whose size is larger than 4 μm or smaller than 0.002 μm have less harm to human health, because after inhalation, most of them are intercepted in the mouth and throat area (Hinds, 1982).

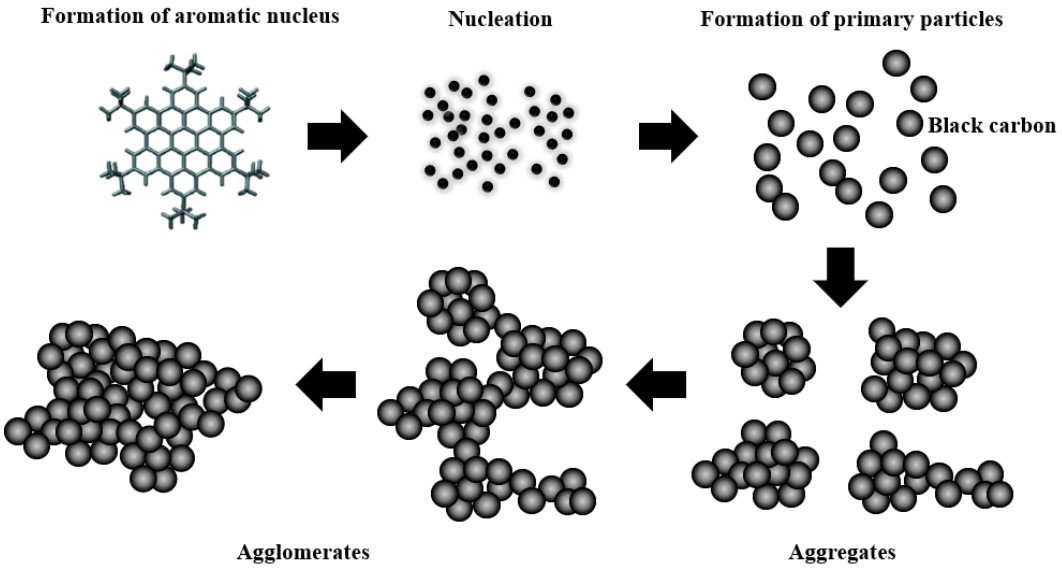


Figure 4-3 Schematic diagram of BC to form particles

The size of BC is smaller, it can reach the alveoli through the human respiratory tract (Marilena Kampa, 1993). Then, it can induce the free radical reaction and causes the consumption of antioxidants and the expression of antioxidant enzymes in the body. When the level of oxidation / antioxidation is unbalanced, oxidative stress (OS) occurs. OS is the main reason for the increase of lung biological index contents through airway inflammation, especially when the body is exposed to PM (Ghio, 2012; Rhoden et al.,

2005). The experiment in mice (Gao et al., 2014) showed increased antioxidants and catalases levels in serum after exposure to BC. And the levels of OS in vivo were increasing. The frequency of micronucleus in bone marrow with genetic damage increased. Even PM smaller than 100 nm in size can penetrate the alveoli, enter the circulation and has a strong deposition effect (Ching and Kajino, 2018). And then it could cause lung and cardiorespiratory diseases (Hua et al., 2020). BC enters the human body and has toxic effects on airway cells (such as respiratory epithelial cells) and macrophages. It will cause generation of reactive oxygen species (ROS), and inducepro-inflammatory reactions to the respiratory tract, lungs and cardiovascular system (Marilena Kampa, 1993; Meldrum et al., 2017; Ostro et al., 2015b), and even affect the nervous system (Colicino et al., 2017; Cowell et al., 2015). Among lung cells, macrophages can produce a large number of ROS / reactive nitrogen species (RNS), and pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-α (TNF-α). These factors can cause inflammation or other pathobiological damage, such as increased expression of IL-6, cell adhesion molecule 1 (CAM1), cytoplasmic and inducible nitric oxide synthase, and manganese superoxide dismutase (MnSOD) and cytoplasmic phospholipase A2. Increased levels of ROS / RNS may play a role in the overall response to particulate pollution by activating enzymes and transcription factors. Experiments in mice have shown that BC-stimulated macrophages activate the mitogen-activated protein kinase (MAPK) signaling pathway, which is implicated in inflammation, apoptosis, reproduction, transformation and differentiation processes (Terzano et al., 2010)), and regulate the transcription of cytokines and chemokines. The accumulation of these factors in the lungs can lead to the accumulation of inflammatory cells and the production of inflammation (Cheng et al., 2019). After instillation of BC into rat trachea, inflammatory changes were found on lung tissue sections, such as thickening of alveolar septum and bronchiole wall, narrowing of alveolar cavity, infiltration of inflammatory cells in stroma, etc (Gao et al., 2014). In the cellular environment, inflammatory cells can promote the production of ROS and other active substances, which aggravate oxidative damage and promote carcinogenesis. ROS may induce lipid peroxidation and DNA mutation (Gurgueira et al., 2002; Li et al., 2008; Xiao et al., 2003). At this stage, studies (Van et al., 2012) believe that the production of ROS in lung cells is the most important mechanism of carcinogenesis.

In the process of BC formation, a large number of PAHs are often produced. At high temperature, carbon atoms have strong adsorption on PAHs after nucleation (Jonker, 2002). After PAHs enter the body with BC, they can be converted into quinones by bio invertase such as cytochrome P450, epoxide hydrolase and dihydrodiol dehydrogenase in lung (Park et al., 2006; Penning et al., 1999), and then ROS is released by redox cycle (Dellinger et al., 2001). If chlorine (Cl_2) is in the burning process, PAHs can also react with Cl_2 to form highly toxic substances such as dioxins (PCDD) (Johansson et al., 2016) and polychlorinated biphenyls (PCBs) (Roth, 1989). BC can also promote the formation of persistent organic pollutants (POPs) and affect the transfer of POPs (Ni et al., 2014). There are different mixing modes between chemical composition and aerosol particles, including external mixture and internal mixture. Externally mixture is an extreme case of mixing state. It is that the chemical components are separated from each other, and the particles are homogeneous mixing of single or the same aerosol type. Internally

mixture is another extreme case. It is that the chemical composition is homogeneously mixed with aerosol particles inside the particles, which can also be called volume homogenous mixing. When chemical components are mixed with particles, the particles are wrapped by chemicals in the form of capsules to form a shell core model, which is also a kind of internally mixture (Bond and Bergstrom, 2007; Curci et al., 2019). Particles with different mixing modes will cause different degrees of adverse effects on human health. Moreover, PAHs adsorbed by BC have a wide variety, diverse structures, toxicity, and persistence. When they enter the body, they can cause cancer and mutagenesis (Abdel-Shafy and Mansour, 2016) and inhibit immune effect (Armstrong et al., 2004). The process of BC adsorbing toxic substances was shown in Figure 4-4.

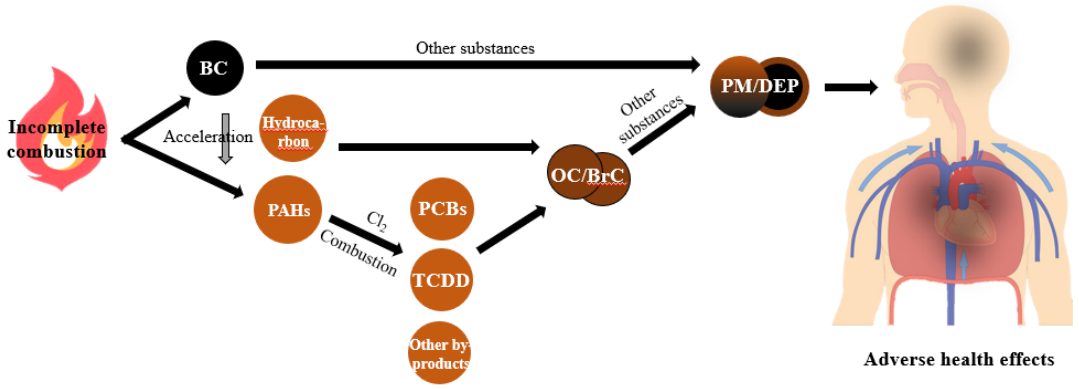


Figure 4-4 The process of BC adsorbing toxic substances

According to the toxicity, carbonaceous aerosols were classified by International Agency for Research on Cancer (IARC). IARC would update the toxicity classification of the carbonaceous aerosols in time with the increase of the experimental evidence. In 2010, carbon black (1333-86-4) was listed as a group 2B carcinogen by IARC. In 2012, carbon soot (Occupational safety) was listed as a group 1. In 2014, Diesel engine exhaust was listed as a group 1. And in 2016, particulate matter (outdoor air) was listed as in group 1.

4.2.2 Animal experiments

At the level of animals, experiments could help us to investigate the toxicity of BC and its mechanism, even though there are not many papers on BC. Therefore, we summarized all of the results of animal experiments by or via searching them in the international databases for a better study of toxicity. The databases were PubMed, Embase, The Cochrane Library and web of science. And we searched articles published between 1900 to September 18th,2021. Black carbon, air pollution, animal and exposed way were the main search terms. And the Figure 4-5 was the searching process.

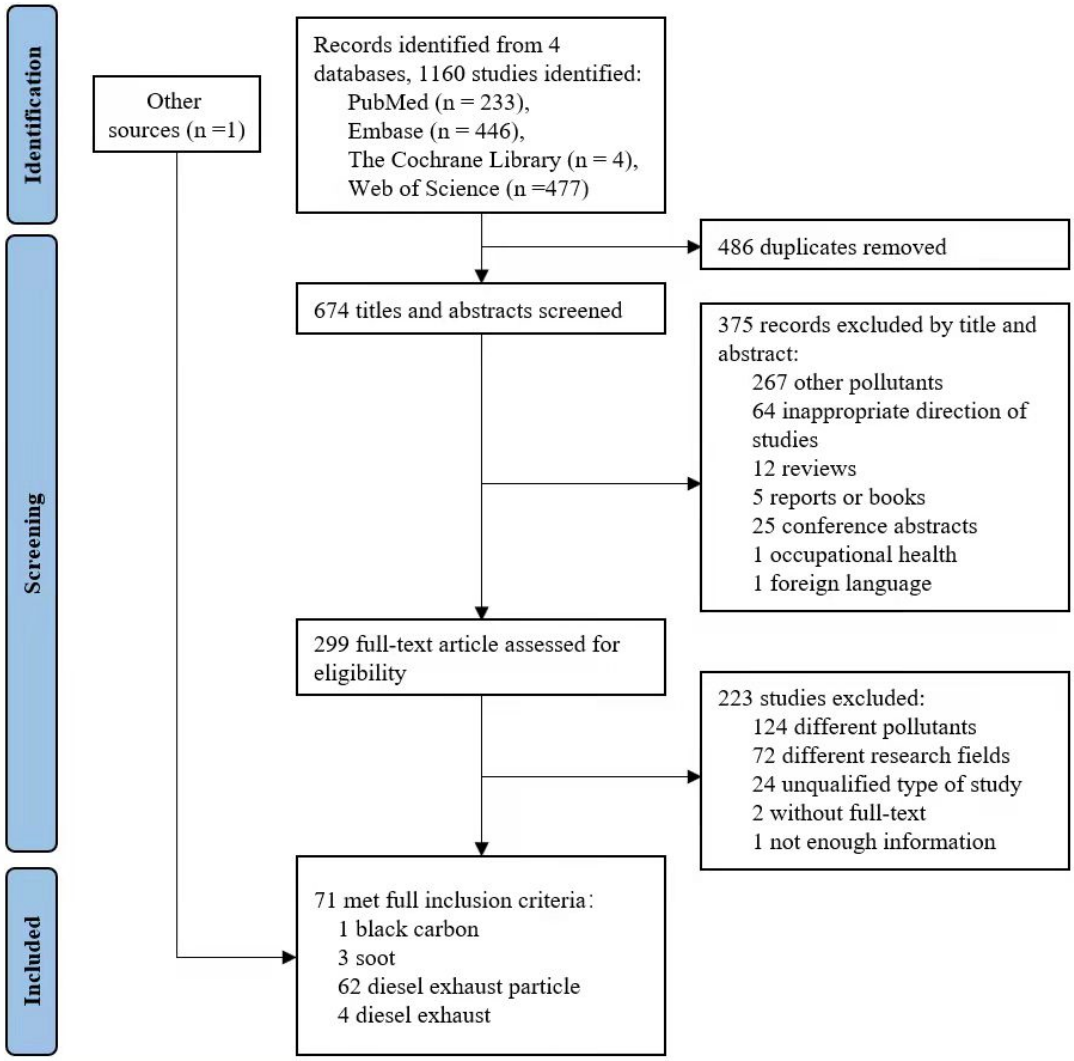


Figure 4-5 Searching process of animal experiment articles

There are subtle differences between soot, DEP, BS, EC, BC and others. So, we distinguished between them by listing the methods used to detect pollutants. It can avoid the author's subjective judgment of pollutants. In addition to this, we have listed other important information, such as basic information of the paper, exposed way, outcomes, and so on. For the extracted data see Table 4-3.

Table 4-3 The extracted data from animal experiment articles

Animal type	Sample size	Exposed method	Exposed way	Pollu-tant	Pollutant measurement	Concentrati-on	Outcome	Finding/exposure-response relationship	Refer-ence
male ICR mice	12 exposure groups of 3 animals each; 4 control groups	To find the appropriate dose for determination of DEPs lung toxicity, the doses of 25, 50 or 100 µg of SRM 2975 were used. ICR mice were randomly separated into four control and twelve exposure groups of 3 animals each. Twelve exposure groups were single intratracheally instilled with 50 µl aqueous suspensions of 25, 50 or 100 µg of SRM 2975 suspended in 0.01 M PBS. The four groups of control were instilled with 50 µl of 0.01 M PBS.	intratracheal instillation	DEP		25, 50 or 100 µg of DEP (1 mg/ml, SRM-2975) suspended in 0.01 M PBS	lung inflammation	DEPs produced mild to moderate pulmonary inflammation and injury, as evidenced by infiltration of neutrophils and active AMs, focal alveolitis and particle-laden AMs accumulation	(Kaewamata wong et al., 2009)
Male Sprague–Dawley rats were obtained at the age of 6 weeks old and body weight of around 250 g from Charles River Co., Ltd		Rats were anesthetized with pentobarbital (50 mg/kg body weight) intraperitoneal injection and randomized to be instilled with DEP or equivalent volume of normal saline intra-tracheally (N= 6 for each group). A dose of DEP 250 µg (DEP low dose) or 500 µg (DEP high dose) was suspended in 0.5 ml of normal saline and sonicated for 20 min before use in the DEP-treated group.	Rats were randomized to be instilled with DEP intratracheally	DEP		low dose group ($4.5\pm1.7\times10^3$ mmHg) high dose group ($2.9\pm2.5\times10^3$ mmHg)	depressed cardiac systolic and diastolic functions after DEP exposure	The cardiac IL-1β gene expression was up-regulated under DEP exposure with a strong trend	(Huang et al., 2010)

Male TO mice (30-35 g, HsdOla:TO, Harlan, UK)		A Becton Dickinson 24 Gauge cannula was inserted via the mouth into the trachea. Either the DEP sus-pensions (15 ug/mouse) or saline-only were instilled intratracheally (i.t.) (50 ul) via a sterile syringe and followed by an air bolus of 50 ul.	Rats were instilled with DEP intratracheally via a sterile syringe	DEP		15 µg/mouse	blood pressure/heart rate/heart rate variability	1.DEP administration induced a significant increase of macrophage 2.DEP caused a significant decrease of SOD activity	(Nemmar et al., 2012)
Eight-week-old male WKY rats	rats were randomly assigned to group 1 (n=4) or group 2 (n=3)	The particle-exposed group 1 was then exposed to 7 days of HEPA-filtered air after a washout, whereas the HEPA-filtered control group 2 was then exposed to 7 days of particles after the washout. The crossover exposure between particles and HEPA-filtered air was repeated 4 times during the experiment. Real-time radio-telemetric data were monitored during the exposure period (particles and HEPA-filtered control).	A continuous whole-body exposure system (ambient particles were homogeneously distributed within each cage in this system)	BC	BC mass concentrations were monitored with an Aethalometer (Magee AE31, USA). Quartz filter samples were used for analysis of EC concentrations with a carbonaceous aerosol analyzer (DRI Model, 2001A Optical Carbon Analyzer, Atmos lytic, USA).	1229.7±728.0 ng/m^3	blood pressure/heart rate/heart rate variability		(Chuang et al., 2017)
Seven-week-	Control	The experimental mice (n= 24) were randomly	intratracheal	DEP		low dose	Pulmonary	induce inflammatory	(Jeong

old, male, C57BL/6NCrlOri mice were purchased from Orient Bio, Inc. (Seongnam-Si, Korea)	group (n = 8), Treatment 1 group (n=8), Treatment 2 group(n=8)	assigned into three groups (n= 8 per group). DEP was dispersed in 50μL distilled water and were administered in a low (5 mg/kg; n= 8) and a high (15 mg/kg; n= 8) dosage (thus creating the low DEP exposure (DEPL) and high DEP exposure (DEPH) groups) by intratracheal instillation for 7 consecutive days. The control (Ctrl; n= 8) group was treated with distilled water for 7 days.	instillation			group (5 mg/kg) high dose group (15 mg/kg)	inflammation and anxious behavior	responses in the lungs by elevating pro-inflammatory cytokine secretion and gene expression.	et al., 2021)
Swiss albino mice (School of Medicine, University of Sa˜o Paulo, SP, Brazil), 8- to 10-week old	zygotes were allotted in groups of 10	Zygotes obtained from super ovulated mice after IVF were randomly cultured in different DEP concentrations (0, 0.2, 2, and 20 mg/cm^2) for 5 days and observed for their capacity to attach and develop on a fibronectin matrix until day 8.	zygotes were cultured in 20-μl drops of KSOM/AA with the predetermined concentrations of DEP (i.e., 0, 1, 10, and 100lg/ml).	DEP		0, 0.2, 2, and 20 mg/cm^2	Early Embryo Development	1. the developmental potential of the zygotes was significantly impaired by the 20ug/cm^2 concentration. At a concentration of 2ug/cm^2, the develop-mental competence of the blastocysts evaluated by D score was significantly reduce. 2. the exposure of zygotes to DEP, led to the disruption of the normal segregation pattern by a marked decrease in the number of ICM cells	(Januario et al., 2010)

adult male rats weighing 150–170 g were bought from University of Nigeria, Enugu campus.	While the control group was made up of thirty rats, the other three groups had 10 rats each making a total of 60.	Control group: Rats were kept away from black soot and received normal drinking water and food. 4-week group: Rats were exposed to soot for 4 weeks consecutively. 8-week group: Rats were exposed to soot for 8 weeks consecutively.12-week group: Rats were exposed to soot for 12 weeks consecutively.	inhalation exposure	soot		soot of Niger Delta in Nigeria	hypothalamic and testicular oxidative stress and apoptosis	1. MDA activity increased significantly following exposure to the soot. 2.alkaline dehydrogenase, alkaline phosphatase and lactate dehydrogenase was a statistically significant decrease 3. led to the upregulation of caspase-3 expression in the hypothalamus and testis	(Onyeso et al., 2020)
C57Bl/6J mice (male, 4-week-old)	120	A Becton Dickinson 18 Gauge cannula was then inserted via the mouse mouth into the trachea. DEP suspension (20 µg/50 µl in PBS) or PBS only was intratracheally instilled using a sterile syringe followed by 150µl air bolus	Intratracheal instillation	DEP			the fertility of male	1.compromised the repair of meiotic DSBs and thus the meiotic progression during spermatogenesis. 2. massively altered the testicular gene expression profile including the	(Yang et al., 2020b)
Male TO mice (30–35 g, HsdOla : TO, Harlan, UK)		A Becton Dickinson 24-gauge cannula was inserted via the mouth into the trachea. Either the DEP suspensions (30 mg per mouse) or saline-only were instilled i.t. (40 mL) via a sterile syringe and followed by an air bolus of 50 ml.	Intratracheal instillation	DEP		30 mg/mouse	lung inflammation and cardiovascular functions	1.DEP induced a significant increase in the number of leukocytes in whole blood and IL-6 concentration in plasma	(Nemmar et al., 2011a)

								2. low concentrations of DEP (0.1–1μg/ml blood) caused platelet aggregation	
Tnf-/- mice (B6, 129S-Tnftm1Gk1), C57 BL/6J and BALBcJ mice were purchased from Taconic Europe		The study consists of four parts: 1) a single exposure of BALBcJ mice to 20 or 80 mg/m^3 SRM1650, 2) a single dose exposure of C57xCBA mice to 80 mg/m^3 SRM2975, 3) a single dose exposure of Tnf-/- mice and Tnf+/+ mice to 20 mg/m^3 SRM2975, and 4) four repeated. exposures of Tnf-/- mice and Tnf+/+ mice to 20 mg/m^3 SRM2975.	inhalation exposure	DEP		low dose group (20 mg/m^3) high dose group (80 mg/m^3)	cytokine expression and neutrophilic inflammation	1.increased the expression level of Mip-2, independently of Tnf status 2. DEP-induced expression of Mcp-1 and Il-6 occurred in the absence of Tnf	(Saber et al., 2006)
Twelve-week-old male ApoE$^{-/-}$ mice		Mice, with either scaffold implantation or hindlimb ischemia, were exposed to either diluted WDE (whole diesel exhaust, containing DEP [DEP] at a concentration of about 1 mg/m^3, as well as all of the gaseous pollutants in the exhaust).	inhalation exposure	DEP		1 mg/m^3	DEP caused cell death	1. increased inflammatory cell infiltration in the tissues and scaffolds. 2.induced vasculogenesis, which was manifested by increased CD31 and α-SMA expression in the scaffolds 3. resulted in decreased eNOS expression, which may lead to hypoxia by	(Xu et al., 2009)

								decreasing the vascular production of nitric oxide	
WKY rats		WYK rats were exposed for 4 weeks to DE (0, 50, 150, 500 μg/m^3) by inhalation. DE particles (DEP) were administered intratracheally once (600μg/mouse) or 8 times (100μg/mouse) across 28 days to male mice (Trem2+/+,Trem2-/-, PHOX+/+, and PHOX-/-).	inhalation exposure	DEP		0, 50, 150, 500 μg/m^3	neuroinflammation	1.TREM2 protein was globally diminished, indicating impaired TREM2 expression 2. TREM2 regulates the DEP-induced gene expression of Ncf1 and Ncf2, genes that encode two cytosolic components of NADPH oxidase	(Greve et al., 2020b)
Male C57Bl/6 mice		At 16 weeks of age, animals were randomly divided into room air- and diesel exhaust particle (DEP)-exposed groups for four weeks.	inhalation exposure	DEP		15 ng of freshly vortexed DEP per exposure in a bolus of approximately 20μL (3 μg/mL in the plasma)	the function of macrophage mitochondrial	1.DEP Increases Plasma Cytokines and Ceramide 2. IL-1β TNF-α were measured, revealing a several-fold increase	(Gibbs et al., 2019)
Female ApoE$^{-/-}$ mice fed a Western diet,		Female ApoE$^{-/-}$mice and wild-type (C57Bl/6) mice were gavaged with DEP (SRM2975) doses corresponding to mucociliary clearance from inhalation exposure (200 or 1000 ng/day, 3times	oral administration	DEP		200 or 1000 ng/day, 3 times a week for 3 months;	function of the gut microbiota	1. In ApoE$^{-/-}$ mice, β-diversity was modified by DEP 2. In C57BL/6 mice, DEP	(Van den Brule et al.,

and wild-type (C57Bl/6) mice		a week for 3 months; and 40, 200 or 1000 ng/day, 3 times a week for 6 months, respectively)				and 40, 200 or 1000 ng/day, 3 times a week for 6 months		reducedα-diversity (Shannon and Simpson indices), and modifiedβ-diversity	2021)
C57BL/6Jpun/pun mice were obtained from the Jackson Laboratory		Pregnant dams were DEP treated by gavage (0.2ml suspension in PBS) for five consecutive days at 10.5–15.5 dpc once a day at doses of 31.25, 62.50, 125, 250, and 500mg/kg/day. A control group received PBS. Another group of mice was administered CB particles suspended in PBS at 500 mg/kg/day. For each group 4–6 dams were exposed	by gavage and inhalation	DEP		31.25, 62.50, 125, 250, and 500mg/kg/day	DNA deletions after transplacental exposure	1. DEP exposure during gestation resulted in significantly elevated frequencies of DNA deletions in offspring. 2. DEP exposure by the inhalation route showed that DEP induce oxidative DNA damage	(Reliene et al., 2005)
ICR male mice that have been reported to be highly responsive to LPS		The LPS group received 100 μg of LPS dissolved in the identical vehicle. The DEP group received 250 μg of suspended DEPs in the same vehicle. The suspension was sonicated for 3 minutes with an ultrasonic disrupter. The LPS DEP group received the combined treatment of LPS and DEPs.	Intratracheal instillation	DEP		949×10^4 $\pm17\times10^4$ EU/ml	lung inflammation	increased local expression of IL-1β, ICAM-1, and chemokines, such as MIP-1α, MCP-1, and KC	(Takano et al., 2002)
10–12-week-old C57Bl/6 wild-type and $ApoE^{-/-}$ mice		C57Bl/6 and $ApoE^{-/-}$mice were intranasally treated with DEP (DEP; standard reference material 1650b, National Institute of Standards in Technology (NIST, USA) or solvent (PBS) 2 μg DEP was solved in 20 μL PBS and sonicated	intranasal instillation	DEP		1 mg/ml	endothelial progenitor cells and on the associated vascular	exposure to DEP reduces the number of circulating EPC and impairs EPC function in two different mouse models, namely	(Poss et al., 2013)

(C57Bl/6 genetic background, bred at our own facilities)		for 5 min before each administration. Instillation was performed in inhalative anesthesia with isoflurane using a micropipette (Greiner).					damage	C57Bl/6 wild-type and ApoE$^{-/-}$mice.	
Sixteen-week-old Male WKY rats		The tail was disinfected with ethanol, and 150µl of vehicle or doses of 0.02 mg or 0.1 mg DEP/kg corresponding to about 8µg or 44 µg DEP/rat were injected into the tail vein. 48 hours after the systemic administration of DEP, the animals were subjected to blood collection and cell counting and perfusion fixation and tissue sampling	inject into the tail vein	DEP		0.02 mg or 0.1 mg DEP/kg per animal	lung inflammation	increase of monocytes and granulocytes numbers	(Nemmar and Inuwa, 2008)
Male and female hamsters (Pfd Gold, University of Leuven, Belgium)		The tracheal zone was shaved and disinfected with ethanol (70%), and the trachea was exposed for the intratracheal administration of 120 µL of vehicle or DEPs (5, 50, or 500 µg per animal)	inject into vein	DEP		5, 50, or 500 µg per animal	thrombosis and lung inflammation	DEPs can enhance peripheral vascular thrombosis, and that they do so in association with platelet activation	(Nemmar et al., 2003)
Male Wistar rats (Taconic Farms Inc., Germantown, NY), aged		A Becton Dickinson 18 Gauge cannula (Franklin Lakes, NJ) was inserted via the mouth into the trachea. DEP suspension (0.5 or 1 mg/kg in 150µl) or vehicle only were instilled (150 µl) via a sterile syringe and followed by an air bolus of	Intratracheal instillation	DEP	analyzed the size of DEP used in the present study by transmission electron	0.5 or 1 mg/kg in 150µl normal saline	Acute Renal Failure	DEP deposited in the lungs can aggravate experimental acute renal failure by the concomitant	(Nemmar et al., 2010b)

10–12 weeks and initially weighing 258±6 g		100 µl			microscopy			administration of cisplatin	
Six-week-old female BALB/c mice, weighing 16–19 g	The mice were divided into four groups, each consisting of 10 mice	Group A, PBS-exposed group; Group B, DEP-exposed group; Group C, HDM-exposed group; and Group D, HDM and DEP co-exposed group	Intratracheal instillation	DEP		100 µg DEP suspended in 20 µl of 0.05% Tween 80-PBS	allergic rhinitis	The mice exposed only to DEP showed no increase in allergic symptoms	(Jung et al., 2021)
Female ApoE$^{-/-}$ knockout mice and C57BL/6J ApoE$^{+/+}$mice		The mice were given i.p. injections of DEP suspended in saline in the following concentrations: 0, 0.5 and 5 mg/kg bodyweight, 1 h prior to sacrifice by cervical dislocation (n= 8 per group); The doses in the in vitro experiments (10 and 100µg/ml) were chosen to mimic a circumstance where all particles were translocated from the peritoneum to the circulation (assuming mice weighing 20 g have 1 ml vascular fluid)	internal exposure: intraperitoneal injection and external exposure: inhalation exposure	DEP		internal exposure: 0, 0.5 and 5 mg/kg bodyweight external exposure: 10 and 100 µg/ml	lung inflammation and cardiovascular functions	acute systemic exposure to DEP at a modest dose impairs the endothelium-dependent vasorelaxation only in mildly atherosclerotic vessels of ApoE$^{-/-}$mice	(Hansen et al., 2007)
Male TNF-R1-deficient mice (C57BL/6-Tnfrsf1atm1	10 rats or 15 mice	Freshly isolated capillaries were exposed to DEPs at the concentrations indicated for 6 h at room temperature without or with modulators	2 mg of DEPs was suspended in 10 ml PBS buffer	DEP		2mg/10ml PBS	brain inflammation	DEP exposure up-regulates P-glycoprotein in brain capillaries and NADPH	(Hartz et al., 2008)

Imx) and wild-type mice (C57BL/6 background)									
Adult male ApoE$^{-/-}$mice (N = 20) and the background strain (C57bl6 mice; N = 16) were purchased from Charles River (Margate, UK)	Adult male ApoE$^{-/-}$ mice (N = 20) and the background strain (C57bl6 mice; N = 16)	ApoE$^{-/-}$mice were fed a'Western diet'(8 weeks) to induce atherosclerotic plaques, with parallel experiments in normal chow fed wild-type mice. During the last 4 weeks of feeding, mice received twice weekly instillation (oropharyngeal aspiration) of 35 µL DEP (1 mg/mL, SRM-2975) or vehicle (saline).	oropharyngeal aspiration	DEP		DEP (1 mg/mL, SRM-2975)	Atherosclerosis	in the murine apolipoprotein E deficiency model, instillation of DEP increased lesion size, produced more lesions per vessel and generated more buried fibrous caps.	(Miller et al., 2013)
Adult male Wistar rats (200-250 g; Charles River, Mar-gate, UK;)	at least 4 animals per treatment group	rats were anesthetised, using 5% isoflurane inhalation (Meriol, Essex, UK), and positioned head-upwards on a board. The vocal chords were visualised by passing apediatric laryngoscope with a plastic cannula into the trachea. Particles (0.5 mg/rat) or vehicle (saline) were then instilled as a 0.5 mL bolus.	intratracheal instillation	DEP		DEP (1 mg/mL, SRM-2975)	pulmonary and systemic inflammation	Exposure of rats to DEP induces both pulmonary and systemic inflammation, but does not modify endothelium-dependent vasodilatation	(Robertson et al., 2012)

Female Balb/c mice (Orient Bio, Seongnam, Korea) weighing 16.10 ± 0.52 g	5 experimental groups (n = 5 per group)	The mice in the naive control group received no treatment for the entire experiment. The mice in the vehicle control group received 50 μL saline containing 0.05% (v/v) Tween 80 (Sigma-Aldrich Corp., St.Louis, MO, USA). The mice in the DEP 25, DEP 50, and DEP 100 groups were intratracheally instilled with25 μg, 50 μg, and 100 μg DEP	intratracheal instillation	DEP		DEP (1 mg/mL, SRM-2976)	lung inflammation	Conclusions DEP may contribute to neutrophilic lung inflammation pathogenesis by modulating ER stress-mediated CXCL1/KC expression in alveolar macrophages	(Kim et al., 2020a)
Forty-two male Big Blue®(Fischer) rats, approximately 8 weeks of age from Stratagene (La Jolla,USA)	Animals were assigned to seven groups (six ani-mals/group)	Animals were assigned to seven groups (six animals/group), which were fed with 0, 0.2, 0.8, 2, 8, 20 or 80 mg DEP/kg Altromin diet prepared by Altromin in Germany	feed	DEP		0, 0.2, 0.8, 2, 8, 20 or 80 mg DEP/kg	DNA damage in lung	Primary DNA damage was observed in the lung after oral exposure to DEP. The level of DNA strand breaks, bulky DNA adducts and oxidized bases increased especially in the intermediate dose levels	(Muller et al., 2004)
Forty-seven male Fischer rats 344, 9 weeks of age, from Taconic, Europe (Ry, Denmark)	The rats were randomly assigned to six groups (n= 8, except the group	0 mg/kg bodyweight (control), 0.064 mg/kg bodyweight (low dose), and 0.64 mg/kg bodyweight (high dose) were exposed to Standard Reference Material 2975 at 0.064 or 0.64 mg/kg bodyweight for 6 and 24 h	oral gavage	DEP		0.064 or 0.64 mg/kg body weight	DNA damage, oxidative stress and DNA repair in colon epithelial cells, liver, and lung	The levels of 8-oxodG in the lung, liver, and colon were significantly increased after high dose DEP-exposure at6 and 24h post-exposure; whereas the 8-oxodG level was unaltered for	(Danielsen et al., 2008)

	exposed 6 h to the low dose of DEP that contained 7 rats)							the low dose DEP-exposure at 6 and 24 h compared to the control.	
male Sprague-Dawley rats		alveolar macrophages were isolated from male Sprague-Dawley rats by bronchoalveolar lavage. alveolar macrophages were incubated with 0, 5, 10, 20, 50, or 100 pg/mL of DEP (2.5 x 105 particles/ pg DEP), methanol-washed DEP, or equivalent concentrations of DEP methanol extracts at 37°C in 5% CO_2.	DEP was dissolved in PBS, add to the medium	DEP		0, 5, 10, 20, 50, or 100 pg/mL of DEP	the release of proinflammatory cytokines, interhkin-1 (IL-I), and tumor necrosis factor-alpha (TNF-α) by alveolar macrophages (AM)	evidence that DEP enhanced the production of IL-l by AM in vitro suggests that this proinflammatory cytokine may play a role in the pulmonary response to DEP inhalation.	(Yang et al., 1997)
40 time-mated, nulliparous, young adult mice (C57BL/6BomTac, Taconic Europe, Ejby,	Control group (n = 20), Treatment group (n=20)	The two groups of mice were exposed to either filtered clean air or approximately 20 mg DEP/m^3 on GDs 7–19 for one hour/day.	inhalation exposure	DEP		20 mg/m^3	postnatal development, behavior, genotoxicity and inflammation	In utero exposure to DEP decreased weight gain during lactation the mRNA expression levels were slightly higher in the DEP exposed pups	(Hougaard et al., 2008)

Denmark)									
Sixteen-week-old male SHR (Taconic Farms Inc., Germantown, NY, USA)	Control group (n = 9), Treatment 1 group (n=6), Treatment 2 group (n=6)	The tail was disinfected with ethanol, and 150µl of vehicle (n= 9) or doses of 0.01 (n= 6) or 0.02 (n= 6) mg DEP/kg corresponding to about 2.8 or 5.6 µg DEP/rat were injected into the tail vein.	inject into the tail vein	DEP		0.01, 0.02 mg/kg	systolic blood pressure, heart rate, and both systemic and pulmonary inflammation in spontaneously hypertensive rats	DEP exposure (0.02 mg/kg) significantly elevated the number of leukocytes in blood, IL-6, tumor necrosis factor alpha and LTB4 concentrations in plasma	(Nemmar et al., 2009)
male C57BL/6 mice 6–8 weeks old	A minimum of 5 animals were used for each endpoint	animals were anesthetized using vaporized halothane and suspended on their incisors. The tongue was distended and a bolus of either 50 µl HBSS vehicle or 25 µg DEP in 50 µl HBSS was injected onto the oropharynx	inject onto the oropharynx	DEP		0.5 µg/µl	allergic inflammation	Th2-type cytokines, such as IL-4 and IL-13, and markers of eosinophil chemotaxis, such as CCL11 and CCR3, were increased	(Jaspers et al., 2009)
Male TO mice (30–35 g, HsdOla:TO, Harlan, UK)		A Becton Dickinson 24 Gauge cannula was inserted via the mouth into the trachea. Either the DEP suspensions (15 µg/mouse) or saline-only were instilled intratracheally (i.t.) (40 µl) via a sterile syringe and followed by an air bolus of 50µl.	intratracheal instillation	DEP		0.1–1µg/ml, 0.25–1 µg/ml	Exacerbation of thrombotic events	1.The direct addition of DEP(0.1–1µg/ml) to untreated mouse blood significantly induced in vitro platelet aggregation 2.In vitro exposure to DEP (0.25–1µg/ml) led to activated intravascular coagulation, both the	(Nemmar et al., 2011b)

								APTT and the PT were shortened	
Female CD1, C57BL/6, or BALB/c mice (Charles River, Margate, UK)		Mice were exposed once daily to either 80 mg of DEPs dissolved in 40 mL of PBS, after 3 exposures, mice were anesthetized before intranasal infection with 1×10^5 CFU of D39 in 10mL of PBS Control mice were treated with 10mL of PBS only.	intratracheal instillation	DEP		0.5 mg/mL DEP	susceptibility to invasive pneumococcal disease	Alveolar macrophages become congested with DEPs, which reduces their phagocytic function and leads to increased production of proinflammatory cytokines.	(Shears et al., 2020)
9-wk-old male Sprague-Dawley (Harlan Hsd:SD) rats	Control group (n = 7), Treatment group (n=8)	rats were randomly divided into two groups: vehicle (0.9% saline+0.02% Tween 80; n=7) and DEP (SRM2975, 0.2 mg/ml in 0.9% saline+0.02% Tween 80; n=8)	inhalation after aerosolize	DEP		8.75 mg/m^3	cardiac dysfunction	through the activation of the AHR, exposure to DEP induces ECM remodeling by shifting the collagenous ECM balance toward degradation, leading to loss of collagen, and ultimately causing ventricular dilation and dysfunction.	(Bradley et al., 2013)
A total of 32 female BALB/c mice, 6 weeks of age	4 group (n = 8 for each group)	4-week and DEP 8-week groups were exposed to 100 μg/m^3 DEPs for 1 hour a day for 5 days a week. Control mice were exposed to saline solution for durations identical to those in the treated mice.	inhalation exposure	DEP		100 μg/m^3	Nasal Inflammatory	With a 4-week exposure, 173 genes were upregulated and 105 genes were downregulated. With an	(Kim et al., 2020a)

								8-week exposure, 371 genes were upregulated and 338 genes were downregulated. Interestingly, longer exposure to DEP triggered larger scale differential gene expression than shorter exposure.	
6-week-old female BALB/c mice	Control group (n = 8), Treatment group (n=8)	The DEP-treatment group (n = 8) inhaled 100 μg/m^3 DEPs via an ultrasonic nebulizer for one hour per day, five days a week, for four weeks, with an output of 1 mL/min and 1 to 5 μm particle size. The control group (n = 8) was treated with saline solution under the same conditions as the experimental group	inhalation after aerosolize	DEP		100 μg/m^3	olfaction diseases	Exposure to DEPs decreases olfactory sensitivity in mice. 397 up-regulated genes and 134 down-regulated genes were differentially expressed by DEP exposure in the mouse nasal tissue.	(Kim et al., 2020b)
Adult male TLR4-deficient (TLR4$^{-/-}$) and female TLR4-heterozygous	DEP group, n=9; VEH group, n=7	Beginning on the morning of E2, time-mated females were treated with DEP delivered by oropharyngeal aspiration. Females received 50μg DEP suspended in 50 μl vehicle (DEP group, n=9) or 50μl vehicle (VEH group, n=7) on E2, E5, E8, E12, and E16	inhalation exposure	DEP		50 μg DEP suspended in 50 μl vehicle	neurodevelopmental disorders	1.DEP exposure increased inflammatory cytokine protein and altered the morphology of microglia 2.DEP-induced activation of microglia is	(Bolton et al., 2017)

(TLR4$^{-/-}$; C57BL/6 background)								dependent on TLR4	
Male TO mice (HsdOla: TO, Harlan, UK)		Four weeks following induction of diabetes, the animals were intratracheally instilled (i.t.) with DEP (0.4 mg/kg) or saline, and several cardiovascular endpoints were measured 24 h thereafter.	intratracheal instillation	DEP		0.4 mg/kg	diabetes	DEP caused leukocytosis and a significant increase in plasma C-reactive protein and 8-isoprostane concentrations in diabetic mice.	(Nemmar et al., 2013)
pregnant ICR mice obtained from SLC Co. (Shizuoka, Japan)	n=30	DEP suspensions (200 μg/kg body weight) were injected subcutaneously into 15 pregnant mice on gestation days 6, 9, 12, 15, and 18. The total dose of DEPs was adjusted to approximately 1 mg/kg body weight.	inject subcutaneously	DEP		1 mg/kg body weight	spatial learning and memory ability reduction	DEP-exposed mice exhibited decreased hippocampal NR2A expression	(Yokota et al., 2015)
pregnant ICR mice obtained from SLC Co. (Shizuoka, Japan)	n=30	DEP suspensions (200 μg/kg body weight) were injected subcutaneously into 15 pregnant mice on gestation days 6, 9, 12, 15, and 18. The total dose of DEPs was adjusted to approximately 1 mg/kg body weight.	intratracheal instillation	DEP		1 mg/kg body weight	anxiogenic effects	prenatal DEP exposure increases anxiety like behavior in male offspring later in life, and increases 5-HT levels in the DRN via chronically increased 5-HT neuronal activity	(Yokota et al., 2016)
male Sprague		Cardiomyocytes were treated for 1 h with DEP; diluted to 0.25, 0.50, 1.0, and 25 μg/ml; and	add to culture medium	DEP		Cardiomyocytes: 0.25, 0.50,	cardiomyocyte and lung	Direct treatment of cardiomyocytes with	(Gorr et al.,

Dawley rats (2 to 4 mo old)		filtered through 5 µm filter paper to remove aggregates. DEP was added in culture at various concentrations to the apical chamber of the polarized lung epithelial cells.				1.0, and 25µg/ml lung epithelial cell: 1mg/ml	function damage	DEP caused contractile dysfunction and alterations in calcium handling	2015)
3-week-old wild-type Balb/c mice		Lungs of mice were exposed by pharyngeal aspiration nine times over 3 weeks to DEP at 1.2 or 6.0 mg/kg body weight, HDM at 0.8, 1.2 or 6.0 mg/kg of DEP in combination with HDM, or the same volume (50 µl) of 0.9% sterile saline	intratracheal instillation	DEP		0.8, 1.2 or 6.0 mg/kg of DEP	allergic asthma	1.2 mg/kg of DEP caused no detectable lung inflammation, but 6.0 mg/kg of DEP induced neutrophilic influx	(Acciani et al., 2012)
adult male Sprague Dawley rats	n=12	In 5 rats (DEP group), DEP dissolved in 0.1 ml PBS was given via endotracheal intubation with the concentration of 100, 200 and 400µg/ml. The lung burden of DEP per rat was 10, 20 and 40 µg at the DEP concentration of 100, 200 and 400 µg/ml, respectively. The same amount of PBS and combined DEP and NAC (5 mmol/L) were given in 4 rats (control group) and in 3 rats (NAC + DEP group)	intratracheal instillation	DEP		100, 200 and 400 µg/ml PBS	cardiovascular impairment	DEP increases APD, spontaneous triggered activity and arrhythmia; DEP increases ROS generation in cardiomyocytes.	(Kim et al., 2012)
female C57BL/6Tac mice	492	mice were exposed to a single dose of collected particles of either 6µg, 18µg or 54µg per mouse by intratracheal instillation (6–8 mice per dose per exposure) First cohort was exposed to RME13 and CB, second cohort was exposed to DEP13, third cohort was exposed to DEP9.7, fourth cohort was exposed to DEP17, and fifth cohort was	intratracheal instillation	DEP	The OC and EC of the extracted particles were measured with a thermal-optical carbon analyzer (Sunset Laboratory Inc.),	6µg, 18µg or 54µg per mouse	Inflammation, liver and lung damage	1. Exposure to diesel exhaust particulates caused lung damage in mice and the accumulation of particulates in the lungs of mice. 2. Diesel exhaust gas	(Bendtsen et al., 2020)

		exposed to HVO13. For each exposure cohort there were four vehicle control mice			using the EUSAAR_2 protocol.			exposure caused inflammation and acute phase reactions in mice 3. Cause an increase in SAA3 mRNA levels 4. Cause DNA damage and ROS generation	
Adult male Sprague-Dawley rats (250–350 g)		DEP (1.0 μg/ml) was dissolved by thorough sonication in the contracting buffer. For function studies, isolated ventricular myocytes were divided into eight groups. Control (Ctrl): cells were cultured overnight in standard medium; HG: cells were cultured overnight in a media with a high concentration of glucose (25.5 mM) (i.e. diabetic-like media); DEP: cells were cultured overnight with DEP (0.1 μg/ml); HG+DEP: cells were cultured overnight in the presence of both HG (25.5 mM) and DEP (0.1 mg/ml); The next four groups were similar to the initial four groups except that all were treated with antioxidants.	add to culture medium	DEP		1.0 μg/ml	cardiomyocyte dysfunction	DEP and high glucose alter the local chemical, mechanical, and/or electrical environment through the activation of ROS generators, potentially including the mitochondria and NADPH oxidases	(Zuo et al., 2011)
Adult male and female C57BL/6 mice		Females received 50 μg DEP suspended in 50 μl vehicle (DEP group; n= 5 dams from cohort 1, n= 3 dams from cohort 2) or VEH group; n= 7 dams from cohort 1, n= 5 dams from cohort 2)	inhalation exposure	DEP		50 μg DEP suspended in 50 μl vehicle	metabolic and neuroinflammation	DEP male offspring mounted an exaggerated peripheral IL-1bresponse to an LPS challenge at	(Bolton et al., 2014)

		every 3 days for a total of 6 doses, as a model of intermittent exposure.						postnatal day (P)30, whereas their central IL-1bresponse did not differ from VEH male offspring, which is suggestive of macrophage priming due to prenatal DEP exposure	
Eight-week-old B6C3F1 male and female mice (Jackson laboratories; Bar Harbor, ME)	DEP-treated group (n=24) and the controls (n=24)	Mice were exposed at a concentration of 1 mg/m^3 or filtered air for 4 hr/day, (5 days/week) from the beginning of gestation until the first week after birth	inhalation exposure	DEP		1 mg/m^3	locomotor activity and repetitive behaviors increase	exposures to DEP during gestation and early life may impair brain development leading to autism-like symptoms	(Rajamani et al., 2013)
pregnant female NMRI mice	n=30	Three groups of pregnant mice were exposed to 350–400 µg DEPs/m^3 for 2, 4 and 6 h daily in a closed system room	inhalation exposure	DEP		350–400 µg DEPs/m^3	anxiety, spatial memory disorders	DEPs exposed mice exhibited decreased hippocampal NR2A and NR3B expression	(Ehsanifar et al., 2019)
Male TO mice (25–30 g, HsdOla:TO, Harlan, UK)		DEP (0.5 mg/kg in 150 µl saline) was intratracheally (i.t.) instilled every 4th day for 4 weeks (7 i.t. instillation). Four days following the last exposure to either DEP or saline (control), various renal endpoints were measured.	intratracheal instillation	DEP		0.5 mg/kg in 150 µl saline	renal oxidative stress, inflammation and DNA damage	The antioxidant calase was significantly decreased in adenine	(Nemmar et al., 2016)

Adult male Wistar rats (200-250 g; Charles River, Margate, UK)		DEP (0.5 mg) or an equivalent volume (0.5 mL) of 0.9% saline was administered by intra-tracheal instillation under light anaesthesia an additional group of instilled saline	intratracheal instillation	DEP		1 mg/ml	susceptibility to myocardial ischemia/reperfusion injury	diesel exhaust particulate increases vulnerability to ischemia-associated arrhythmia and reperfusion injury. These effects are mediated through activation of pulmonary TRPV1, the sympathetic nervous system and locally generated oxidative stress	(Robertson et al., 2014)
Male ICR mice (6 weeks old, 29-33 g)		ICR mice were divided into six experimental groups which received intratracheal inoculation of vehicle, LPS alone (2.5 mg/kg), organic chemicals in DEP (DEP-OC: 4 mg/kg) extracted with dichloromethane, residual carbonaceous nuclei after the extraction (washed DEP: 4 mg/kg), DEP-OC+LPS, or washed DEP+LPS	intratracheal instillation	DEP		4 mg/kg body weight	lung inflammation	exposure to washed DEP enhances circulatory level of chemokines during lung inflammation	(Arimoto et al., 2007)
Male ICR mice 6 to 7 weeks of age and weighing 29 to 33 g (Japan Clea Co., Tokyo, Japan)		ICR mice were divided into six experimental groups which received intratracheal inoculation of vehicle, LPS (lipopolysaccharide) alone (2.5 mg/kg), organic chemicals in DEP (DEP-OC: 4 mg/kg) extracted with dichloromethane, residual carbonaceous nuclei after the extraction (washed DEP: 5 mg/kg), DEP-OC+LPS, or washed DEP+LPS	intratracheal instillation	DEP		5 mg/kg	lung inflammation	both DEP components exacerbate vascular permeability and the increased fibrinogen and E-selectin levels induced by LPS	(Inoue et al., 2006)

5-week old female C57BL/KsJ-db/db Jcl (db/db) mice and C57BL/KsJ-db/+m Jcl(db/+m) mice	Control group (n = 16), Treatment group (n=24)	Db/db mice and db/+m mice were randomly divided into four experimental groups: the db/db-vehicle group, the db/db-DEP group, the db/+m-vehicle group, and the db/+m-DEP group. The vehicle groups intratracheally received 100 µl of phosphate-buffered saline at pH 7.4 containing 0.05% Tween-80 every two weeks. The DEP groups intratracheally received 100 µg DEP in the same vehicle every two weeks.	intratracheal instillation	DEP		1 µg/µl	fatty change of the liver	pulmonary exposure to DEP, particulate air pollutants, enhances fatty change in the livers of diabetic obese mice. The enhancement is concomitant with oxidative stress in the liver.	(Tomaru et al., 2007)
Female B6C3F1 mice (6-8 week old)		The mice were exposed to 1, 5, or 15 mg DEP/kg of body weight 3 times in a period of 2 weeks, i.e., Monday and Friday of the first week and Wednesday of the second week, or 6 times over 4 weeks. For the AFC experiment, 2 additional doses, 0.05 and 0.2 mg/kg, were included. The volume of instillation was 25 µl/10 g of body weight. Control animals received the same volume of sterile saline.	inhalation exposure	DEP		1, 5, or 15 mg DEP/kg of body weight	immune response	Exposure to DEP also resulted in a significant decrease in the absolute numbers and the percentages of total spleen cells for total, $CD4^+$, and $CD8^+$ T cells	(Yang et al., 2003)
Male BALB/c ByJ mice		BALB/c ByJ mice were randomly divided into four experimental groups. Two groups received nasal instillations of saline and the other two groups received 3 mg/ml SHE during 5 days per week for 3 weeks. One group in each pair also received 150 µg of DEP in the same instillations 3 days per week.	intratracheal instillation	DEP		150 µg/20µl saline	inducing asthma to low doses of allergens	inhalation of DEP increased neutrophils and decreased total monocytes	(De Homdedeu et al., 2021)

cardiac myocytes of wistar rats		Each concentration of DEPE (5 µg dry DEP was suspended in 5 ml PBS containing 0.05% Tween 80) was dissolved in serum-free D-MEM/F-12 (10% of volume), and incubated in humidified 5% CO_2– 95% air at 37°C with cells. For experiments of chronic exposure to DEPE, cells were incubated for 24 or 48 h. For experiments of short-time exposure of DEPE, cells were incubated for 1, 2, 4, or 8 h and then medium containing DEPE was replaced by normal serum-free medium and incubated for further 24 h.	DEP was dissolved in PBS, add to the medium	DEP		0,20,40,60,80 ,100µg/ml	cause cardiac myocytes death	Cardiac myocytes showed 50% damage with 50 µg/ml DEPE exposure for 24 h or 4 h and incubated with normal medium for a further 24 h. DEPE-induced cytotoxicity was markedly reduced by SOD activity, catalase activity, and MPG levels	(Okayama et al., 2006)
male BALB/c mice	Control group (n = 30), Treatment group (n=30)	male BALB/c mice were divided into two groups: (a) Saline: nasal instillation of saline (n = 30); and (b) DEP: nasal instillation of 30 µg of DEP/10 µl of saline (n = 30). Nasal instillations were performed 5 days a week, over 30 and 60 days	intratracheal instillation	DEP		30 µg of DEP/10 µl of saline	respiratory tract inflammation	a low-dose of DEP over 60 days induces respiratory tract inflammation The expression of Muc5ac mRNA increased with 60 days of DEP exposure	(Yoshizaki et al., 2010)
Male Brown Norway rats [BN/CrlBR] weighing 200 -250 g		rats were exposed to either filtered air or DEP (20.62±1.31 mg/m^3) for 4 h/day for 5 consecutive days using a nose-only directed flow exposure unit followed by intratracheal inoculation with 100,000 Listeria at 2 h after the last DEP exposure	inhalation exposure	DEP	DEP concentrations in the exposure unit were monitored by both gravimetric	20.62±1.31 mg/m^3	Suppression of immune response	DEP inhibited AM production of IL- 1β, TNF-α, and IL-12 but enhanced Listeria-induced AM production of IL-10, which has been	(Yin et al., 2004)

					sampling of dust collected on a polycarbonate membrane filter (37mm, 0.45µm, Poretics Corporation, Livermore, CA) at a sampling rate of 1 l/min and a Grimm Model 1.108 portable dust monitor (GRIMM Technologies, Inc., Douglasville, GA)			shown to prolong the survival of intracellular pathogens such as Listeria	
Male Brown Norway (BN) rats [BN/CrlBR] weighing 200–250 g		rats were exposed to either filtered air or DEP (21.2 ± 2.3 mg/m^3) for 4 h/day for 5 consecutive days using a nose-only directed flow exposure unit Brown Norway rats were exposed to filtered air or DEP by inhalation at a dose of 21.2 ± 2.3 mg/m^3, 4 h /day for 5 days, and intratracheally instilled with saline or 100,000 Listeria monocytogenes (Listeria) 7 days after the final DEP exposure.	inhalation exposure	DEP	DEP concentrations in the exposure unit were monitored by both gravimetric sampling of dust collected on a polycarbonate	21.2 ± 2.3 mg/m^3	Suppression of immune response	DEP was found to inhibit Listeria-induced production of IL-1band TNF-α, which are responsible for the innate immunity, and IL-12, which initiates the development of T helper (Th)1 responses, but	(Yin et al., 2005)

					membrane filter (37mm, 0.45µm, Poretics Corporation, Livermore, CA) at a sampling rate of 1 l/min and a Grimm Model 1.108 portable dust monitor (GRIMM Technologies, Inc., Douglasville, GA)			enhance Listeria-induced AM production of IL-10, which prolongs Listeria survival in these phagocytes.	
C57 mice (10-week)		C57 mice were received a tail vein injection of DEP at high dose (0.5 µg/g of body weight) or low dose (0.25 µg/g of body weight) (7.5 or 15 µg DEP suspended in 200 µl saline), and sacrificed at 1-h post-injection. The dose was calculated by assuming a 3-day exposure at 125 (DEP-low) or 250 µg/m^3 (DEP-high), and 2% of DEP was translocated to the blood stream. 200 µl saline injection was used as the control	inject into the tail vein	DEP		high dose (0.5 µg/g of body weight) low dose (0.25 µg/g of body weight)	inflammation and vascular effects	Acute systemic DEP exposure caused a significant increase in TNF-α, peripheral neutrophil and band cell counts	(Bai and Van Eeden, 2013)
Male BALB/cOla Hsd mice (7–	n=18	3 mice for each experimental group were intratracheally instilled, and the experiments were replicated twice, for a total of 6 sham, 6	intratracheal instillation	DEP		0.5 µg/µL saline	oxidative stress and Inflammation	DEP exposures induced inflammatory pathways in mouse brain and DEP	(Milani et al., 2020)

8 weeks)		biomass burning-derived (BB) particles-treated, and 6 DEP-treated mice, Intratracheal instillations with 50 µg of BB or DEP in 100 µL of isotonic saline solution or with 100 µL of isotonic saline solution were achieved by means of a MicroSprayer®Aerosolizer system					in brain	showed strong oxidative stress	
9week-old C57BL/6J male mice	the mice were randomly divided into 4 exposure groups with 15 mice in each group	A cannula (18 Gauge, Becton Dickinson, USA) was inserted via the mouth into the trachea. The exposed samples PBS, DEP, water-soluble DEP (WS), water-insoluble DEP (WIS) exposure groups with 20 µL each) were intratracheally instilled via a sterile syringe and followed by 150 µL air bolus.	intratracheal instillation	DEP		2 mg/ml	Blood Coagulation Function	BT, FIB, APTT and PT altered or showed a lower tendency after DEP, WS and WIS exposure	(Lei et al., 2021)
Adult male Sprague–Dawley rats (250–300 g)	Control group (n = 4), Treatment group (n=12)	In 12 rats (DEP group), DEP dissolved in 0.1 ml PBS was given via endotracheal intubation at the concentrations of 200 µg/ml for 1 h. The lung burden of DEP per rat was 20 µg at the DEP concentrations of 200 µg/ml, respectively. For the control (n=4), the same amounts of PBS were given via endotracheal intubation, respectively.	intratracheal instillation	DEP		200 mg/l	retinal thickening	Among the retinal structure, inner plexiform, inner and outer nuclear and rod/cone cell layers were significantly thickened after DEP exposure	(Kim et al., 2016)
female white rats (Rattus novergicus)	Control group (n = 10), Treatment 1 group	Control group without soot particulate exposure-(n=10); Treatment 1 group (n=2) exposed by soot particulate with the concentration of 532 mg/m^3 an hour each day for 30 days; Treatment 2 group exposed by soot particulate with the	inhalation exposure	soot		high dose (1064 mg/m^3) low dose (532 mg/m^3)	cardiovascular system disruption	The exposure to soot particulates significantly increased MAPK expression in experimental rats	(Yutanto, 2020)

	(n=12), Treatment 2 group (n=12)	concentration of 1064 mg/m^3 an hour each day for 30 days- (n=12)							
female rats (Rattus novergicus)	Control group (n=10), Treatment 1 group (n=12), Treatment 2 group (n=12)	consisted of 3 groups: Control group (n=10), without soot particulate exposure; Treatment 1 group (n=12), exposed by soot particulate with the concentration of 532 mg/m^3 an hour each day for 30 days; Treatment 2 group (n=12), exposed by soot particulate with the concentration of 1064 mg/m^3 an hour each day for 30 days	inhalation exposure	soot particulate		high dose (1064 mg/m^3) low dose (532 mg/m^3)	cardiovascular system disruption	The exposure to soot particles increased VCAM-1 expression significantly in laboratory animals	(Leonard and Aminuddin, 2020)
Male BALB/c ByJ mice (~25 gr, 6 weeks old)		in the same instillation two experimental groups received 150 mg of DEP in each of the three challenges. The experimental groups were: SS, saline-sensitized and saline-challenged; DEP, saline-sensitized and DEP-challenged; AP, AP-sensitized and AP-challenged; and AP-DEP, AP-sensitized and challenged with a mixture of AP and DEP	intratracheal instillation	DEP		1 mg/mL, SRM-2975	asthma	Mice exposed to DEP alone showed increased levels of neutrophils and NKs, reduced numbers of monocytes and alveolar macrophages, and increased levels of CD11+Ly6C-DCs.	(De Homdedeu et al., 2020)
Twelve-week-old male Wistar rats	n= 5–8 in each group	The tail was disinfected with ethanol, and 150µl of vehicle or dose 0.02 mg DEP/kg corresponding to about 4.4 µg DEP/animal were injected into the tail vein of rats. After 6 h, 18 h, 48 h and 168 h after systemically	injected into the tail vein	DEP		0.02 mg/kg	systolic blood pressure (SBP), systemic inflammation, oxidative	the platelet numbers were significantly decreased 6 h following the systemic administration of DEP. The IL-6 concentrations	(Nemmar et al., 2010a)

		injecting rats with DEP, conducted SBP measurements, blood cell counting, plasma analysis and histopathology of several major organs.					status, and morphological alterations in lungs, heart, liver and kidneys in wistar rats	in plasma were increased at 6 h and 18 h. Similarly, superoxide dismutase activity was significantly increased at 6 and 18 h following DEP exposure.	
Male ddy mice, (slc: ddy) weighing 39.6-46.0 g		All three substances, DEP, soluble-component and residual particle-component were dispersed at concentrations of 4 and 8 mg/ml using a sonicator (UH-50; SMT, Tokyo, Japan) in ice-cold PBS containing 0.05% Tween 80	intratracheal instillation	DEP		4 mg/ml, 8 mg/ml	cardiovascular function and oxidative stress	inhalation of the particle component of DEP enhances myocardial oxidative stress, and promote excessive production of cytokines, IL-6 and G-CSF	(Yokota et al., 2008)
Male WKY rats (10–12 weeks of age)		rats (n = 20 /group) were exposed for 5 hr/day, 1 day/week for 16 weeks, to either ozone or DEP or to a combination of ozone + DEP, the desired chamber concentrations were 0.5 ppm ozone and 2.0 mg/m^3 DEP	inhalation exposure	DEP		2.0 mg/m^3	vascular and cardiac impairments	exposed to DEP alone for 16 weeks, biomarkers of vascular impairments in the aorta elevate, with the loss of phospholipid fatty acids in myocardial mitochondria. there is a possible role of oxidized lipids and protein through LOX-1 and/or RAGE signaling	(Kodavanti et al., 2011)
Male Wistar	n=22	Rats of both strains were divided into 2 groups.	inhalation after	DEP		100 µg/mL	vascular	Although in vitro	(Labra

rats (Charles River Laboratories, France) and male SHR (Janvier, France)		Group 1 received PBS at pH 7.2 containing 0.05 % Tween 80, and group 2 received suspended DEP (0.8 mg) in the same vehicle, 3 times a week for 4 weeks. The rats were all 18–20 weeks old at the time of the final DEP administration and were euthanized 4 hours after the last instillation	aerosolize				oxidative stress and hypertension	exposure to DEP produces a vascular oxidative stress, repeated in vivo exposures to DEP only impair vascular function in SHR, via an upregulation of p22phox	nche et al., 2012)

From the search results, animals exposed to BC, DEP and soot were adversely affected by OS, inflammation, lipid peroxidation, atherosclerosis, changes in heart rate variability, arrhythmia, ST segment depression, changes in vascular function, etc.

4.2.2.1 Black Carbon

Few experiments were directly researching the health impact of being exposed to BC. BC exposure of rats used a continuous whole-body exposure system (ambient particles were homogeneously distributed within each cage in this system). The BC concentrations were monitored with an Aethalometer.

During the experiment, a single variable was often controlled for control experiments: rats were randomly divided into control group and experimental group, in which rats in the control group inhaled air that BC has purified, while rats in the experimental group were exposed to BC. The main ways of BC exposure were inhalation exposure (Chuang et al., 2017).

Through literature review, it is found that BC exposure mainly caused vascular injury and heart disease (Chuang et al., 2017) in rats in pathology, and BC exposure mainly caused the increase in blood pressure, heart rate, and heart rate variability in rats.

4.2.2.2 Diesel exhaust particle

In terms of pollutant sources, most of the pollutants used in animal experimental research were diesel exhaust particles (DEP), DEP were mainly from some standard samples a reference for the chemical and toxicological constitutes of the standardized DEPs such as SRM-2975 (NIST) (Miller et al., 2013) or DEP were collected from standard diesel engines (Yokota et al., 2016).

Through literature, Mice are mainly used to do acute, subacute and chronic toxicity tests, and rats are used to simulate some disease models such as Cardiovascular diseases (Nemmar et al., 2009), diabetes (Nemmar et al., 2013) and so on, in the aspect of experimental design.

During the experiment, a single variable was often controlled for control experiments: mice (or rats) were randomly divided into control group and experimental group, in which mice (or rats) in the control group inhaled air that DEP has purified, while mice (or rats) in the experimental group were exposed to DEP. The main ways of DEP exposure were intratracheal instillation (Bendtsen et al., 2020), oral gavage (Danielsen et al., 2008), feed (Muller et al., 2004), intraperitoneal injection (Huang et al., 2010), inhalation after aerosolize (Bradley et al., 2013), inhalation exposure (Greve et al., 2020a) and injected into the tail vein (Nemmar and Inuwa, 2008).

Through literature review, it is found that DEP exposure mainly caused inflammatory reaction (Jeong et al., 2021), lung injury (Bendtsen et al., 2020), vascular injury and heart disease (Nemmar et al., 2012) in mice (rats) in pathology, and DEP exposure mainly caused the increase of ROS (reactive oxygen species) in the cells (Bendtsen et al., 2020), the level of inflammatory cytokines (Kim et al., 2020a) in mouse (rat) cells, DNA damage (Danielsen et al., 2008) and some changes in mRNA levels after translation (Hougaard et al., 2008). At the same time, some intracellular signal transduction pathways were activated and the expression levels of related proteins were changed (Greve et al., 2020a) in toxicology.

4.2.3 Human clinical studies

In addition to animal experiment articles, the human clinical study is the important part of the study of toxicity mechanism. As the same of animal experiment parts, there aren't many studies. We still select the same four authoritative databases to search for human clinical studies. Searching time was 1900 to September 19th, 2021. The searching process was shown in **错误!未找到引用源。** Figure 4-6.

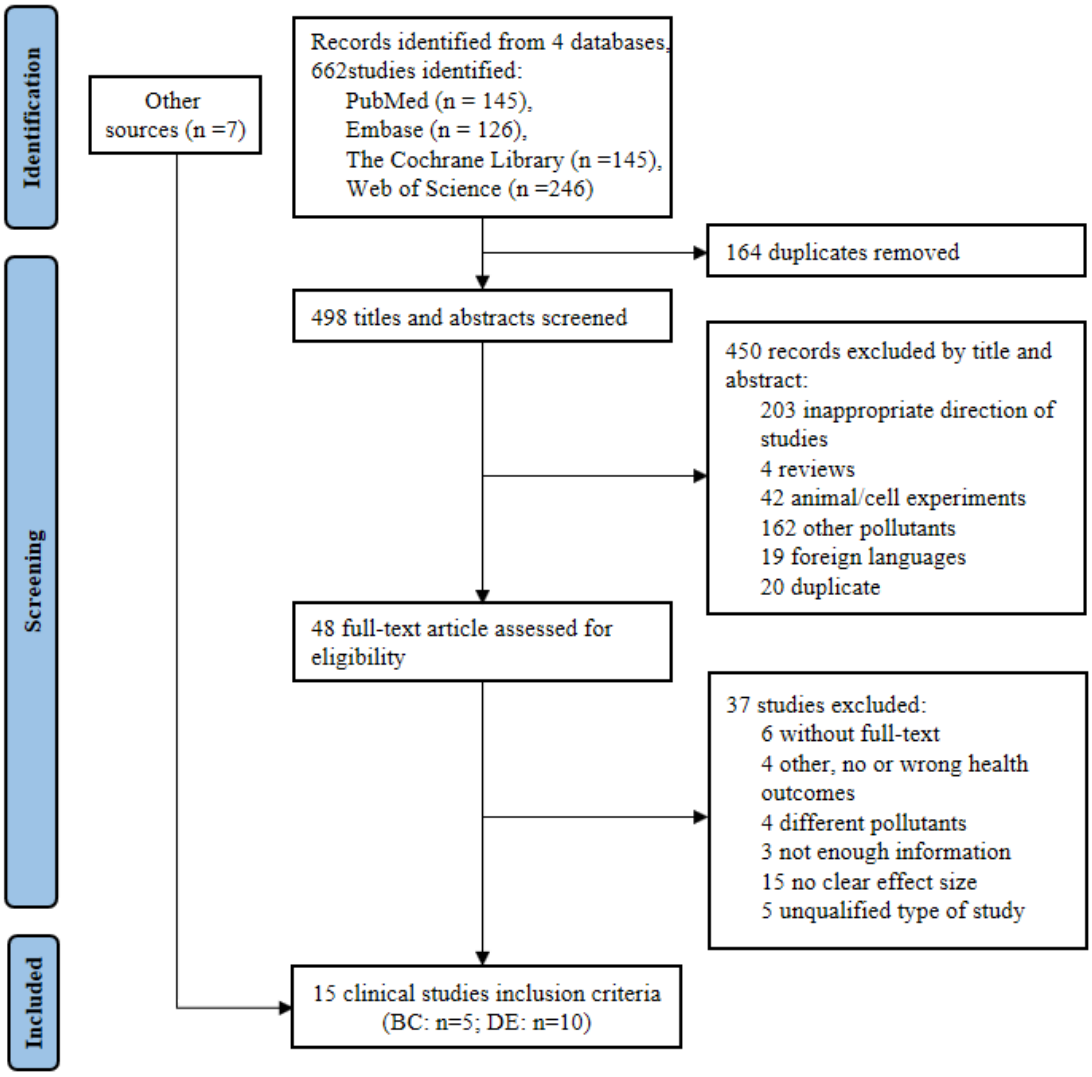


Figure 4-6 Searching process of human clinical studies

We have listed important information, such as basic information of the paper, exposed way, outcomes and so on. The extracted data see Table 4-4.

Table 4-4 The extracted data of human clinical studies

Subject	Age	Sam-ple size	Period	Study region	Study design	Pollutant	Pollutant measurement	Concentration	Outcome	Exposure-response relationship	Reference
never-smoker subjects, with stable type 2 diabetes but otherwise healthy (9 men and 10 women)	30-60	19		USA	Inhaled either filtered air (0-10 particles/cm^3) or elemental carbon UFP by mouthpiece, for 2 hours at rest, in a double-blind, randomized, crossover study design. A digital 12-lead electrocardiogram (ECG) was recorded continuously for 48 hours, beginning 1 hour prior to exposure.	ultrafine particles consisting of EC exposure for 2 hours	Particle number (condensation particle counters, model 3220a; TSI, Inc., St. Paul MN); size distributions (Scanning Mobility Particle Sizer, model 3071; TSI, Inc.)	elemental carbon UFP (~107 particles/cm^3, ~50 $\mu g/m^3$, count median diameter 32 nm)	Inhalation of elemental carbon ultrafine particles alters heart rate and heart rate variability in people with type 2 diabetes. Our findings suggest that effects may occur and persist hours after a single 2-hour exposure.	Analysis of 5-minute segments of the ECG during quiet rest showed reduced high-frequency heart rate variability with UFP relative to air exposure ($p=0.014$), paralleled by non-significant reductions in time-domain heart rate variability parameters. In the analysis of longer durations of the ECG, we found that UFP exposure increased the heart rate relative to air exposure. During the 21- to 45-hour interval after exposure, the average heart rate increased approximately 8 beats per minute with UFP, compared to 5 beats per minute with air ($p=0.045$). There were no UFP effects on cardiac	(Vora et al., 2014)

										rhythm or repolarization.	
self-reported healthy, non-asthmatic, without prescribed medication, non-smoking and non-pregnant participants living in the Copenhagen region.	21-71	83	2017/5-2017/11 (without July)	Denmark	The study design was a crossover, repeated measures. On well-characterized real-life DE exposure in humans. In the present study, 29 healthy volunteers were exposed to DE while sitting as passengers in diesel-powered trains. Exposure in electric trains was used as control scenario. Each train scenario consisted of three consecutive days (6 h/day) ending with biomarker samplings.	UFP, BC exposure for 6h/d and 3 consecutive days	Nano Tracer and Disc Mini portable devices UFP (Disc Mini and Nano Tracer), BC (Micro Aeth AE51)	UFP: 1.2-1.8 × 10^5 particles/cm^3 BC: 8.3 μg/m^3 $PM_{2.5}$:36 μg/m^3 DE :300 μg/m^3	Exposure to DE inside diesel-powered trains for 3 days was associated with reduced lung function and systemic effects in terms of altered heart rate variability and increased levels of DNA strand breaks in PBMCs compared with electric trains.	Exposure to DE was associated with reduced lung function and increased levels of DNA strand breaks in peripheral blood mononuclear cells (PBMCs), whereas there were unaltered levels of oxidatively damaged DNA, soluble cell adhesion molecules, acute phase proteins in blood and urinary excretion of metabolites of polycyclic aromatic hydrocarbons. And the microvascular function was unaltered. An increase in the low frequency of heart rate variability measures was observed, whereas time-domain measures were unaltered.	(Andersen et al., 2019)

15 healthy and 15 asthmatics	18-45	30	before 1992	USA	Volunteer subjects were studied in groups of one to four. Downey, California Every subject was exposed on four separate occasions, usually separated by 7-day intervals. The four separate exposures-clean air (control), carbon aerosol at a nominal concentration of 200 µg/m^3, H_2SO_4 aerosol at a nominal concentration of 100 µg/m^3, and acid and carbon combined—were presented in random order under double-blind conditions. Each subject was exposed for 60-min on any	carbon aerosol [a] exposure for 1 hour and 7 consecutive days	ambient particulate carbon carbon aerosol: on-line particle laser spectrometer system (PMS 100-HV CSASP)	carbon aerosol: 200 µg/m^3 H_2SO_4 aerosol: 100 µg/m^3 (acid and carbon)	Coexisting carbon aerosol did not increase respiratory irritancy of H_2SO_4, in most healthy and asthmatic subjects exposed for 1 hour under simulated "worst-case" ambient conditions.	Group data showed no more than small equivocal effects of any exposure on any health measure. One individual's responses were consistent with a clinically significant excess airway constriction from H_2SO_4 plus carbon, and 2-3 others showed slight excess responses to the combined pollutants, but all these observations might have reflected chance variations.	(Anderson et al., 1992)

					given day, with alternating 10-min periods of exercise and rest.						
No smoking history, no cardiopulmon-ary disease history	40-75	77		USA	Using a 3-period crossover design, participants were randomized to attend three 2-hour-long exposure sessions separated by 1-week washout periods. Each participant was exposed to high, medium, and low TRAP concentrations in a room near an interstate highway. Particle number concentrations, BC concentrations, and temperature were monitored	traffic-related air pollution (TRAP): including BC and UFP exposure for 2-3 hours	BC: aethalometer (Magee Scientific; model AE16) at 1-minute resolution PNC (Particle number concentrations): particle counter (TSI, Inc; model 3873; d_{50}=7 nm) at 1-second resolution	1.low exposure mean particle number and BC concentrations, 2500 particles/cm^3 and 149 ng/m^3) 2.medium exposure mean particle number and BC concentrations, 11000 particles/cm^3 and 409 ng/m^3 3.high exposure mean particle number and BC concentrations, 30000	Reducing indoor concentrations of TRAP was effective in preventing acute increases in systolic blood pressure (SBP).	Using a 3-period crossover design, 77 participants were randomized to attend three 2-hour-long exposure sessions separated by 1-week washout periods. Each participant was exposed to high, medium, and low TRAP concentrations in a room near an interstate highway. Particle number concentrations, BC concentrations, and temperature were monitored continuously. SBP, diastolic BP, and heart rate were measured every 10 minutes. Outcomes were analyzed with a linear mixed model.	(Hudda et al., 2021)

					continuously. Systolic BP (SBP), diastolic BP, and heart rate were measured every 10 minutes. Outcomes were analyzed with a linear mixed model.			particles/cm^3 and 826 ng/m^3			
31 with mild and 29 with moderate asthma	adults	60	2003-2005(between November and March) confined to weekdays and avoid pollen seasons and rainy days）	UK	In this randomized, crossover study, participants walked for 2 hours (10:30 a.m. to 12:30 p.m.) along the western end of Oxford Street, participants walked about 6 km during each exposure, at a steady pace on predefined paths, resting for 15 minutes every half hour. Exposure sessions, separated by more than 3	EC and UFC: including EB exposure for 2 hours	real-time condensation particle counter (Model 3007, TSI)	Oxford Street：Elemental carbon 7.5 μg/m^3,（range: 3.9-16 ） Hyde Park: Elemental carbon: 3 μg/m^3,（range: 0.4-6.7）	The epidemiologic evidence that associates the degree of traffic exposure with lung function in asthma.	Walking for 2 hours on Oxford Street induced asymptomatic but consistent reductions in the forced expiratory volume in 1 second (FEV1) (up to 6.1%) and forced vital capacity (FVC) (up to 5.4%) that were significantly larger than the reductions in FEV1 and FVC after exposure in Hyde Park (P=0.04 and P=0.01, respectively, for the overall effect of exposure, and P<0.005 at some time points). These changes were accompanied by increases in	(McCreanor et al., 2007)

					weeks, were confined to weekdays between November and March (to avoid pollen seasons; rainy days were also avoided. Equal numbers of participants were randomly assigned to each exposure sequence.					biomarkers of neutrophilic inflammation (sputum myeloperoxidase, 4.24 ng per milliliter after exposure in Hyde Park vs. 24.5 ng per milliliter after exposure on Oxford Street; P=0.05) and airway acidification (maximum decrease in pH, 0.04% after exposure in Hyde Park and 1.9% after exposure on Oxford Street; P=0.003).	
130 nurses from two hospitals in Belgium, of which 56 (56%) were assigned at random to this study. healthy adults (92% women). All participants reported to be free of clinical cardiovascular	mean age:40.7	54	2013/4-2013/5	Belgium	A panel study design was used to investigate the association between measures of arterial stiffness and short-term exposure to BC. BC exposure was monitored during one workweek. Functional and structural properties	BC exposure for 2 hours and 7 consecutive days	micro-aethalometer the portable Micro Aeth® Model AE51 BC aerosol monitor (Aeth Labs, San Francisco, CA, USA).	BC: 599.8 - 728.9 ng/m^3	Short-term elevations in personal BC exposure, even within hours, are associated with increased arterial stiffness. This response may reflect a pathway by which air pollution triggers cardiovascular	Median personal BC exposures within the same day ranged from599.8 to 728.9 ng/m3 and were associated with carotid arterial stiffness measures. Young's elastic modulus and pulse wave velocity, both measures of stiffness, were positively associated with BC exposure, while the distensibility and compliance coefficient,	(Provost et al., 2016)

diseases and diabetes.					of the carotid artery were examined ultrasonographically on two separate days. The effect of different short-term personal BC exposure windows (1, 2, 4, 6, 8, 24 and 48 h before the ultrasound examination) on carotid artery stiffness was estimated using mixed models while adjusting for other known correlates of arterial stiffness.				events.	measures of elasticity, were negatively associated with BC exposure. The strongest associations were observed with BC exposure 8 h before the clinical examination. For each 100 ng/m^3 increase in exposure within this time window, Young's elastic modulus increased by 2.38% (95% Cl: 0.81 to 3.97; P=0.0033), while the distensibility coefficient decreased by 2.27% (95% Cl: -3.62 to -0.92; P=0.0008).	
non-smokers, health females	19-46	26		Canada	26 non-smokers were studied under each of three experimental conditions (filtered air with placebo, diesel exhaust with	DE exposure for 2 hours every day and for 6 days.	real-time concentration of particles nephelometer	DE:300 g/m^3 (of particulate matter smaller than 2.5 microns)	Anti-oxidant (N-acetylcysteine) supplementation protects against increased airway responsiveness associated with	Anti-oxidant supplementation reduced baseline airway responsiveness in hyper-responsive individuals by 20% (p=0.001). In hyper-responsive individuals,	(Carlsten et al., 2016)

					placebo, and diesel exhaust with N-acetylcysteine) using a randomized, double-blind, crossover design, with a 2-week washout between conditions. Methacholine challenge was performed pre-exposure (baseline airway responsiveness) and post-exposure (effect of exposure).				DE inhalation and reduces need for supplement bronchodilators in those with baseline airway hyper-responsiveness. Individuals with variants in genes of oxidative stress metabolism when exposed to DE are protected from increases in airway responsiveness if taking anti-oxidant supplementation.	airway responsiveness increased 42% following DE compared with FA (p=0.03) and this increase was abrogated with anti-oxidant supplementation (diesel exhaust with N-acetylcysteine vs. filtered air with placebo, p=0.85).	
healthy, nonsmoking volunteers (3males and 7 females)	25-31	10		USA	The study was conducted in a double-blind manner, with randomized exposures to DEP or	DEP（Diesel exhaust particles) exposure	dust analyzer (Version 5.30E; Grimm Labortechnik GmbH, Germany);	DEP: 200 mg/m^3	The present study confirms that exposure to ambient concentrations of DEP provokes an	There were no changes in cardiovascular parameters or lung function following exposure to DEP. Levels of exhaled CO were increased ater exposure to DEP, and	(Julia A. Nightingale , 1999)

					clean air. Before each exposure, baseline spirometry was conducted, baseline measurements of pulse rate, blood pressure, and exhaled CO were made, and blood was taken. Subjects were then exposed at rest to DEP or to air for 2 hours in a challenge chamber. After exposure, spirometry was repeated and pulse, blood pressure, and exhaled CO were measured immediately, and a further sample of blood was taken. Clinical measurements were	for 2 hours.	Las-X spectrometer (Particle Measuring Systems, Boulder, CO)		inflammatory response in the airways of normal subjects that is characterized by an influx of activated neutrophils accompanied by an increase in exhaled CO levels, indicative of oxidant stress.	were maximal at 1 h (air: 2.9 ± 0.2 ppm (mean ± SEM); DEP: 4.4 ± 0.3 ppm; $p<0.001$). There was an increase in sputum neutrophils and myeloperoxidase (MPO) at 4 h after DEP exposure as compared with 4 h after air exposure (neutrophils: 41 6 ± 4% versus 32 ± 4%; MPO: 151 ng/ml versus 115 ng/ml, $p <0.01$), but no change in concentrations of inflammatory markers in peripheral blood.	

					then repeated half-hourly for 4 hours. At 4 hours, methacholine challenge was performed and an induced sputum sample was collected. Subjects returned at 24 hours after exposure and all measurements other than sputum induction were repeated.						
nonsmoking, atopic asthmatics with stable disease	22-57	14	in winter	America	Each subject was exposed to DE (particles with a 50% cut-off aerodynamic diameter of 10 mm (PM_{10}) 300 mg/m^3) and air during 1 hour on two separate occasions. Lung function was	DE exposure for 1hour	infrared-instrument (Foxboro Co., East Bridgewater, MA, USA); chemilumines cence instrument, (ECO-Physics CLD 700, Boo	DE:300 g/m^3	This study indicated that short-term exposure to diesel exhaust, equal to high ambient levels of particulate matter, is associated with adverse effects in asthmatic airways,	All were hyperresponsive to methacholine. Each subject was exposed to DE (particles with a 50% cut-off aerodynamic diameter of 10 mm (PM_{10}) 300 mg/m^3) and air during 1 h on two separate occasions. Lung function was measured before and immediately after the exposures. Sputum	(C. Nordenha, 2001)

					measured before and immediately after the exposures. Sputum induction was performed 6 hours, and methacholine inhalation test 24 hours, after each exposure.		Instruments, Stockholm, Sweden)		even in the presence of inhaled corticosteroid therapy.	induction was performed 6 h, and methacholine inhalation test 24 h, after each exposure.	
healthy volunteers (8 females and 7 males)	21-40	15	2000	Sweden	Fifteen healthy subjects were exposed to DE at an average particulate matter concentration of 270 μg/m^3 and filtered air for 1 h. Bronchoscopy with endobronchial mucosal biopsy sampling and airway lavage was performed 6 h post-exposure.	DE, OC (origan carbon) exposure for 1 hour and at least for 3 weeks.		DE:300 g/m^3 （OC/TC(Volvo TD45, 4.5 L four cylinders) ：94.5%）	DE generated under urban running conditions increased bronchial adhesion molecule expressions, together with the novel finding of bronchoalveolar eosinophilia, which has not been shown after exposure to DE at idling. Variations	Fifteen healthy subjects were exposed to DE at an average particulate matter concentration of 270 μg/m^3 and filtered air for 1 h. Bronchoscopy with endobronchial mucosal biopsy sampling and airway lavage was performed 6 h postexposure.	(Maria Sehlstedt, 2010)

									in airway inflammatory response to DE generated under diverse running condition may be related to differences in exhaust composition.		
18 healthy male nonsmokers with normal physical, body mass index: 21.7 ± 0.5 kg/m^2	mean age: 22.2 ± 0.5	18		Belgium	Eighteen subjects were exposed to either nonfiltered ambient air (AA) or DE for 12 either nonfiltered ambient air (AA) or DE for 120-min using a randomized, crossover, double-blinded design with the different exposures occurring at least 1 weak apart. Pulmonary hemodynamic	DE exposure for 2 hours	GRIMM Laser Aerosol Spectrometer 1109 (GRIMM Aerosol Technik, Ainring, Germany)	DE： 300 μg $PM_{2.5}/m^3$	Acute exposure to DE increased pulmonary vasomotor tone by decreasing the distensibility of pulmonary resistive vessels at high cardiac output.	Effects of DE on PVR, on the coefficient of distensibilty of pulmonary vessels, and on right and left ventricular function were evaluated at rest (n=18), during dobutamine stress echocardiography (n=10), and during exercise stress echocardiography performed in hypoxia (n=8). Serum endothelin-1 and fractional exhaled nitric oxide were also measured. At rest, exposure to DE did not affect PVR. During	(Wauters et al., 2015)

					parameters were calculated using echocardiography, which was initiated 2 hours after exposure. Ten subjects performed the dobutamine stress protocol under AA and DE conditions. Pulmonary hemodynamic parameters were calculated using echocardiography, which was initiated 2 hours after exposure. Ten subjects performed the dobutamine stress protocol under AA and DE conditions. Eight subjects performed the exercise in acute					dobutamine stress, the slope of the mean pulmonary artery pressure-cardiac output relationship increased from 2.8-0.5 mmHg·min·l⩾1in AA to 3.9-0.5 mmHg·min·l⩾1 in DE	

					hypoxia stress protocol.						
all participants were free of cardiometabolic and respiratory disease, and not pregnant.	22-33	19	2015	Columb-ia	In a double-blind, repeated-measures design, participants with EIB completed four visits: FA-placebo (FA-PLA), FA-SAL, DE-PLA, DE-SAL. After the inhalation of either 400 µg of SAL or PLA, participants sat in the exposure chamber for 60-min, breathing either FA or DE. Participants then cycled for 30-min at 50 % of peak work rate while breathing FA or DE. Respiratory responses were assessed via spirometry, work of breathing (WOB),	DE exposure for 1 hour	(Diesel on-road emissions were simulated with a 5.5-kW diesel engine Diesel on-road emissions were simulated with a 5.5-kW diesel engine.)	DE： $PM_{2.5}$ = 300 µg/m^3	The use of SAL prior to moderate-intensity exercise when breathing high levels of DE, does not reduce respiratory function or exercise ventilatory responses for up to 60-min following exercise.	Bronchodilation in response to SAL and acute cycling was observed, independent of FA/DE exposure. Specifically, FEV1 was increased by 7.7 % (confidence interval (Cl): 7.2-8.2 %; $p < 0.01$) in response to SAL, and MEFVAUC was increased after cycling by 1.1 % (0.9-1.3 %; $p = 0.03$). Despite a significant decrease in total WOB by 6.2 J/min (4.7-7.5 J/min; p=0.049) and a reduction in $\dot{V}E/\dot{V}E$, CAP by 5.8 % (5-6 %, $p < 0.01$) in the SAL exposures, no changes were observed in dyspnea. The DE exposure significantly increased $\dot{V}E/\dot{V}E$, CAP by 2.4 % (0.9-3.9 %; $p < 0.01$), but this did not affect dyspnea.	(Sarah Koch 2021)

					fractional use of ventilatory capacity (V˙E/ V˙E, CAP), area under the maximal expiratory flow-volume curve (MEFVAUC), and dyspnea during and following cycling.						
allergen sensitized participants (7 males and 7 females, no smoking history)	23-50	14		Canada	Participants completed this randomized, double-blinded, cross-over, controlled exposure study. each participant underwent four exposures (allergen-alone exposure, De and allergen co-exposure, particle-depleted DE (PDDE) and allergen co-exposure, and sham exposure) on	DE, PDDE (particle-depleted DE) exposure for 2 hours	2.5 kW applied to the diesel generator	mean concentration of $PM_{2.5}$ in DE (292.2 (95% Cl 279.5-304.9) $\mu g/m^3$); mean concentration of $PM_{2.5}$ in PDDE (18.9 (14.4-23.4) $\mu g/m^3$).	Short- term co-exposure to aeroallergen and DE alters immune regulatory proteins in lungs; surfactant levels are dependent on particle depletion.	Allergen-alone exposure led to accumulation of surfactant protein D (SPD; p=0.02). co-exposure to allergen and De did not elicit the same increase of SPD as did allergen alone; diesel particulate reduction restored allergen- induced SPD accumulation. soluble receptor for advanced glycation end products was higher with particle reduction than without it. in the systemic circulation, there was a transient increase in SPD and club	(Sarah Koch 2021)

					different order-randomized dates. serum and bronchoalveolar lavage (Bal) were assayed for pattern recognition molecules, cytokines, chemokines and inflammatory mediators.					cell protein 16 (cc16) 4 hours after allergen alone. cc16 was augmented by PDDE, but not DE. % eosinophils in Bal ($p<0.005$), eotaxin-3 ($p<0.0001$), interleukin 5 (il-5; $p<0.0001$) and thymus and activation regulated chemokine ($p=0.0001$) were each increased in Bal by allergen. il-5, SPD and % eosinophils in Bal were correlated with decreased FEV1.	
blinded atopic volunteers	19-49	18	2015	British	volunteers were exposed to filtered air or f diesel exhaust in random fashion. 1 hour post-exposure, diluent-controlled segmental allergen challenge was performed; 2 days later, samples from	DE expose for 1 hour	Diesel on-road emissions were simulated with a 5.5-kW diesel engine Diesel on-road emissions were simulated with a 5.5-kW	DE: 300 mg $PM_{2.5}/m^3$	Inhalation of diesel exhaust at environmentally relevant concentrations augments allergen-induced allergic inflammation in the lower airways of atopic	Diesel exhaust augmented the allergen-induced increase in airway eosinophils, interleukin 5 (IL-5) and eosinophil cationic protein (ECP) and the GSTT1 null genotype was significantly associated with the augmented IL-5 response. Diesel exhaust alone also augmented	(Carlsten et al., 2016)

					the challenged segments were obtained by bronchoscopic lavage. Samples were analyzed for markers and modifiers of allergic inflammation (eosinophils, Th2 cytokines) and adaptive immune cell activation. Mixed effects models with ordinal contrasts compared effects of single and combined exposures on these end points.		diesel engine.		individuals and the GSTT1 genotype enhances this response. Allergic individuals are a susceptible population to the deleterious airway effects of diesel exhaust.	markers of non-allergic inflammation and monocyte chemotactic protein (MCP)-1 and suppressed activity of macrophages and myeloid dendritic cells.	
Adults do not pregnant, and free of cardiometabolic and respiratory disease. Study participants	18-35	18	2015/5-2016/7	Vancouver and British Columbia，Canada	Double-blind, counter-balanced, randomized crossover study. On four exposure visits, volunteers inhaled either 400 μg of the	DE	using 10-min averages; real-time data from the nephelometer (Radiance Research	DE: 300μg $PM_{2.5}/m^3$ expose for 1 hour	Acute physical activity induces a vasodilatory response in the micro-and macrovasculatur in healthy adults	The cycling bout increased CRAE (T2-T1 difference (95th % Cl): 4.88 μm (4.73, 5.00 μm), $p < 0.001$; T3-T1 difference: 2.10 μm (1.62, 2.58 μm), $p=0.031$) and CRVE (T2-T1 difference:	(Chris Carlsten, 2020)

were asked to refrain from exercise to avoid EIB or bronchodilation and muscular fatigue.					β2-agonist salbutamol or placebo before resting for 60-min, followed by a 30-min cycling bout. During rest and cycling, participants inhaled FA or DE. Microvascular (central retinal arteriolar and venular equivalents, CRAE and CRVE, respectively) and macrovascular parameters (blood pressure (BP) and heart rate (HR)) were assessed at baseline (T1), 10 min (T2) and 70 min (T3) after cycling.		model M903) which provides bscat [a], then calculated as: PM=bscat *1E6 *0.45. Particle size distribution between 10 and 600 nm with a mode at 100 nm were determined with a TSI Scanning Mobility Particle Scanner (Model 3936; TSI, Shoreview, MN).		by increasing CRAE and CRVE, and by reducing systolic BP post exercise, despite breathing DE. The DE-associated increase in HR might be indicative of an increased sympathetic response to physical activity while breathing DE.	3.78 µm (3.63, 3.92 µm), p < 0.001; T3-T1 difference: 3.73 µm (3.63, 3.92 µm), p < 0.001). The exposure to DE had no effect on CRAE (FA-DE difference at T2: 0.46 µm (−0.02, 0.92 µm); p=0.790; FA-DE difference at T3: 1.76 µm (1.36, 2.16 µm), p=0.213) and CRVE (FA-DE difference at T2: 0.26 µm (-0.35, 0.88 µm), p=0.906; FA-DE difference at T3: 0.55 µm (0.05, 1.06 µm), p=0.750). Compared to T1, systolic BP was decreased at T2 by 2.5 mmHg (2.8, 2.3 mmHg, p=0.047), independent of inhaled exposure. Heart rate at T2 was significantly increased by 3 bpm (2, 3 bpm, p=0.025) after the DE-exposure when compared to FA.	

BC or any other alternative (optical) methods such as reflection on filters are seldom assessed (or reported) in toxicity studies on ambient air, either in controlled human clinical studies. For this reason, this chapter will also consider exposure to DE or DEP. From the search results, human clinical studies are mainly about cardiopulmonary function and vascular function after exposure to BC, UFP, DEP, and DE. And the countries where the subjects are located are all in Europe.

4.2.3.1 Study design

For the human clinical study, the randomized controlled trial (RCT) is the most important study design. It has three principles, namely randomization, control, and blinding. When the subject was human, crossover design and double-blind were usually selected. The difference between the human clinical study and the observational study is whether to intervene with the subjects. Therefore, RCT can obtain the causality and the quantitative relationship between the intervention and health effects. They are more reliable than observational studies.

4.2.3.2 Black Carbon

In the search results of human clinical studies, most studies analyzed BC and UFP together. The results showed that BC and UFP might be associated with heart rate and cardiorespiratory functions. However, the contribution of BC and UFP to human health effects couldn't be completely separated.

4.2.3.3 Diesel exhaust particle and diesel exhaust

Through literature review, it is found that exposure to DE affects respiratory function and arterial stiffness. Leading to systemic inflammation, nervous system and cardiovascular system damage, especially in susceptible people with asthma, coronary heart disease or other diseases.

At present, it is not possible to say definitively whether health effects due to exposure to BC or PM mass are different qualitatively (for example, different health outcomes) and/or quantitatively from each other. This is partly due to the fact that an insufficient number of controlled health studies have been implemented which involve human subjects with simultaneous BC or EC measurements and other PM speciation.

4.3 Good practice statement about carbonaceous aerosol in WHO AQGs[1]

This review analyzed epidemiological studies and animal studies. However, there are few related studies, especially articles that study BC alone. From this review of the literature concluded, evidence links BC with cardiorespiratory health effects, for short- and long-term exposures. And in studies that take BC/EC and $PM_{2.5}$/UFP into account simultaneously, associations remained robust for BC/EC.

[1] World health Organization. WHO global air quality guidelines[R]. European Union: World health organization, 2021.

In 2015, the World Health Assembly adopted a landmark resolution on air quality and health, recognizing air pollution as a risk factor for non-communicable diseases such as ischemic heart disease, stroke, chronic obstructive pulmonary disease, asthma and cancer, and the economic toll they take. These guidelines (such as World health organization global air quality guidelines (WHO AQGs)), taking into account the latest body of evidence on the health impacts of different air pollutants, are a key step in that global response.

As yet, insufficient data are also available to provide recommendations for AQG levels and interim targets for BC/EC and UFP. However, due to health concerns related to these pollutants, actions to enhance further research on their risks and approaches for mitigation are warranted. Therefore, to address concerns about the health and environmental effects of BC/EC and UFP, some good practice statements are summarized in Table 4-5.

Table 4-5 Summary of good practice statements

Pollutants	Good practice statements
BC/EC	1. Make systematic measurements of black carbon and/or elemental carbon. Such measurements should not replace or reduce existing monitoring of those pollutants for which guidelines currently exist. 2. Undertake the production of emission inventories, exposure assessments and source apportionment for BC/EC. 3. Take measures to reduce BC/EC emissions from within the relevant jurisdiction and, where appropriate, develop standards (or targets) for ambient BC/EC concentrations.
UFP	1. Quantify ambient UFP in terms of PNC for a size range with a lower limit of ⩽ 10 nm and no restriction on the upper limit. 2. Expand the common air quality monitoring strategy by integrating UFP monitoring into the existing air quality monitoring. Include size-segregated real-time PNC measurements at selected air monitoring stations in addition to and simultaneously with other airborne pollutants and characteristics of PM. 3. Distinguish between low and high PNC to guide decisions on the priorities of UFP source emission control. Low PNC can be considered < 1000 particles/cm^3 (24-hour mean). High PNC can be considered > 10000 particles/cm^3 (24-hour mean) or 20000 particles/cm^3 (1-hour mean). 4. Utilize emerging science and technology to advance approaches to the assessment of exposure to UFP for their application in epidemiological studies and UFP management

PNC: particle number concentration.

BC is produced by incomplete combustion of fuel or biomass. Because of the large specific surface area and small particle size of BC, it is easily to adsorb toxic substances and could enter the deep respiratory tract through breathing. Therefore, it has the stronger health impacts. Exposure to BC for a short or long term, people will have varying degrees of adverse effects. In this study, the results of systematic review and meta-analysis showed that short-term exposure to BC might be associated with total mortality and respiratory mortality and long-term exposure might be associated with lung cancer mortality. From the aspects of toxicological mechanism, animal experiments and human clinical studies, most animal studies take DEP, but there are few studies on human clinical trials at this stage. The impact of BC on health cannot be ignored and it should be addressed concerns about the health and environmental effects of BC/EC.

Reference

Abdel-Shafy, H.I., and Mansour, M.S.M. (2016). A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation. Egyptian Journal of Petroleum *25*, 107-123.

Acciani, T., Brandt, E., Pastura, P., Hershey, G., and Le Cras, T. (2012). Low dose diesel exhaust particle exposure exacerbates allergic asthma in young mice. European Respiratory Journal *40*.

Agency, U.S.E.P. (2012). Report to Congress on Black Carbon.

Alexeeff, S.E., Roy, A., Shan, J., Liu, X., Messier, K., Apte, J.S., Portier, C., Sidney, S., and Van Den Eeden, S.K. (2018). High-resolution mapping of traffic related air pollution with Google street view cars and incidence of cardiovascular events within neighborhoods in Oakland, CA. Environmental Health *17*, 13.

Ali, M.U., Siyi, L., Yousaf, B., Abbas, Q., Hameed, R., Zheng, C., Kuang, X., and Wong, M.H. (2020). Emission sources and full spectrum of health impacts of black carbon associated polycyclic aromatic hydrocarbons (PAHs) in urban environment: A review. Critical Reviews in Environmental Science and Technology, 1-40.

Analitis, A., Katsouyanni, K., Dimakopoulou, K., Samoli, E., Nikoloulopoulos, A.K., Petasakis, Y., Touloumi, G., Schwartz, J., Anderson, H.R., Cambra, K.*, et al.* (2006). Short-term effects of ambient particles on cardiovascular and respiratory mortality. Epidemiology *17*, 230-233.

Andersen, M.H.G., Frederiksen, M., Saber, A.T., Wils, R.S., Fonseca, A.S., Koponen, I.K., Johannesson, S., Roursgaard, M., Loft, S., Møller, P.*, et al.* (2019). Health effects of exposure to diesel exhaust in diesel-powered trains. Particle and Fibre Toxicology *16*.

Anderson, H.R., Bremner, S.A., Atkinson, R.W., Harrison, R.M., and Walters, S. (2001). Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occupational and Environmental Medicine *58*, 504-510.

Anderson, K.R., Avol, E.L., Edwards, S.A., Shamoo, D.A., Peng, R.C., Linn, W.S., and Hackney, J.D. (1992). Controlled exposures of volunteers to respirable carbon and sulfuric acid aerosols. Journal of the Air & Waste Management Association *42*, 770-776.

Andreae, M.O., and Gelencsér, A. (2006). Black carbon or brown carbon? The nature of light-absorbing carbonaceous aerosols. Atmospheric Chemistry and Physics *6*, 3131-3148.

Arimoto, T., Takano, H., Inoue, K., Yanagisawa, R., Yoshino, S., Yamaki, K., and Yoshikawa, T. (2007). Pulmonary exposure to diesel exhaust particle components enhances circulatory chemokines during lung inflammation. International Journal of Immunopathology and Pharmacology *20*, 197-201.

Armstrong, B., Hutchinson, E., Unwin, J., and Fletcher, T. (2004). Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. Environ Health Perspect *112*, 970-978.

Atkinson, R.W., Analitis, A., Samoli, E., Fuller, G.W., Green, D.C., Mudway, I.S., Anderson, H.R., and Kelly, F.J. (2016). Short-term exposure to traffic-related air pollution and daily mortality in London, UK. Journal of Exposure Science and Environmental Epidemiology *26*, 125-132.

Bai, N., and Van Eeden, S.F. (2013). Systemic and vascular effects of circulating diesel exhaust particulate matter. Inhalation Toxicology *25*, 725-734.

Ballester, F., Corella, D., PerezHoyos, S., and Hervas, A. (1996). Air pollution and mortality in Valencia, Spain: A study using the APHEA methodology. Journal of Epidemiology and Community Health *50*, 527-533.

Ballester, F., Saez, M., Perez-Hoyos, S., Iniguez, C., arillas, A., Tobias, A., Bellido, J., Taracido, M., Arribas, F., Daponte, A.*, et al.* (2002). The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. Occupational and Environmental Medicine *59*, 300-308.

Beelen, R., Hoek, G., Br, v.d., t, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., Jerrett, M., Hughes, E., Armstrong, B.*, et al.* (2008). Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environmental Health Perspectives *116*, 196-202.

Beelen, R., Hoek, G., Houthuijs, D., Br, v.d., t, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., Armstrong, B., and Brunekreef, B. (2009). The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. Occupational and Environmental Medicine *66*, 243-250.

Bendtsen, K.M., Gren, L., Malmborg, V.B., Shukla, P.C., Tuner, M., Essig, Y.J., Krais, A.M., Clausen, P.A., Berthing, T., Loeschner, K.*, et al.* (2020). Particle characterization and toxicity in C57BL/6 mice following instillation of five different diesel exhaust particles designed to differ in physicochemical properties. Part Fibre Toxicol *17*, 38.

Beverl, , I.J., Carder, M., Cohen, G.R., Heal, M.R., and Agius, R.M. (2014). Associations between short/medium-term variations in black smoke air pollution and mortality in the Glasgow conurbation, UK. Environment International *62*, 126-132.

Beverl, , I.J., Cohen, G.R., Heal, M.R., Carder, M., Yap, C., Robertson, C., Hart, C.L., and Agius, R.M. (2012). A Comparison of Short-term and Long-term Air Pollution Exposure Associations with Mortality in Two Cohorts in Scotland. Environmental Health Perspectives *120*, 1280-1285.

Bo, Z., Dan, T., Meng, L., Fei, L., Chaopeng, H., Guannan, G., Haiyan, L., Xin, L., Liqun, P., and Ji, Q. (2018). Trends in China's anthropogenic emissions since 2010 as the consequence of clean air actions. Atmospheric Chemistry & Physics Discussions, 1-27.

Boezen, H.M., Vonk, J.M., van der Zee, S.C., Gerritsen, J., Hoek, G., Brunekreef, B., Schouten, J.P., and Postma, D.S. (2005). Susceptibility to air pollution in elderly males and females. European Respiratory Journal *25*, 1018-1024.

Bolton, J.L., Auten, R.L., and Bilbo, S.D. (2014). Prenatal air pollution exposure induces sexually dimorphic fetal programming of metabolic and neuroinflammatory outcomes in adult offspring. Brain, Behavior, and Immunity *37*, 30-44.

Bolton, J.L., Marinero, S., Hassanzadeh, T., Natesan, D., Le, D., Belliveau, C., Mason, S.N., Auten, R.L., and Bilbo, S.D. (2017). Gestational exposure to air pollution alters cortical volume, microglial morphology, and microglia-neuron interactions in a sex-specific manner. Frontiers in Synaptic Neuroscience *9*.

Bond, T.C., and Bergstrom, R.W. (2007). Light Absorption by Carbonaceous Particles: An Investigative Review. Aerosol Science and Technology *40*, 27-67.

Bond, T.C., Doherty, S.J., Fahey, D.W., Forster, P.M., Berntsen, T., DeAngelo, B.J., Flanner, M.G., Ghan, S., Kärcher, B., Koch, D.*, et al.* (2013). Bounding the role of black carbon in the climate system: A scientific assessment. Journal of Geophysical Research: Atmospheres *118*, 5380-5552.

Bose, S., Romero, K., Psoter, K.J., Curriero, F.C., Chen, C., Johnson, C.M., Kaji, D., Breysse, P.N., Williams, D.L., Ramanathan, M.*, et al.* (2018). Association of traffic air pollution and rhinitis quality of life in Peruvian children with asthma. Plos One *13*, 13.

Bradley, J.M., Cryar, K.A., El Hajj, M.C., El Hajj, E.C., and Gardner, J.D. (2013). Exposure to diesel exhaust particulates induces cardiac dysfunction and remodeling. Journal of Applied Physiology *115*, 1099-1106.

Bremner, S.A., Anderson, H.R., Atkinson, R.W., McMichael, A.J., Strachan, D.P., Bl, , J.M., and Bower, J.S. (1999). Short-term associations between outdoor air pollution and mortality in London 1992-4. Occup Environ Med *56*, 237-244.

C. Nordenha, J.P., M-C. Ledin, J-O. Levin, T. Sandstro¨m, E. A¨ delroth (2001). Diesel exhaust enhances airway responsiveness in asthmatic subjects. European Respiratory Journal *17*, 909-915.

Cakmak, S., Dales, R.E., and Blanco, C. (2009a). Components of Particulate Air Pollution and Mortality in Chile. International Journal of Occupational and Environmental Health *15*, 152-158.

Cakmak, S., Dales, R.E., Gultekin, T., Vidal, C.B., Farnendaz, M., Rubio, M.A., and Oyola, P. (2009b). Components of Particulate Air Pollution and Emergency Department Visits in Chile. Archives of Environmental & Occupational Health *64*, 148-155.

Cao, J.J., Xu, H.M., Xu, Q., Chen, B.H., and Kan, H.D. (2012). Fine Particulate Matter Constituents and Cardiopulmonary Mortality in a Heavily Polluted Chinese City. Environmental Health Perspectives *120*, 373-378.

Carder, M., McNamee, R., Beverl, , I., Elton, R., Van Tongeren, M., Cohen, G.R., Boyd, J., MacNee, W., and Agius, R.M. (2008). Interacting effects of particulate pollution and cold temperature on cardiorespiratory mortality in Scotland. Occupational and Environmental Medicine *65*, 197-204.

Carlsten, C., Blomberg, A., Pui, M., Sandstrom, T., Wong, S.W., Alexis, N., and Hirota, J. (2016). Diesel exhaust augments allergen-induced lower airway inflammation in allergic individuals: A controlled human exposure study. Thorax *71*, 35-44.

Cassee, F.R., Héroux, M.-E., Gerlofs-Nijland, M.E., and Kelly, F.J. (2013). Particulate matter beyond mass: recent health evidence on the role of fractions, chemical constituents and sources of emission. Inhalation Toxicology *25*, 802-812.

Chen, Y., Chen, R., Chen, Y., Dong, X., Zhu, J., Liu, C., van Donkelaar, A., Martin, R.V., Li, H., Kan, H.*, et al.* (2021). The prospective effects of long-term exposure to ambient PM(2.5) and constituents on mortality in rural East China. Chemosphere *280*, 130740.

Cheng, Z., Chu, H., Wang, S., Huang, Y., Hou, X., Zhang, Q., Zhou, W., Jia, L., Meng, Q., Shang, L.*, et al.* (2019). TAK1 knock-down in macrophage alleviate lung inflammation induced by black carbon and aged black carbon. Environmental Pollution *253*, 507-515.

Ching, J., and Kajino, M. (2018). Aerosol mixing state matters for particles deposition in human respiratory system. Sci Rep *8*, 8864.

Chris Carlsten, A.B., Mandy Pui, Thomas Sandstrom, Sze Wing Wong,Neil Alexis, Jeremy Hirota (2020). Vascular effects of physical activity are not modified by short-term inhaled diesel exhaust: results of a controlled human exposure study. Environmental research *183*.

Chuang, H.C., Lin, Y.J., Chou, C.C.K., Hwang, J.S., Chen, C.C., Yan, Y.H., Hsieh, H.I., Chuang, K.J., and Cheng, T.J. (2017). Alterations in cardiovascular function by particulate matter in rats using a crossover design. Environmental Pollution *231*, 812-820.

Clark, C., Sbihi, H., Tamburic, L., Brauer, M., Frank, L.D., and Davies, H.W. (2017). Association of Long-Term Exposure to Transportation Noise and Traffic-Related Air Pollution with the Incidence of Diabetes: A Prospective Cohort Study. Environmental Health Perspectives *125*, 10.

Colicino, E., Wilson, A., Frisardi, M.C., Prada, D., Power, M.C., Hoxha, M., Dioni, L., Spiro, A., Vokonas, P.S., Weisskopf, M.G.*, et al.* (2017). Telomere Length, Long-Term Black Carbon Exposure, and Cognitive Function in a Cohort of Older Men: The VA Normative Aging Study. Environ Health Perspect *125*, 76-81.

Cowell, W.J., Bellinger, D.C., Coull, B.A., Gennings, C., Wright, R.O., and Wright, R.J. (2015). Associations between Prenatal Exposure to Black Carbon and Memory Domains in Urban Children: Modification by Sex and Prenatal Stress. PLoS One *10*, e0142492.

Curci, G., Alyuz, U., Baro, R., Bianconi, R., Bieser, J., Christensen, J.H., Colette, A., Farrow, A., Francis, X., Jimenez-Guerrero, P.*, et al.* (2019). Modelling black carbon absorption of solar

radiation: combining external and internal mixing assumptions. Atmos Chem Phys *19*, 181-204.

Dab, W., Medina, S., Quenel, P., LeMoullec, Y., LeTertre, A., Thelot, B., Monteil, C., Lameloise, P., Pirard, P., Momas, I.*, et al.* (1996). Short term respiratory health effects of ambient air pollution: Results of the APHEA project in Paris. Journal of Epidemiology and Community Health *50*, S42-S46.

Danielsen, P.H., Risom, L., Wallin, H., Autrup, H., Vogel, U., Loft, S., and Møller, P. (2008). DNA damage in rats after a single oral exposure to diesel exhaust particles. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis *637*, 49-55.

De Homdedeu, M., Cruz, M., Sanchez-Díez, S., I, O., Romero-Mesones, C., J, V., Velde G, V., and X, M. (2020). The immunomodulatory effects of diesel exhaust particles in asthma. Environmental Pollution *263*.

De Homdedeu, M., Cruz, M.J., Sánchez-Díez, S., Gómez-Ollés, S., Ojanguren, I., Ma, D., and Muñoz, X. (2021). Role of diesel exhaust particles in the induction of allergic asthma to low doses of soybean. Environmental Research *196*.

Dehbi, H.M., Blangiardo, M., Gulliver, J., Fecht, D., de Hoogh, K., Al-Kanaani, Z., Tillin, T., Hardy, R., Chaturvedi, N., and Hansell, A.L. (2017). Air pollution and cardiovascular mortality with over 25 years follow-up: A combined analysis of two British cohorts. Environment International *99*, 275-281.

Dellinger, B., Pryor, W.A., Cueto, R., Squadrito, G.L., Hegde, V., and Deutsch, W.A. (2001). Role of Free Radicals in the Toxicity of Airborne Fine Particulate Matter. Chemical Research in Toxicology *14*, 1371.

Dockery, D.W., Luttmann-Gibson, H., Rich, D.Q., Link, M.S., Mittleman, M.A., Gold, D.R., Koutrakis, P., Schwartz, J.D., and Verrier, R.L. (2005). Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect *113*, 670-674.

Doiron, D., Bourbeau, J., de Hoogh, K., and Hansell, A.L. (2021). Ambient air pollution exposure and chronic bronchitis in the Lifelines cohort. Thorax.

Egger, M. (1997). Bias in meta-analysis detected by a simple, graphical test. J Bmj British Medical Journal *316*.

Ehsanifar, M., Jafari, A.J., Nikzad, H., Zavareh, M.S., Atlasi, M.A., Mohammadi, H., and Tameh, A.A. (2019). Prenatal exposure to diesel exhaust particles causes anxiety, spatial memory disorders with alters expression of hippocampal pro-inflammatory cytokines and NMDA receptor subunits in adult male mice offspring. Ecotoxicology and Environmental Safety *176*, 34-41.

Elliott, P., Shaddick, G., Wakefield, J.C., de Hoogh, C., and Briggs, D.J. (2007). Long-term associations of outdoor air pollution with mortality in Great Britain. Thorax *62*, 1088-1094.

Er Hoorn, S., Murray, K., Nedkoff, L., Hankey, G.J., Flicker, L., Yeap, B.B., Almeida, O.P., Norman, P., Brunekreef, B., Nieuwenhuijsen, M.*, et al.* (2021). Long-term exposure to outdoor air pollution and risk factors for cardiovascular disease within a cohort of older men in Perth. Plos One *16*, 18.

Filleul, L., Le Tertre, A., Baldi, I., and Tessier, J.F. (2004). Difference in the relation between daily mortality and air pollution among elderly band all-ages populations in southwestern France. Environmental Research *94*, 249-253.

Filleul, L., Rondeau, V., entorren, S., Le Moual, N., Cantagrel, A., Annesi-Maesano, I., Charpin, D., Declercq, C., Neukirch, F., Paris, C.*, et al.* (2005). Twenty five year mortality and air pollution: results from the French PAARC survey. Occupational and Environmental Medicine *62*, 453-460.

Fischer, P., Hoek, G., Brunekreef, B., Verhoeff, A., and van Wijnen, J. (2003). Air pollution and mortality in the Netherlands: are the elderly more at risk? European Respiratory Journal *21*, 34S-38S.

Fischer, P.H., Marra, M., Ameling, C.B., Velders, G.J.M., Hoogerbrugge, R., de Vries, W., Wesseling, J., Janssen, N.A.H., and Houthuijs, D. (2020). Particulate air pollution from different sources and mortality in 7.5 million adults - The Dutch Environmental Longitudinal Study (DUELS). Science of the Total Environment *705*, 7.

Fleisch, A.F., Gold, D.R., Rifas-Shiman, S.L., Koutrakis, P., Schwartz, J.D., Kloog, I., Melly, S., Coull, B.A., Zanobetti, A., Gillman, M.W.*, et al.* (2014). Air Pollution Exposure and Abnormal Glucose Tolerance during Pregnancy: The Project Viva Cohort. Environmental Health Perspectives *122*, 378-383.

Gan, W.Q., FitzGerald, J.M., Carlsten, C., Sadatsafavi, M., and Brauer, M. (2013). Associations of Ambient Air Pollution with Chronic Obstructive Pulmonary Disease Hospitalization and Mortality. American Journal of Respiratory and Critical Care Medicine *187*, 721-727.

Gan, W.Q., Koehoorn, M., Davies, H.W., Demers, P.A., Tamburic, L., and Brauer, M. (2011). Long-Term Exposure to Traffic-Related Air Pollution and the Risk of Coronary Heart Disease Hospitalization and Mortality. Environmental Health Perspectives *119*, 501-507.

Gao, X., Shang, J., Yang, J.L., Li, Q., Chen, T., Pang, Y.J., Zhang, W.X., Luan, X.G., Zhu, T., and Jia, G. (2014). Comparison of genetic damage in mice exposed to black carbon and ozone-oxidized black carbon. Beijing Da Xue Xue Bao Yi Xue Ban *46*, 400-404.

Geng, F.H., Hua, J., Mu, Z., Peng, L., Xu, X.H., Chen, R.J., and Kan, H.D. (2013). Differentiating the associations of black carbon and fine particle with daily mortality in a Chinese city. Environmental Research *120*, 27-32.

Gentile, D.A., Morphew, T., Elliott, J., Presto, A.A., and Skoner, D.P. (2020). Asthma prevalence and control among schoolchildren residing near outdoor air pollution sites. Journal of Asthma, 11.

Ghio, A.J., M. S. Carraway , and M. C. Madden (2012). Composition of Air Pollution Particles and

Oxidative Stress in Cells, Tissues, and Living Systems. Journal of Toxicology and Environmental Health *15*, 1-21.

Gibbs, J.L., Dallon, B.W., Lewis, J.B., Walton, C.M., Arroyo, J.A., Reynolds, P.R., and Bikman, B.T. (2019). Diesel exhaust particle exposure compromises alveolar macrophage mitochondrial bioenergetics. International Journal of Molecular Sciences *20*.

Gittins, M., McNamee, R., Carder, M., Beverl, , I., and Agius, R.M. (2013). Has the short-term effect of black smoke exposure on pneumonia mortality been underestimated because hospitalisation is ignored: findings from a case-crossover study. Environmental Health *12*, 8.

Gong, T.Y., Sun, Z.B., Zhang, X.L., Zhang, Y., Wang, S.G., Han, L., Zhao, D.L., Ding, D.P., and Zheng, C.J. (2019). Associations of black carbon and PM2.5 with daily cardiovascular mortality in Beijing, China. Atmospheric Environment *214*, 8.

Gorr, M.W., Youtz, D.J., Eichenseer, C.M., Smith, K.E., Nelin, T.D., Cormet-Boyaka, E., and Wold, L.E. (2015). In vitro particulate matter exposure causes direct and lung-mediated indirect effects on cardiomyocyte function. American Journal of Physiology - Heart and Circulatory Physiology *309*, H53-H62.

Greve, H.J., Mumaw, C.L., Messenger, E.J., Kodavanti, P.R.S., Royl, L., J., Kodavanti, U.P., and Block, M.L. (2020a). Diesel exhaust impairs TREM2 to dysregulate neuroinflammation. Journal of Neuroinflammation *17*.

Greve, H.J., Mumaw, C.L., Messenger, E.J., Kodavanti, P.R.S., Royland, J.L., Kodavanti, U.P., and Block, M.L. (2020b). Diesel exhaust impairs TREM2 to dysregulate neuroinflammation. Journal of Neuroinflammation *17*.

Grytting, V. S., P. Chand, M. Lag, J. Ovrevik and M. Refsnes (2022). "The pro-inflammatory effects of combined exposure to diesel exhaust particles and mineral particles in human bronchial epithelial cells." Part Fibre Toxicol 19(1): 14.

Grytting, V. S., M. Refsnes, J. Øvrevik, M. S. Halle, J. Schönenberger, R. van der Lelij, B. Snilsberg, T. Skuland, R. Blom and M. Låg (2021). "Respirable stone particles differ in their ability to induce cytotoxicity and pro-inflammatory responses in cell models of the human airways." Particle and Fibre Toxicology 18(1): 18.

Gurgueira, S.A., Lawrence, J., Coull, B., Murthy, G.G.K., and perspectives, B.G.-F.J.E.h. (2002). Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. Environmental health perspectives *110*, págs. 749-755.

Hansell, A., Ghosh, R.E., Blangiardo, M., Perkins, C., Vienneau, D., Goffe, K., Briggs, D., and Gulliver, J. (2016). Historic air pollution exposure and long-term mortality risks in England and Wales: prospective longitudinal cohort study. Thorax *71*, 330-338.

Hansen, C.S., Sheykhzade, M., Møller, P., Folkmann, J.K., Amtorp, O., Jonassen, T., and Loft, S.

(2007). Diesel exhaust particles induce endothelial dysfunction in apoE-/- mice. Toxicology and Applied Pharmacology *219*, 24-32.

Hartz, A.M.S., Bauer, B., Block, M.L., Hong, J.S., and Miller, D.S. (2008). Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. FASEB Journal *22*, 2723-2733.

Hasslöf, H., Molnár, P., Andersson, E.M., Spanne, M., Gustafsson, S., Stroh, E., Engström, G., and Stockfelt, L. (2020). Long-term exposure to air pollution and atherosclerosis in the carotid arteries in the Malmö diet and cancer cohort. Environmental Research *191*.

Heo, J., Schauer, J.J., Yi, O., Paek, D., Kim, H., and Yi, S.M. (2014). Fine Particle Air Pollution and Mortality Importance of Specific Sources and Chemical Species. Epidemiology *25*, 379-388.

Hiltermann, T.J.N., Stolk, J., van der Zee, S.C., Brunekreef, B., de Bruijne, C.R., Fischer, P.H., Ameling, C.B., Sterk, P.J., Hiemstra, P.S., and van Bree, L. (1998). Asthma severity and susceptibility to air pollution. European Respiratory Journal *11*, 686-693.

Hinds (1982). Aerosol technology: properties, behavior, and measurement of airborne particles (Aerosol technology: properties, behavior, and measurement of airborne particles).

Ho, H.C., Wong, M.S., and Chan, T.C. (2020). Spatially differentiating the effects of long-term air pollution on specific causes of death from cardiovascular and respiratory mortality in Hong Kong: a territory-wide register-based study. Air Quality Atmosphere and Health *13*, 721-730.

Hoek, G., Beelen, R., de Hoogh, K., Vienneau, D., Gulliver, J., Fischer, P., and Briggs, D. (2008). A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmospheric Environment *42*, 7561-7578.

Hoek, G., Brunekreef, B., Goldbohm, S., Fischer, P., Br, v.d., and t, P.A. (2002a). Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet *360*, 1203-1209.

Hoek, G., Brunekreef, B., Verhoeff, A., van Wijnen, J., and Fischer, P. (2000). Daily mortality and air pollution in the Netherlands. Journal of the Air & Waste Management Association *50*, 1380-1389.

Hoek, G., Meliefste, K., Cyrys, J., Lewné, M., Bellander, T., Brauer, M., Fischer, P., Gehring, U., Heinrich, J., and Vliet, P.V.J.A.E. (2002b). Spatial variability of fine particle concentrations in three European areas. *36*, 4077-4088.

Hong, H., Shuncheng, L., Junji, C., Changwei, Z., Xingeng, C., and Shaojia, F. (2005). Characterization of indoor/outdoor organic and elemental carbon in PM2.5 during summer in Guangzhou City. Acta Scientiae Circumstantiae *25*, 1242-1249.

Hougaard, K.S., Jensen, K.A., Nordly, P., Taxvig, C., Vogel, U., Saber, A.T., and Wallin, H. (2008).

Effects of prenatal exposure to diesel exhaust particles on postnatal development, behavior, genotoxicity and inflammation in mice. Particle and Fibre Toxicology *5*.

Hu, Q.S., Wang, D., Yue, D.L., Xu, C.F., Hu, B., Cheng, P., Zhai, Y.H., Mai, H.Y., Li, P., Gong, J., *et al.* (2021). Association of ambient particle pollution with gestational diabetes mellitus and fasting blood glucose levels in pregnant women from two Chinese birth cohorts. Science of the Total Environment *762*, 10.

Hua, Y., Liu, F., Wu, H., Lee, C.-F., and Li, Y. (2020). Effects of alcohol addition to traditional fuels on soot formation: A review. International Journal of Engine Research.

Huang, C.H., Lin, L.Y., Tsai, M.S., Hsu, C.Y., Chen, H.W., Wang, T.D., Chang, W.T., Cheng, T.J., and Chen, W.J. (2010). Acute cardiac dysfunction after short-term diesel exhaust particles exposure. Toxicology Letters *192*, 349-355.

Hudda, N., Eliasziw, M., Hersey, S.O., Reisner, E., Brook, R.D., Zamore, W., Durant, J.L., and Brugge, D. (2021). Effect of Reducing Ambient Traffic-Related Air Pollution on Blood Pressure: a Randomized Crossover Trial. Hypertension (dallas, tex : 1979) *77*, 823-832.

Hussein, T., C. Johansson, H. Karlsson and H.-C. Hansson (2008). "Factors affecting non-tailpipe aerosol particle emissions from paved roads: On-road measurements in Stockholm, Sweden." Atmospheric Environment 42(4): 688-702.

Hvidtfeldt, U.A., Severi, G., Andersen, Z.J., Atkinson, R., Bauwelinck, M., Bell, er, T., Boutron-Ruault, M.C., Br, t, J., *et al.* (2021). Long-term low-level ambient air pollution exposure and risk of lung cancer – A pooled analysis of 7 European cohorts. Environment International *146*.

Hvidtfeldt, U.A., Sorensen, M., Geels, C., Ketzel, M., Khan, J., Tjonnel, , A., Overvad, K., Br, t, J., *et al.* (2019). Long-term residential exposure to PM2.5, PM10, black carbon, NO2, and ozone and mortality in a Danish cohort. Environment International *123*, 265-272.

Inoue, K.I., Takano, H., Sakurai, M., Oda, T., Tamura, H., Yanagisawa, R., Shimada, A., and Yoshikawa, T. (2006). Pulmonary exposure to diesel exhaust particles enhances coagulatory disturbance with endothelial damage and systemic inflammation related to lung inflammation. Experimental Biology and Medicine *231*, 1626-1632.

Ischer, P., Ameling, C., Marra, M., and Cassee, F.R. (2009). Absence of trends in relative risk estimates for the association between Black Smoke and daily mortality over a 34 years period in The Netherlands. Atmospheric Environment *43*, 481-485.

Ito, K., Mathes, R., Ross, Z., Nadas, A., Thurston, G., and Matte, T. (2011). Fine Particulate Matter Constituents Associated with Cardiovascular Hospitalizations and Mortality in New York City. Environmental Health Perspectives *119*, 467-473.

J.A.OGREN, and R.J.CHARLSON (1983). Elemental carbon in the atmosphere: cycle and lifetime. J Tellus B.

Januario, D., Perin, P.M., Maluf, M., Lichtenfels, A.J., and Saldiva, P.H.N. (2010). Biological Effects and Dose-Response Assessment of Diesel Exhaust Particles on In Vitro Early Embryo Development in Mice. Toxicological Sciences *117*, 200-208.

Jaspers, I., Sheridan, P.A., Zhang, W., Brighton, L.E., Chason, K.D., Hua, X., and Tilley, S.L. (2009). Exacerbation of allergic inflammation in mice exposed to diesel exhaust particles prior to viral infection. Part Fibre Toxicol *6*, 22.

Jensen, K.A., Suo-Anttila, J.M., and Blevins, L.G. (2007). Measurement of Soot Morphology, Chemistry, and Optical Properties in the Visible and near-Infrared Spectrum in the Flame Zone and Overfire Region of Large Jp-8 Pool Fires. Combustion Science and Technology *179*, 2453-2487.

Jenwitheesuk, K., Peansukwech, U., and Jenwitheesuk, K. (2020). Accumulated ambient air pollution and colon cancer incidence in Thailand. Scientific Reports *10*, 12.

Jeong, S., Lee, J.H., Ha, J.H., Kim, J., Kim, I., and Bae, S. (2021). An exploratory study of the relationships between diesel engine exhaust particle inhalation, pulmonary inflammation and anxious behavior. International Journal of Environmental Research and Public Health *18*, 1-14.

Jia, X. (2014). The relationship between indoor and outdoor particulate matter and the health risk assessment based on chemical components and source apportionment (Nankai University).

Jiafeng, F., Meng, Q., Qian, L., and Hongmei, W. (2018). The emission estimation and spatial distribution of black carbon aerosol. Science & Technology Review *036*, 38-46.

Johansson, K.O., Dillstrom, T., Monti, M., El Gabaly, F., Campbell, M.F., Schrader, P.E., Popolan-Vaida, D.M., Richards-Henderson, N.K., Wilson, K.R., Violi, A.*, et al.* (2016). Formation and emission of large furans and oxygenated hydrocarbons from flames. Proc Natl Acad Sci U S A *113*, 8374-8379.

Jones, R.R., Hoek, G., Fisher, J.A., Hasheminassab, S., Wang, D., Ward, M.H., Sioutas, C., Vermeulen, R., and Silverman, D.T. (2020). Land use regression models for ultrafine particles, fine particles, and black carbon in Southern California. Science of The Total Environment *699*, 134234.

Jonker, M.T.O., & Koelmans, A. A. (2002). Sorption of Polycyclic Aromatic Hydrocarbons and Polychlorinated Biphenyls to Soot and Soot-like Materials in the Aqueous Environment: Mechanistic Considerations. Environmental Science & Technology *36*, 3725–3734.

Julia A. Nightingale, R.M., Paul Cullinan, Louise E. Donnelly, Duncan F. Rogers, Robert Kinnersley, K. Fan Chung, Peter J. Barnes, Michael Ashmore, and Anthony Newman-Taylor (1999). Airway inflammation after controlled exposure to diesel exhaust particulates. American journal of respiratory and critical care medicine.

Jung, H.J., Ko, Y.K., Shim, W.S., Kim, H.J., Kim, D.Y., Rhee, C.S., Park, M.K., and Han, D.H. (2021). Diesel exhaust particles increase nasal symptoms and IL-17A in house dust mite-induced allergic mice. Scientific reports *11*, 16300.

Kaewamatawong, T., Shimada, A., Morita, T., Banlunara, W., and Bintvihok, A. (2009). Acute and Subacute Pulmonary Effects of Diesel Exhaust Particles in Mice: Pathological Changes and Translocation Pathways to the Circulation. Thai Journal of Veterinary Medicine *39*, 311-318.

Kim, D.I., Song, M.K., Kim, H.I., Han, K.M., and Lee, K. (2020a). Diesel Exhaust Particulates Induce Neutrophilic Lung Inflammation by Modulating Endoplasmic Reticulum Stress-Mediated CXCL1/KC Expression in Alveolar Macrophages. Molecules *25*, 16.

Kim, H.S., Kim, B.G., Park, S., Kim, N., Jang, A.S., Seo, Y.R., and Park, M.K. (2020a). Gene Expression Analysis to Investigate Biological Networks Underlying Nasal Inflammatory Dysfunctions Induced by Diesel Exhaust Particles Using an In Vivo System. Annals of Otology, Rhinology and Laryngology *129*, 245-255.

Kim, J.B., Kim, C., Choi, E., Park, S., Park, H., Pak, H.N., Lee, M.H., Shin, D.C., Hwang, K.C., and Joung, B. (2012). Particulate air pollution induces arrhythmia via oxidative stress and calcium calmodulin kinase II activation. Toxicology and Applied Pharmacology *259*, 66-73.

Kim, S., Park, H., Park, H., Joung, B., and Kim, E. (2016). The acute respiratory exposure by intratracheal instillation of Sprague-Dawley rats with diesel particulate matter induces retinal thickening. Cutaneous and Ocular Toxicology *35*, 275-280.

Kim, S.J., Kim, N., Park, S.H., Kim, H.S., Song, J.J., Son, B.S., Jang, A.S., Park, M.K., and Seo, Y.R. (2020b). Genomic approach to explore altered signaling networks of olfaction in response to diesel exhaust particles in mice. Scientific reports *10*, 16972.

Kim, S.Y., Dutton, S.J., Sheppard, L., Hannigan, M.P., Miller, S.L., Milford, J.B., Peel, J.L., and Vedal, S. (2015). The short-term association of selected components of fine particulate matter and mortality in the Denver Aerosol Sources and Health (DASH) study. Environmental Health *14*, 11.

Klimont, Z., Kupiainen, K., Heyes, C., Purohit, P., Cofala, J., Rafaj, P., Borken-Kleefeld, J., and Schöpp, W. (2017). Global anthropogenic emissions of particulate matter including black carbon. Atmos Chem Phys *17*, 8681-8723.

Kodavanti, U.P., Thomas, R., Ledbetter, A.D., Schladweiler, M.C., Shannahan, J.H., Wallenborn, J.G., Lund, A.K., Campen, M.J., Butler, E.O., Gottipolu, R.R*., et al.* (2011). Vascular and cardiac impairments in rats inhaling ozone and diesel exhaust particles. Environmental Health Perspectives *119*, 312-318.

Koelmans, A.A., Jonker, M.T., Cornelissen, G., Bucheli, T.D., Van Noort, P.C., and Gustafsson, O. (2006). Black carbon: the reverse of its dark side. Chemosphere *63*, 365-377.

Kupiainen, K., R. Ritola, A. Stojiljkovic, L. Pirjola, A. Malinen and J. Niemi (2016). "Contribution of mineral dust sources to street side ambient and suspension PM10 samples." Atmospheric Environment 147: 178-189.

Kurokawa, J., and Ohara, T. (2019). Long-term historical trends in air pollutant emissions in Asia:

Regional Emission inventory in ASia (REAS) version 3.1. Atmospheric Chemistry and Physics.

Kwon, H.S., Ryu, M.H., and Carlsten, C. (2020). Ultrafine particles: unique physicochemical properties relevant to health and disease. Exp Mol Med *52*, 318-328.

Labranche, N., El Khattabi, C., Dewachter, L., Dreyfuss, C., Fontaine, J., Van De Borne, P., Berkenboom, G., and Pochet, S. (2012). Vascular oxidative stress induced by diesel exhaust microparticles: Synergism with hypertension. Journal of Cardiovascular Pharmacology *60*, 530-537.

Lack, D.A., Moosmüller, H., Mcmeeking, G.R., Chakra Ba Rty, R.K., and umgardner, D.B. (2014). Characterizing elemental, equivalent black, and refractory black carbon aerosol particles: a review of techniques, their limitations and uncertainties. Analytical and Bioanalytical Chemistry *406*, 99-122.

Laskin, A., Laskin, J., and Nizkorodov, S.A. (2015). Chemistry of atmospheric brown carbon. Chem Rev *115*, 4335-4382.

Lavigne, E., Talarico, R., van Donkelaar, A., Martin, R.V., Stieb, D.M., Crighton, E., Weichenthal, S., Smith-Doiron, M., Burnett, R.T., and Chen, H. (2021). Fine particulate matter concentration and composition and the incidence of childhood asthma. Environment International *152*, 7.

Le Tertre, A., Quenel, P., Eilstein, D., Medina, S., Prouvost, H., Pascal, L., Boumghar, A., Saviuc, P., Zeghnoun, A., Filleul, L.*, et al.* (2002). Short-term effects of air pollution on mortality in nine French cities: A quantitative summary. Archives of Environmental Health *57*, 311-319.

Lei, J., Li, Z., Huang, X., Li, X., Zhang, G., Kan, H., Chen, R., and Zhang, Y. (2021). The acute effect of diesel exhaust particles and different fractions exposure on blood coagulation function in mice. International Journal of Environmental Research and Public Health *18*.

Lei, Y., Zhang, Q., He, K.B., and Streets, D.G. (2011). Primary anthropogenic aerosol emission trends for China, 1990–2005. Atmos Chem Phys *11*, 931-954.

Leonard, E., and Aminuddin, M. (2020). The effect of soot particulate towards vascular cell adhesion molecule-1 (Vcam-1) expression in the mechanism of cardiovascular system disruption. Medico-Legal Update *20*, 830-835.

Li, N., Xia, T., and Nel, A.E. (2008). The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. Free Radic Biol Med *44*, 1689-1699.

Lipsett, M., and Campleman, S. (1999). Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am J Public Health *89*, 1009-1017.

Liu, S., Jorgensen, J.T., Ljungman, P., Pershagen, G., Bell, er, T., Le, er, K., Magnusson, P.K.E., Rizzuto, D.*, et al.* (2021). Long-term exposure to low-level air pollution and incidence of chronic obstructive pulmonary disease: The ELAPSE project. Environment International *146*, 8.

Ljungman, P.L.S., Andersson, N., Stockfelt, L., Andersson, E.M., Sommar, J.N., Eneroth, K., Gidhagen, L., Johansson, C., Lager, A., Le*, et al.* (2019). Long-Term Exposure to Particulate Air Pollution, Black Carbon, and Their Source Components in Relation to Ischemic Heart Disease and Stroke. Environmental Health Perspectives *127*, 11.

Long, C.M., Nascarella, M.A., and Valberg, P.A. (2013). Carbon black vs. black carbon and other airborne materials containing elemental carbon: Physical and chemical distinctions. Environmental Pollution *181*.

Lu, Z., Zhang, Q., and Streets, D.G. (2011). Sulfur dioxide and primary carbonaceous aerosol emissions in China and India, 1996–2010. Atmos Chem Phys *11*, 9839-9864.

Luping, T., Guihong, L., Ni, L., and Xiongyi, Y. (2020). Research progress of determination methods for environmental black carbon. environmental chemistry *v.39*, 170-182.

Ma, Q., Cai, S., Wang, S., Zhao, B., Martin, R. V., Brauer, M., Cohen, A., Jiang, J., Zhou, W., Hao, J., Frostad, J., Forouzanfar, M. H., Burnett, R. T. (2017). Impacts of coal burning on ambient PM2.5 pollution in China. Atmospheric Chemistry & Physics.

Mar, T.F., Norris, G.A., Koenig, J.Q., and Larson, T.V. (2000). Associations between air pollution and mortality in Phoenix, 1995-1997. Environmental Health Perspectives *108*, 347-353.

Maria Sehlstedt, A.F.B., Christoffer Boman, Anders Blomberg, Thomas Sandström,and Jamshid Pourazar (2010). Airway inflammatory response to diesel exhaust generated at urban cycle running conditions. Inhalation Toxicology *22*, 1144-1150.

Marilena Kampa, E.C. (1993). Human health effects of air pollution. Environmental Pollution *151*, 362-367.

McCreanor, J., Cullinan, P., Nieuwenhuijsen, M.J., Stewart-Evans, J., Malliarou, E., Jarup, L., Harrington, R., Svartengren, M., Han, I.K., Ohman-Strickland, P.*, et al.* (2007). Respiratory effects of exposure to diesel traffic in persons with asthma. New England journal of medicine *357*, 2348-2358.

Meldrum, K., Guo, C., Marczylo, E.L., Gant, T.W., Smith, R., and Leonard, M.O. (2017). Mechanistic insight into the impact of nanomaterials on asthma and allergic airway disease. Part Fibre Toxicol *14*, 45.

Milani, C., Farina, F., Botto, L., Massimino, L., Lonati, E., Donzelli, E., Ballarini, E., Crippa, L., Marmiroli, P., Bulbarelli, A.*, et al.* (2020). Systemic exposure to air pollution induces oxidative stress and inflammation in mouse brain, contributing to neurodegeneration onset. International Journal of Molecular Sciences *21*.

Miller, M.R., McLean, S.G., Duffin, R., Lawal, A.O., Araujo, J.A., Shaw, C.A., Mills, N.L., Donaldson, K., Newby, D.E., and Hadoke, P.W.F. (2013). Diesel exhaust particulate increases the size and complexity of lesions in atherosclerotic mice. Particle and Fibre Toxicology *10*.

Moazami, T. N., B. Hilt, K. Soras, K. V. H. Svendsen, H. J. Dahlman, M. Refsnes, M. Lag, J. Ovrevik and R. B. Jorgensen (2022). "Short-term exposure to stone minerals used in asphalt affect lung function and promote pulmonary inflammation among healthy adults." Scand J Work Environ Health 48(5): 410-418.

Moosmüller, H., Chakrabarty, R.K., and Arnott, W.P. (2009). Aerosol light absorption and its measurement: A review. JOURNAL OF QUANTITATIVE SPECTROSCOPY AND RADIATIVE TRANSFER *110*, 844-878.

Mordukhovich, I., Coull, B., Kloog, I., Koutrakis, P., Vokonas, P., and Schwartz, J. (2015). Exposure to sub-chronic and long-term particulate air pollution and heart rate variability in an elderly cohort: the Normative Aging Study. Environmental Health *14*, 10.

Mortamais, M., Gutierrez, L.A., de Hoogh, K., Chen, J., Vienneau, D., Carrière, I., Letellier, N., Helmer, C., Gabelle, A., Mura, T.*, et al.* (2021). Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study. Environ Int *148*, 106376.

Muller, A.K., Farombi, E.O., Moller, P., Autrup, H.N., Vogel, U., Wallin, H., Dragsted, L.O., Loft, S., and Binderup, M.L. (2004). DNA damage in lung after oral exposure to diesel exhaust particles in Big Blue (R) rats. Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis *550*, 123-132.

Nemmar, A., Al-Salam, S., Zia, S., Dhanasekaran, S., Shudadevi, M., and Ali, B.H. (2010a). Time-course effects of systemically administered diesel exhaust particles in rats. Toxicology Letters *194*, 58-65.

Nemmar, A., Al-Salam, S., Zia, S., Marzouqi, F., Al-Dhaheri, A., Subramaniyan, D., Dhanasekaran, S., Yasin, J., Ali, B.H., and Kazzam, E.E. (2011a). Contrasting actions of diesel exhaust particles on the pulmonary and cardiovascular systems and the effects of thymoquinone. British Journal of Pharmacology *164*, 1871-1882.

Nemmar, A., Al-Salam, S., Zia, S., Yasin, J., Al Husseni, I., and Ali, B.H. (2010b). Diesel Exhaust Particles in the Lung Aggravate Experimental Acute Renal Failure. Toxicological Sciences *113*, 267-277.

Nemmar, A., Dhanasekaran, S., Yasin, J., Ba-Omar, H., Fahim, M.A., Kazzam, E.E., and Ali, B.H. (2009). Evaluation of the direct systemic and cardiopulmonary effects of diesel particles in spontaneously hypertensive rats. Toxicology *262*, 50-56.

Nemmar, A., Hoet, P.H.M., Dinsdale, D., Vermylen, J., Hoylaerts, M.F., and Nemery, B. (2003). Diesel exhaust particles in lung acutely enhance experimental peripheral thrombosis. Circulation *107*, 1202-1208.

Nemmar, A., and Inuwa, I.M. (2008). Diesel exhaust particles in blood trigger systemic and pulmonary morphological alterations. Toxicology Letters *176*, 20-30.

Nemmar, A., Karaca, T., Beegam, S., Yuvaraju, P., Yasin, J., Hamadi, N.K., and Ali, B.H. (2016). Prolonged pulmonary exposure to diesel exhaust particles exacerbates renal oxidative stress, inflammation and DNA damage in mice with adenine-induced chronic renal failure. Cellular Physiology and Biochemistry *38*, 1703-1713.

Nemmar, A., Subramaniyan, D., Yasin, J., and Ali, B.H. (2013). Impact of experimental type 1 diabetes mellitus on systemic and coagulation vulnerability in mice acutely exposed to diesel exhaust particles. Particle and Fibre Toxicology *10*, 10.

Nemmar, A., Subramaniyan, D., Zia, S., Yasin, J., and Ali, B.H. (2012). Airway resistance, inflammation and oxidative stress following exposure to diesel exhaust particle in angiotensin II-induced hypertension in mice. Toxicology *292*, 162-168.

Nemmar, A., Zia, S., Subramaniyan, D., Fahim, M.A., and Ali, B.H. (2011b). Exacerbation of thrombotic events by diesel exhaust particle in mouse model of hypertension. Toxicology *285*, 39-45.

Ni, M., Huang, J., Lu, S., Li, X., Yan, J., and Cen, K. (2014). A review on black carbon emissions, worldwide and in China. Chemosphere *107*, 83-93.

Nicole, A., H., Janssen, and, Kees, Meliefste, and, Oliver, Fuchs, and Environment, a.J.A. (2008). High and low volume sampling of particulate matter at sites with different traffic profiles in the Netherlands and Germany: Results from the HEPMEAP study - ScienceDirect. *42*, 1110-1120.

Nitter, T. B., B. Hilt, K. V. H. Svendsen, M. Buhagen and R. B. Jorgensen (2021). "Association between exposure to different stone aggregates from asphalt and blood coagulability: A human exposure chamber study." Sci Total Environ 778: 146309.

Okayama, Y., Kuwahara, M., Suzuki, A., and Tsubone, H. (2006). Role of reactive oxygen species on diesel exhaust particle-induced cytotoxicity in rat cardiac myocytes. Journal of Toxicology and Environmental Health - Part A: Current Issues *69*, 1699-1710.

Onyeso, G., Bohr, E.L., Nkpaa, K.W., Amadi, P.N., and Ugwu, A.C. (2020). Black soot exposure induced hypothalamic and testicular oxidative stress and apoptosis in male rats. Andrologia *52*.

Ostro, B., Feng, W.Y., Broadwin, R., Green, S., and Lipsett, M. (2007). The effects of components of fine particulate air pollution on mortality in California: Results from CALFINE. Environmental Health Perspectives *115*, 13-19.

Ostro, B., Hu, J.L., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., and Kleeman, M.J. (2015a). Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort. Environmental Health Perspectives *123*, 549-556.

Ostro, B., Lipsett, M., Reynolds, P., Goldberg, D., Hertz, A., Garcia, C., Henderson, K.D., and Bernstein, L. (2010). Long-Term Exposure to Constituents of Fine Particulate Air Pollution and

Mortality: Results from the California Teachers Study. Environmental Health Perspectives *118*, 363-369.

Ostro, B., Tobias, A., Karanasiou, A., Samoli, E., Querol, X., Rodopoulou, S., Basagana, X., Eleftheriadis, K., Diapouli, E., Vratolis, S.*, et al.* (2015b). The risks of acute exposure to black carbon in Southern Europe: results from the MED-PARTICLES project. Occup Environ Med *72*, 123-129.

Pace, W.B.K.B.T.G. (2002). Methods for Improving Global Inventories of Black Carbon and Organic Carbon Particulates. Journal of Geophysical Research.

Park, J.H., Troxel, A.B., Harvey, R.G., and Penning, T.M. (2006). Polycyclic aromatic hydrocarbon (PAH) o-quinones produced by the aldo-keto-reductases (AKRs) generate abasic sites, oxidized pyrimidines, and 8-oxo-dGuo via reactive oxygen species. Chemical Research in Toxicology *19*, 719.

Peacock, J.L., Anderson, H.R., Bremner, S.A., Marston, L., Seemungal, T.A., Strachan, D.P., and Wedzicha, J.A. (2011). Outdoor air pollution and respiratory health in patients with COPD. Thorax *66*, 591-596.

Penning, T.M., Burczynski, M.E., Hung, C.F., Mccoull, K.D., and Tsuruda, L.S. (1999). Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. Chemrestoxicol *12*, 1.

Petzold, A., Ogren, J.A., Fiebig, M., Laj, P., Li, S.M., Baltensperger, U., Holzer-Popp, T., Kinne, S., Pappalardo, G., and Sugimoto, N. (2013). Recommendations for reporting "black carbon" measurements. J Atmospheric Chemistry Physics *13*, 8365-8379.

Poss, J., Lorenz, D., Werner, C., Pavlikova, V., Gensch, C., Speer, T., Alessandrini, F., Berezowski, V., Kuntz, M., Mempel, M.*, et al.* (2013). Diesel Exhaust Particles Impair Endothelial Progenitor Cells, Compromise Endothelial Integrity, Reduce Neoangiogenesis, and Increase Atherogenesis in Mice. Cardiovascular Toxicology *13*, 290-300.

Prescott, G.J., Cohen, G.R., Elton, R.A., Fowkes, F.G.R., and Agius, R.M. (1998). Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. Occupational and Environmental Medicine *55*, 697-704.

Provost, E.B., Louwies, T., Cox, B., op 't Roodt, J., Solmi, F., Dons, E., Int Panis, L., De Boever, P., and Nawrot, T.S. (2016). Short-term fluctuations in personal black carbon exposure are associated with rapid changes in carotid arterial stiffening. Environment International *88*, 228-234.

Qin SG, T.J., Wen Yp (2001). Black carbon and its importance in climate change studies. Meteorological Monthly *27(11)*, 3-7.

Qin, W., Zhang, Y., Chen, J., Yu, Q., Cheng, S., Li, W., Liu, X., and Tian, H. (2019). Variation, sources and historical trend of black carbon in Beijing, China based on ground observation and

MERRA-2 reanalysis data. Environmental Pollution *245*, 853-863.

Quincey, P., Butterfield, D., Green, D., and Fuller, G.W. (2011). Black Smoke and Black Carbon: Further investigation of the relationship between these ambient air metrics. Atmospheric Environment *45*, 3528-3534.

Raaschou-Nielsen, O., Thorsteinson, E., Antonsen, S., Holst, G.J., Sigsgaard, T., Geels, C., Frohn, L.M., Christensen, J.H., Br, t, J.*, et al.* (2020). Long-term exposure to air pollution and mortality in the Danish population a nationwide study. Eclinicalmedicine *28*, 10.

Rajamani, K.T., Doherty-Lyons, S., Bolden, C., Willis, D., Hoffman, C., Zelikoff, J., Chen, L.C., and Gu, H. (2013). Prenatal and Early-Life Exposure to High-Level Diesel Exhaust Particles Leads to Increased Locomotor Activity and Repetitive Behaviors in Mice. Autism Research *6*, 248-257.

Reisinger, P., Wonaschütz, A., Hitzenberger, R., Petzold, A., Bauer, H., Jankowski, N., Puxbaum, H., Chi, X., and Maenhaut, W. (2008). Intercomparison of Measurement Techniques for Black or Elemental Carbon Under Urban Background Conditions in Wintertime: Influence of Biomass Combustion. Environmental Science & Technology *42*, 884-889.

Reliene, R., Hlavacova, A., Mahadevan, B., Baird, W.M., and Schiestl, R.H. (2005). Diesel exhaust particles cause increased levels of DNA deletions after transplacental exposure in mice. Mutation Research-Fundamental and Molecular Mechanisms of Mutagenesis *570*, 245-252.

Rhoden, C.R., Wellenius, G.A., Ghelfi, E., Lawrence, J., and González-Flecha, B. (2005). PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. Biochimica Et Biophysica Acta General Subjects *1725*, 305-313.

Rivas, I., Donaire-Gonzalez, D., Bouso, L., Esnaola, M., Pandolfi, M., Castro, M., Viana, M., Lvarez-Pedrerol, M., Nieuwenhuijsen, M., and Alastuey, A. (2016). Spatiotemporally resolved black carbon concentration, schoolchildren's exposure and dose in Barcelona. Wiley-Blackwell Online Open *26*.

Robertson, S., Gray, G.A., Duffin, R., McLean, S.G., Shaw, C.A., Hadoke, P.W.F., Newby, D.E., and Miller, M.R. (2012). Diesel exhaust particulate induces pulmonary and systemic inflammation in rats without impairing endothelial function ex vivo or in vivo. Particle and Fibre Toxicology *9*, 13.

Robertson, S., Thomson, A.L., Carter, R., Stott, H.R., Shaw, C.A., Hadoke, P.W.F., Newby, D.E., Miller, M.R., and Gray, G.A. (2014). Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and β1 adrenoreceptors. Particle and Fibre Toxicology *11*, 1-10.

Roth, L.S.G.Z.J.B.H.B.W. (1989). Carbonaceous particles in fly ash -a source for the de-novo-synthesis of organochlorocompounds. Chemosphere *19*, 283-290.

Saber, A.T., Jacobsen, N.R., Bornholdt, J., Kjær, S.L., Dybdahl, M., Risom, L., Loft, S., Vogel, U.,

and Wallin, H. (2006). Cytokine expression in mice exposed to diesel exhaust particles by inhalation. Role of tumor necrosis factor. Particle and Fibre Toxicology *3*.

Sarah Koch , Joseph F. Welch , Raymond Tran a, Andrew H. Ramsook , Andy Hung , Christopher Carlsten , Jordan A. Guenette , Michael S. Koehle (2021). Ventilatory responses to constant load exercise following the inhalation of a short-acting ß2-agonist in a laboratory-controlled diesel exhaust exposure study in individuals with exercise-induced bronchoconstriction. Environment international *146*.

Shears, R.K., Jacques, L.C., Naylor, G., Miyashita, L., Khandaker, S., Lebre, F., Lavelle, E.C., Grigg, J., French, N., Neill, D.R.*, et al.* (2020). Exposure to diesel exhaust particles increases susceptibility to invasive pneumococcal disease. Journal of Allergy and Clinical Immunology *145*, 1272-1284.e1276.

Shrestha, G., Traina, S., and Swanston, C. (2010). Black Carbon's Properties and Role in the Environment: A Comprehensive Review. Sustainability *2*, 294-320.

Sifaki-Pistolla, D., Lionis, C., Koinis, F., Georgoulias, V., Tzanakis, N., and Canc Registry Crete, C.R.C. (2017). Lung cancer and annual mean exposure to outdoor air pollution in Crete, Greece. European Journal of Cancer Prevention *26*, S208-S214.

Skuland, T., V. S. Grytting, M. Lag, R. B. Jorgensen, B. Snilsberg, D. Leseman, A. Kubatova, J. Emond, F. R. Cassee, J. A. Holme, et al. (2022). "Road tunnel-derived coarse, fine and ultrafine particulate matter: physical and chemical characterization and pro-inflammatory responses in human bronchial epithelial cells." Part Fibre Toxicol 19(1): 45.

Skuland, T. S., M. Refsnes, P. Magnusson, M. Oczkowski, J. Gromadzka-Ostrowska, M. Kruszewski, R. Mruk, O. Myhre, A. Lankoff and J. Ovrevik (2017). "Proinflammatory effects of diesel exhaust particles from moderate blend concentrations of 1st and 2nd generation biodiesel in BEAS-2B bronchial epithelial cells-The FuelHealth project." Environ Toxicol Pharmacol 52: 138-142.

Spira-Cohen, A., Chen, L.C., Kendall, M., Lall, R., and Thurston, G.D. (2011). Personal Exposures to Traffic-Related Air Pollution and Acute Respiratory Health among Bronx Schoolchildren with Asthma. Environmental Health Perspectives *119*, 559-565.

Stanković, A., Nikić, D., Nikolić, M., and Bogdanović, D. (2007). Short-term effects of air pollution on cardiovascular mortality in elderly in Niš, Serbia. Central European Journal of Public Health *15*, 95-98.

Streets, D.G., Bond, T. C., Carmichael, G. R., Fernandes, S. D., Fu, Q., He, D., Klimont, Z., Nelson, S. M., Tsai, N. Y., Wang, M. Q., Woo, J.-H., Yarber, K. F. (2003). An inventory of gaseous and primary aerosol emissions in Asia in the year 2000. Journal of Geophysical Research: Atmospheres *108*.

Sun, S.Z., Cao, W.N., Pun, V.C., Qiu, H., Ge, Y., and Tian, L.W. (2019). Respirable Particulate Constituents and Risk of Cause-Specific Mortality in the Hong Kong Population. Environmental Science & Technology *53*, 9810-9817.

Sun, S.Z., Qiu, H., Ho, K.F., and Tian, L.W. (2016). Chemical components of respirable particulate matter associated with emergency hospital admissions for type 2 diabetes mellitus in Hong Kong. Environment International *97*, 93-99.

Sunyer, J., Castellsague, J., Saez, M., Tobias, A., and Anto, J.M. (1996). Air pollution and mortality in Barcelona. Journal of Epidemiology and Community Health *50*, S76-S80.

Takano, H., Yanagisawa, R., Ichinose, T., Sadakane, K., Yoshino, S., Yoshikawa, T., and Morita, M. (2002). Diesel exhaust particles enhance lung injury related to bacterial endotoxin through expression of proinflammatory cytokines, chemokines, and intercellular adhesion molecule-1. American Journal of Respiratory and Critical Care Medicine *165*, 1329-1335.

Terzano, C., Stefano, F.D., Conti, V., Graziani, E., and Petroianni, A. (2010). Air pollution ultrafine particles: Toxicity beyond the lung. European review for medical pharmacological ences *14*, 809-821.

Thurston, G.D., Burnett, R.T., Turner, M.C., Shi, Y.L., Krewski, D., Lall, R., Ito, K., Jerrett, M., Gapstur, S.M., Diver, W.R.*, et al.* (2016). Ischemic Heart Disease Mortality and Long-Term Exposure to Source-Related Components of US Fine Particle Air Pollution. Environmental Health Perspectives *124*, 785-794.

Tomaru, M., Takano, H., Inoue, K.I., Yanagisawa, R., Osakabe, N., Yasuda, A., Shimada, A., Kato, Y., and Uematsu, H. (2007). Pulmonary exposure to diesel exhaust particles enhances fatty change of the liver in obese diabetic mice. International Journal of Molecular Medicine *19*, 17-22.

Tran, L.K., Quang, T.N., Hue, N.T., Van Dat, M., Morawska, L., Nieuwenhuijsen, M., and Thai, P.K. (2018). Exploratory assessment of outdoor and indoor airborne black carbon in different locations of Hanoi, Vietnam. Sci Total Environ *642*, 1233-1241.

Tripathy, S., Tunno, B.J., Michanowicz, D.R., Kinnee, E., Shmool, J., Gillooly, S., and Clougherty, J.E.J.S.o.T.T.E. (2019). Hybrid land use regression modeling for estimating spatio-temporal exposures to PM2.5, BC, and metal components across a metropolitan area of complex terrain and industrial sources. *673*, 54-63.

Ueda, K., Yamagami, M., Ikemori, F., Hisatsune, K., and Nitta, H. (2016). Associations Between Fine Particulate Matter Components and Daily Mortality in Nagoya, Japan. Journal of Epidemiology *26*, 249-257.

Van, B.D., Hullmann, M., and Schins, R.P. (2012). Toxicology of ambient particulate matter. EXS *101*, 165.

Van den Brule, S., Rappe, M., Ambroise, J., Bouzin, C., Dessy, C., Paquot, A., Muccioli, G.G., and

Lison, D. (2021). Diesel exhaust particles alter the profile and function of the gut microbiota upon subchronic oral administration in mice. Particle and Fibre Toxicology *18*.

Von Klot, S., Gryparis, A., Tonne, C., Yanosky, J., Coull, B.A., Goldberg, R.J., Lessard, D., Melly, S.J., Suh, H.H., and Schwartz, J. (2009). Elemental Carbon Exposure at Residence and Survival After Acute Myocardial Infarction. Epidemiology *20*, 547-554.

Vora, R., Zareba, W., Utell, M.J., Pietropaoli, A.P., Chalupa, D., Little, E.L., Oakes, D., Bausch, J., Wiltshire, J., and Frampton, M.W. (2014). Inhalation of ultrafine carbon particles alters heart rate and heart rate variability in people with type 2 diabetes. Particle and fibre toxicology *11*, 31.

Wang, W.D., Liu, C., Ying, Z.K., Lei, X.N., Wang, C.P., Huo, J.T., Zhao, Q.B., Zhang, Y.H., Duan, Y.S., Chen, R.J.*, et al.* (2019). Particulate air pollution and ischemic stroke hospitalization: How the associations vary by constituents in Shanghai, China. Science of the Total Environment *695*, 8.

Wauters, A., Vicenzi, M., De Becker, B., Riga, J.P., Esmaeilzadeh, F., Faoro, V., Vachiéry, J.L., van de Borne, P., and Argacha, J.F. (2015). At high cardiac output, diesel exhaust exposure increases pulmonary vascular resistance and decreases distensibility of pulmonary resistive vessels. American journal of physiology Heart and circulatory physiology *309*, H2137-2144.

Wilker, E.H., Mostofsky, E., Fossa, A., Koutrakis, P., Warren, A., Charidimou, A., Mittleman, M.A., and Viswanathan, A. (2018). Ambient Pollutants and Spontaneous Intracerebral Hemorrhage in Greater Boston. stroke *49*, 2764-2766.

Xiao, G.G., Wang, M., Li, N., Loo, J.A., and Nel, A.E. (2003). Use of Proteomics to Demonstrate a Hierarchical Oxidative Stress Response to Diesel Exhaust Particle Chemicals in a Macrophage Cell Line. Journal of Biological Chemistry *278*, 50781-50790.

Xu, H., Ren, Y., Zhang, W., Meng, W., and Tao, S. (2021). Updated Global Black Carbon Emissions from 1960 to 2017: Improvements, Trends, and Drivers. Environmental science & technology *55*, 7869-7879.

Xu, X.H., Kherada, N., Hong, X.R., Quan, C.L., Zheng, L., Wang, A.X., Wold, L.E., Lippmann, M., Chen, L.C., Rajagopalan, S.*, et al.* (2009). Diesel exhaust exposure induces angiogenesis. Toxicology Letters *191*, 57-68.

Yamazaki, S., Shima, M., Nakadate, T., Ohara, T., Omori, T., Ono, M., Sato, T., and Nitta, H. (2014). Association between traffic-related air pollution and development of asthma in school children: Cohort study in Japan. Journal of Exposure Science and Environmental Epidemiology *24*, 372-379.

Yang, H.M., Butterworth, L., Munson, A.E., and Meade, B.J. (2003). Respiratory exposure to diesel exhaust particles decreases the spleen IgM response to a T cell-dependent antigen in female B6C3F1 mice. Toxicological Sciences *71*, 207-216.

Yang, H.M., Ma, J.Y.C., Castranova, V., and Ma, J.K.H. (1997). Effects of diesel exhaust particles on the release of interleukin-1 and tumor necrosis factor-alpha from rat alveolar macrophages.

Experimental Lung Research *23*, 269-284.

Yang, J., Zhou, M.G., Li, M.M., Yin, P., Hu, J.L., Zhang, C.L., Wang, H., Liu, Q.Y., and Wang, B.G. (2020a). Fine particulate matter constituents and cause-specific mortality in China: A nationwide modelling study. Environment International *143*, 7.

Yang, W., Xu, Y., Pan, H., Tian, F., Wang, Y., Xia, M., Hu, J., Yang, M., Tao, S., Sun, S.*, et al.* (2020b). Chronic exposure to diesel exhaust particulate matter impairs meiotic progression during spermatogenesis in a mouse model. Ecotoxicology and Environmental Safety *202*.

Yang, Y., Tang, R., Qiu, H., Lai, P.C., Wong, P., Thach, T.Q., Allen, R., Brauer, M., Tian, L.W., and Barratt, B. (2018). Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. Environment International *117*, 99-106.

Yap, C., Beverl, , I.J., Heal, M.R., Cohen, G.R., Robertson, C., Henderson, D.E.J., Ferguson, N.S., Hart, C.L., Morris, G.*, et al.* (2012). Association between long-term exposure to air pollution and specific causes of mortality in Scotland. Occupational and Environmental Medicine *69*, 916-924.

Yin, X.J., Dong, C.C., Ma, J.Y.C., Antonini, J.M., Roberts, J.R., Barger, M.W., and Ma, J.K.H. (2005). Sustained effect of inhaled diesel exhaust particles on T-lymphocyte-mediated immune responses against Listeria monocytogenes. Toxicological Sciences *88*, 73-81.

Yin, X.J.J., Dong, C.C., Ma, J.Y.C., Antonini, J.M., Roberts, J.R., Stanley, C.F., Schafer, R., and Ma, J.K.H. (2004). Suppression of cell-mediated immune responses to Listeria infection by repeated exposure to diesel exhaust particles in brown Norway rats. Toxicological Sciences *77*, 263-271.

Yokota, S., Oshio, S., and Takeda, K. (2016). In utero exposure to diesel exhaust particles induces anxiogenic effects on male offspring via chronic activation of serotonergic neuron in dorsal raphe nucleus. Journal of Toxicological Sciences *41*, 583-593.

Yokota, S., Sato, A., Umezawa, M., Oshio, S., and Takeda, K. (2015). In utero exposure of mice to diesel exhaust particles affects spatial learning and memory with reduced N-methyl-D-aspartate receptor expression in the hippocampus of male offspring. Neurotoxicology *50*, 108-115.

Yokota, S., Seki, T., Naito, Y., Tachibana, S., Hirabayashi, N., Nakasaka, T., Ohara, N., and Kobayashi, H. (2008). Tracheal instillation of diesel exhaust particles component causes blood and pulmonary neutrophilia and enhances myocardial oxidative stress in mice. Journal of Toxicological Sciences *33*, 609-620.

Yoo, S.E., Park, J.S., Lee, S.H., Park, C.H., Lee, C.W., Lee, S.B., Yu, S.D., Kim, S.Y., and Kim, H. (2019). Comparison of Short-Term Associations between PM2.5 Components and Mortality across Six Major Cities in South Korea. International Journal of Environmental Research and Public Health *16*, 13.

Yoshizaki, K., Brito, J.M., Toledo, A.C., Nakagawa, N.K., Piccin, V.S., Junqueira, M.S., Negri, E.M., Carvalho, A.L.N., Ligeiro De Oliveira, A.P., Tavares De Lima, W.*, et al.* (2010). Subchronic effects

of nasally instilled diesel exhaust particulates on the nasal and airway epithelia in mice. Inhalation Toxicology *22*, 610-617.

Yutanto, D. (2020). The effect of soot particulate towards MAPK expression in the mechanism of cardiovascular system disruption. Medico-Legal Update *20*, 267-272.

Zeghnoun, A., Czernichow, P., Beaudeau, P., Hautemaniere, A., Froment, L., Le Tertre, A., and Quenel, P. (2001). Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995. Archives of Environmental Health *56*, 327-335.

Zhang, Q., Streets, D.G., Carmichael, G.R., He, K.B., Huo, H., Kannari, A., Klimont, Z., Park, I.S., Reddy, S., and Fu, J.S. (2009). Asian emissions in 2006 for the NASA INTEX-B mission. Atmospheric Chemistry & Physics Discussions *9*, 5131-5153.

Zhang, Y., Zhang, X.L., Fan, X.G., Ni, C.J., Sun, Z.B., Wang, S.G., Fan, J., and Zheng, C.J. (2020). Modifying effects of temperature on human mortality related to black carbon particulates in Beijing, China. Atmospheric Environment *243*, 9.

Zhao, Y., Nielsen, C.P., Lei, Y., Mcelroy, M.B., and Hao, J. (2011). Quantifying the uncertainties of a bottom-up emission inventory of anthropogenic atmospheric pollutants in China. ATMOSPHERIC CHEMISTRY AND PHYSICS *11*.

Zhao, Y., Zhang, J., and Nielsen, C.P. (2012). The effects of recent control policies on trends in emissions of anthropogenic atmospheric pollutants and CO2 in China. Atmospheric Chemistry & Physics Discussions *12*, 24985-25036.

Zhi Guorui, C.J., Yang Junchao (2015). Origin,properties,measurement and emission estimation of brown carbon aerosols. Research of Environmental Sciences *28*, 18.

Zhou, J.A., Ito, K., Lall, R., Lippmann, M., and Thurston, G. (2011). Time-Series Analysis of Mortality Effects of Fine Particulate Matter Components in Detroit and Seattle. Environmental Health Perspectives *119*, 461-466.

Zuo, L., Youtz, D.J., and Wold, L.E. (2011). Particulate Matter Exposure Exacerbates High Glucose-Induced Cardiomyocyte Dysfunction through ROS Generation. Plos One *6*, 8.