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Medium term moderate to low-level air pollution exposure is associated with higher C-reactive protein among healthy Danish blood donors

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ABSTRACT

Air pollution is a significant contributor to the global burden of disease with a plethora of associated health effects such as pulmonary and systemic inflammation. C-reactive protein (CRP) is associated with a wide range of diseases and is associated with several exposures. Studies on the effect of air pollution exposure on CRP levels in low to moderate pollution settings have shown inconsistent results.

In this cross-sectional study high sensitivity CRP measurements on 18,463 Danish blood donors were linked to modelled air pollution data for NO_x, NO_2, O_3, CO, SO_2, NH_3, mineral dust, black carbon, organic carbon, sea salt, secondary inorganic aerosols and its components, primary $PM_{2.5}$, secondary organic aerosols, total $PM_{2.5}$, and total PM_{10} at their residential address over the previous month. Associations were analysed using ordered logistic regression with CRP quartile as individuals outcome and air pollution exposure as scaled deciles. Analyses were adjusted for health related and socioeconomic covariates using health questionnaires and Danish register data.

Exposure to different air pollution components was generally associated with higher CRP (odds ratio estimates ranging from 1.11 to 1.67), while exposure to a few air pollution components was associated with lower CRP. For example, exposure to NO_2 increased the odds of high CRP 1.32-fold (95%CI 1.16–1.49), while exposure to NH3 decreased the odds of high CRP 0.81-fold (95%CI 0.73–0.89).

This large study among healthy individuals found air pollution exposure to be associated with increased levels of CRP even in a setting with low to moderate air pollution levels.

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1. Introduction

Air pollution exposure has serious impact on health and the World Health Organisation estimates 4.2 million deaths annually are attributable to ambient air pollution (WHO, 2022). In addition to the associations with heart, lung, and infectious diseases (Tanaka et al., 2013; Shah et al., 2013; Kurt et al., 2016), various types of air pollution has been reported to influence levels of inflammatory biomarkers such as TNF-α, IL-6, IL-8, and C-reactive protein (CRP) (Dutta et al., 2012; Wu et al., 2018).

CRP is a general inflammation marker that binds microbial polysaccharides and activates the classical complement pathway by binding to complement component 1q. CRP is synthesised in the liver and may be greatly increased in plasma during infections while in obesity and chronic diseases, such as atherosclerosis, CRP may be in the range for low-grade inflammation (LGI) defined as CRP between 3 and 10 mg/L (Dinh et al., 2019; Rosvall et al., 2007; Libby et al., 2002). The relationship between CRP and air pollution is not entirely clear, but several studies have found CRP to increase with air pollution exposure (Pilz et al., 2018; Hennig et al., 2014; Zhang et al., 2017; Green et al., 2015). In these studies, the exposure is often higher than what would be expected in a Scandinavian setting or the changes in CRP are limited. Admittedly the air pollution levels in the German studies are only slightly higher than what is expected in a Scandinavian setting. Additionally, no connection between outdoor air pollution and CRP was found in cohorts with mixed exposure windows in the UK, USA, and Israel (Forbes et al., 2009; Dabass et al., 2016; Steinvil et al., 2008) reflecting that moderate pollution levels may not be a strong driver for CRP levels. Furthermore, although air pollution exposure increases CRP in children, adults seem less susceptible and in several randomized trials there was no effect of exposure on CRP level (Li et al., 2012). This evidence indicates that high air pollution levels may increase CRP but in settings with moderate and low air pollution levels the effect on CRP is likely, but the magnitude is uncertain. Commonly examined pollutants in health research are particulate matter (PM) sized <10 μm (PM_{10}) or <2.5 μm ($PM_{2.5}$), nitrogen oxides (NO_X), and ozone (O_3), but the potential impact of other measurable pollutants remains to be investigated.

Using a large cohort of healthy Danish blood donors, we aimed to achieve a better understanding of the effect of NO_X, nitrogen dioxide (NO_2), O_3, carbon monoxide (CO), sulphur dioxide (SO_2), ammonia (NH_3), $PPM_{2.5}$, black carbon (BC), organic carbon (OC), mineral dust, sea salt, secondary inorganic aerosols (SIA) and its components: sulphate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), secondary organic aerosols (SOA), total $PM_{2.5}$, and total PM_{10}on CRP levels in a setting with moderate/low air pollution levels, as known influences on CRP, such as body mass index (BMI), smoking, and oral contraceptives, can be accounted for.

2. Methods

2.1. Study population

The present study used participants from the Danish Blood Donor Study (DBDS) enrolled from March 2010 to December 2010. The DBDS and the CRP measurements have previously been described in detail (Dinh et al., 2019; Sørensen et al., 2014; Erikstrup et al., 2022). In brief, the DBDS is an ongoing multicentre public health study including Danish blood donors aged 18–70. Participants answer health related questionnaires, provide blood samples, and allow linkage of data with national registers. Exclusions are summarised in Table 1. Females reporting taking oral contraceptives (because of a known influence on CRP levels (Sørensen et al., 2014)). After exclusions a total of 15,281 individuals were available for analysis.

Table 1
Exclusions of participants.

Population	Total
A hsCRP measurement in DBDS	18,463
Not residing in Denmark in 30 days prior to hsCRP measurement with available information on air pollutants	39
No available questionnaire from DBDS at hsCRP measurement	479
Incomplete information on BMI and smoking from questionnaires	402
Taking oral contraceptives at the time of hsCRP measurement	2159
hsCRP measurements not between 0.05 and 10 mg/L	103
Available for analysis	15,281

2.2. Outcome

Blood samples were collected in EDTA-containing gel-separated tubes and centrifuged within 6 h in Central Denmark Region (n = 4371) and the Capital Region of Denmark (n = 14,092) at the date of study inclusion. CRP was measured in a thawed plasma sample from each of the 18,463 participants using an automated high-sensitivity CRP (hsCRP) assay (Ortho Vitros 5600, Ortho Clinical Diagnostics, Rochester, NY, USA). Individuals with CRP levels above 10 mg/L were excluded. We then categorized the CRP levels in quartiles (Q1: below 0.12 mg/L, Q2: 0.12–0.45 mg/L, Q3: 0.45–1.18 mg/L, Q4: 1.18 mg/L and above), and based on levels below 3 mg/L, and 3 mg/L and above as this is the lower limit for LGI. Measurements below the detection limit of 0.1 mg/L were assigned the value 0.05 mg/L. Distribution of measurements in detection range is shown in Supplementary Fig. 1.

2.3. Exposure

The integrated Danish air pollution modelling system DEHM/UBM (combining the Danish Eulerian Hemispheric Model (DEHM) and the Urban Background Model (UBM)) was used to calculate the hourly average concentrations of air pollution at a spatial resolution of 1 km × 1 km. The system has been previously described and evaluated with measurements (Raaschou-Nielsen et al., 2020, 2023; Brandt et al., 2003, 2012; Frohn et al., 2022). DEHM is a Eulerian long-range atmospheric chemistry-transport model. The model is setup with four domains – one mother domain covering the Northern hemisphere with a 150 km × 150 km resolution to account for inter-continental transport of air pollution and three two-way nested domains to obtain higher resolution over selected areas. The first nested domain covers Europe with a 50 km × 50 km resolution, the second nested domain covers Northern Europe with a 16.67 km × 16.67 km resolution, and the last domain covers Denmark with a 5.6 km × 5.6 km resolution. The model calculates atmospheric transport and chemistry of 80 chemical species – both gases and primary emitted and secondary formed particles, including both inorganic and organic particles (Brandt et al., 2012). To obtain even higher resolution over Denmark, the UBM model is implemented and uses results from DEHM as boundary conditions. UBM is a plume-in-grid model and covers Denmark with a 1 km × 1 km resolution. UBM calculates concentrations of the gases NOx, NO_2, O_3, SO_2, as well as the primary emitted particles mineral dust, black carbon (BC) and organic carbon (OC). The secondary particles are calculated using DEHM, as these are regional scale air pollutants. The air pollution models are driven by the meteorological model, WRF, and the whole model system can calculate hourly values of air pollutants from 1979 until present.

Exposure was defined as accumulated mean daily exposure of NO_X, NO_2, O_3, CO, SO_2, NH_3, $PPM_{2.5}$, BC, OC, mineral dust, sea salt, SIA and its components: SO_4^{2-}, NO_3^-, NH_4^+, SOA, total $PM_{2.5}$, and total PM_{10} within 1 month (30 days) before the sample date, accounting for residential changes, if any. A 30-day exposure window was chosen for the main analysis as we were interested in medium term exposure, this kept the exposure mainly within the same season as the sample and for the most part donors would not have a donation within the exposure period. For a sensitivity analysis, the exposure within 1 week (7 days) before the

sample date was also defined. $PPM_{2.5}$ is the sum of concentrations of BC, OC, and mineral dust. SIA likewise is the sum of SO_4^{2-}, NO_3^-, and NH_4^+.

2.4. Covariates

The participants were linked with information on age, sex, BMI (continuous), smoking (current smoker or non-smoker), somatic illness (defined as any international classification of diseases 10th revision diagnosis code recorded in the Danish National Patient Register (Lynge et al., 2011) with one of the 19 somatic conditions from the Charlson Comorbidity Index (Charlson et al., 1987), a general method for categorising patient comorbidities, prior to the sample date), labour market affiliation, educational attainment, income, and season (March–May, June–September, October–December) of sampling.

Socioeconomic variables were defined based on variables from Statistics Denmark (Petersson et al., 2011; Jensen and Rasmussen, 2011); educational attainment categorized into three groups (primary school, high school/vocational training, and higher education), employment status categorized into five groups (top level (self-employed with 5+ employees, managers, employees with highest level of qualifications), medium level (self-employed with 0–4 employees, employees with medium level of qualifications), basic level (employees with basic or unknown level of qualifications, trainees), unemployed, and retired). This grouping has been used previously (Raaschou-Nielsen et al., 2020)), and income defined as age-, sex and calendar year specific quintiles based on the entire Danish population. We calculated population density within a radius of 1000 m around the residential location and modelled it as a log-transformed continuous variable. All covariates were defined at the sample date. Every Danish resident is given a unique personal identifier in the Danish Civil Registration System (Pedersen, 2011) allowing for linkage of data across registers. Covariates were selected by including known influencers of CRP levels for which we had data available. Socioeconomic variables available were included to accommodate for possible socioeconomic differences in CRP.

2.5. Statistical analysis

Baseline characteristics among participants with different CRP-levels were compared using Chi2 tests for the categorical variables; continuous variables were compared using Kruskal–Wallis tests.

We used ordered logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for a higher CRP level (CRP defined by quartiles) according to exposure to air pollutants. We scaled the air pollutants to range from 0 (lowest decile) to 1 (highest decile) and estimated the effect of one unit increase corresponding to a comparison between the highest and the lowest decile. Ordered logistic regression was well-suited for accommodating the large proportion of measurements assigned a value of half the detection limit. We also defined air pollution exposure as a categorical variable using the lowest decile as reference. Further, we used logistic regression to estimate ORs with 95% CIs for LGI. Moreover, we used a fixed increase in the air pollutants (e.g., 0.1, 1, 5, 10 $\mu g/m^3$) assuming a linear exposure-response association. To examine possible sex-, and smoking-related differences, we also analysed the ORs stratified by sex and smoking.

We fitted models in a stepwise manner. All estimates were adjusted for age and sex. In the fully adjusted model, we included BMI, smoking, comorbidity, socioeconomics, population density, and season while the adjusted model excluded season. Analysis was performed in Stata (StataCorp LCC, College Station, Texas) version 15.0.

2.6. Ethics

Oral and written informed consent was obtained from all participants. The DBDS was approved by the Committee on Health Research Ethics in Central Denmark Region (1-10-72-95-13) and by the Danish Data Protection Agency (P-2019-99).

3. Results

3.1. Participant characteristics

The characteristics of the study population are described in Table 2. All characteristics differed between the highest and lowest CRP quartile except the proportion with somatic illness. The difference in mean pollution exposure between the highest and lowest CRP quartile was generally quite small for every air pollutant.

3.2. Associations between exposure and CRP

To assess associations between air pollution exposure and CRP level we performed ordered logistic regression on CRP quartiles for 30-day exposure in scaled deciles. Analysis showed increased ORs of higher CRP for all pollutants, but O_3, OC, NH_3, NO_3^-, and SOA across models as displayed in Table 3. O_3, NH_3, and SOA were associated with lower CRP in all models.

Fig. 1 displays the ORs for CRP quartiles for the frequently described air pollutants NO_x, NO_2, $PM_{2.5}$, and PM_{10} as scaled deciles.

In ordered logistic regressions with the lowest air pollution decile set as reference displayed in Supplementary Table 2, the results generally reflected the analysis displayed in Table 3. For the pollutants NO_x, NO_2, CO, SO_2, mineral dust, BC, OC, $PPM_{2.5}$, NH_4^+, SIA, sea salt, $PM_{2.5}$, and PM_{10}, increased ORs were seen within the highest exposure deciles, while some of the lower deciles were associated with lower CRP. Except for sea salt, the highest OR was seen in the most exposed decile for the air pollutants associated with increased CRP.

In a logistic regression with LGI as outcome, shown in Table 4, the results generally reflected those in Table 3 but without an association for NH_4^+, SO_4^{2-}, SIA and Sea salt.

In accordance with our main results, all air pollutants except NO_3^- were associated with CRP, when we estimated the ORs using a fixed increase in the air pollutants. Thus NO_x, NO_2, CO, SO_2, mineral dust, BC, OC, $PPM_{2.5}$, sea salt, SO_4^{2-}, NH_4^+, SIA, $PM_{2.5}$, and PM_{10} were positively associated with higher CRP quartile, and O_3, NH_3, and SOA were negatively associated with higher CRP (Table 5).

3.3. Sensitivity analyses

When estimating the ORs based on accumulated mean daily exposure of air pollutants within 7 days before sample date, we found similar patterns (Supplementary Table 1) although the effect of NO_x, NO_2, and SO_4^{2-} were not significant and OC was. The effects of air pollution exposure did not seem markedly different between males and females, as shown in Supplementary Tables 3 and 4, nor between smokers and non-smokers, as shown in Supplementary Tables 5 and 6 Sensitivity analysis without participants with a Charlson comorbidity index greater than zero also reflected the main analysis (Supplementary Table 7).

4. Discussion

In this cohort of healthy individuals exposed to low/moderate air pollution levels, we find that higher air pollution exposure is associated with higher CRP levels. Differences in levels of air pollution exposure between CRP quartiles were subtle. However, our findings of associations indicate how even small differences in air pollution levels may drive an increase in immune activation.

We choose a 30-day exposure window for the main analysis as we were mainly interested in the more immediate inflammatory effects than potential chronic effects conveyed by long term exposure. A 30-day window kept the exposure mainly within the same season as the sample and for the most part donors would not have a donation within the exposure period and because other studies have considered 30-day exposure windows and found an association with CRP (Gogna et al., 2021; Adami et al., 2021). In one instance a weak association was only

Table 2
Characteristics for the study population.

Characteristics	Q1	Q2	Q3	Q4	Total
N (%)	3825 (25.03)	3806 (24.91)	3832 (25.08)	3818 (24.99)	15,281 (100.00)
CRP (mg/L)*	<0.12	0.12–0.45	0.45–1.18	>1.18	0.45 (0.12–1.18)
Age (years), median (IQR)*	37 (28–47)	41 (31–50)	43 (33–52)	44 (33–53)	41 (31–50)
Sex, No. (%)*					
Female	1484 (38.80)	1479 (38.86)	1488 (38.83)	1658 (43.43)	6109 (39.98)
Male	2341 (61.20)	2327 (61.14)	2344 (61.17)	2160 (56.57)	9172 (60.02)
Season of sampling, No. (%)*					
March–May	987 (25.80)	1139 (29.93)	1217 (31.76)	1241 (32.50)	4584 (30.00)
June–September	2756 (72.05)	2446 (64.27)	2386 (62.27)	2342 (61.34)	9930 (64.98)
October–December	82 (2.14)	221 (5.81)	229 (5.98)	235 (6.16)	767 (5.02)
BMI, median (IQR)*	23.2 (21.6–24.9)	24.25 (22.40–26.20)	25.20 (23.31–27.46)	26.7 (24.2–29.9)	24.68 (22.66–27.10)
Smokers, No. (%)*					
No	3311 (86.56)	3243 (85.21)	3181 (83.01)	3022 (79.15)	12,757 (83.48)
Yes	514 (13.44)	563 (14.79)	651 (16.99)	796 (20.85)	2524 (16.52)
Any somatic illness, No. (%)					
No	3660 (95.69)	3633 (95.45)	3665 (95.64)	3640 (95.34)	14,598 (95.53)
Yes	165 (4.31)	173 (4.55)	167 (4.36)	178 (4.66)	683 (4.47)
Highest educational level, No. (%)*					
Primary school	384 (10.04)	360 (9.46)	462 (12.06)	503 (13.17)	1709 (11.18)
High school/vocational training	1602 (41.88)	1714 (45.03)	1769 (46.16)	1942 (50.86)	7027 (45.99)
Higher education	1820 (47.58)	1711 (44.96)	1581 (41.26)	1351 (35.39)	6463 (42.29)
Unknown	19 (0.50)	21 (0.55)	20 (0.52)	22 (0.58)	82 (0.54)
Employment status, No. (%)*					
Employed, top level	1015 (26.54)	1011 (26.56)	851 (22.21)	742 (19.43)	3619 (23.68)
Employed, medium level	941 (24.60)	1053 (27.67)	1121 (29.25)	1087 (28.47)	4202 (27.50)
Employed, basic level	1746 (45.65)	1584 (41.62)	1684 (43.95)	1744 (45.68)	6758 (44.22)
Unemployed	58 (1.52)	58 (1.52)	50 (1.30)	80 (2.10)	246 (1.61)
Retired	65 (1.70)	100 (2.63)	126 (3.29)	165 (4.32)	456 (2.98)
Income quartiles, No. (%)*					
Lowest quartile	327 (8.55)	286 (7.51)	280 (7.31)	293 (7.67)	1186 (7.76)
Second quartile	775 (20.26)	684 (17.97)	712 (18.58)	795 (20.82)	2966 (19.41)
Third quartile	1092 (28.55)	1127 (29.61)	1189 (31.03)	1226 (32.11)	4634 (30.33)
Highest quartile	1631 (42.64)	1709 (44.90)	1651 (43.08)	1504 (39.39)	6495 (42.50)
Population density, mean (SD)*[a]	16,108 (15,788)	13,871 (14,535)	12,778 (13,888)	12,339 (13,668)	13,774 (14,565)
Air pollutants μg/m^3, mean (SD)					
NO_x	17.93 (4.58)	17.81 (4.74)	17.78 (5.05)	17.83 (5.07)	17.84 (4.86)
NO_2	15.66 (3.58)	15.50 (3.76)	15.47 (3.99)	15.51 (4.01)	15.54 (3.84)
O_3*	62.77 (8.76)	60.46 (10.03)	60.39 (10.48)	60.38 (10.63)	61.00 (10.05)
CO*	149.62 (32.08)	153.71 (35.05)	154.68 (37.85)	155.35 (38.37)	153.34 (35.99)
SO_2*	2.42 (1.56)	2.43 (1.25)	2.48 (1.44)	2.52 (1.45)	2.46 (1.43)
NH_3	1.30 (0.79)	1.36 (0.95)	1.37 (0.98)	1.34 (0.91)	1.34 (0.91)
Mineral dust*	0.69 (0.41)	0.73 (0.43)	0.75 (0.47)	0.77 (0.48)	0.74 (0.45)
BC*	0.54 (0.27)	0.57 (0.28)	0.58 (0.31)	0.59 (0.31)	0.57 (0.30)
OC*	1.16 (0.77)	1.26 (0.83)	1.31 (0.90)	1.35 (0.92)	1.27 (0.86)
$PPM_{2.5}$*	2.39 (1.43)	2.57 (1.53)	2.64 (1.66)	2.71 (1.70)	2.58 (1.59)
Sea salt*	0.59 (0.14)	0.61 (0.13)	0.60 (0.14)	0.60 (0.14)	0.60 (0.14)
SO_4^{2-}*	1.17 (0.26)	1.15 (0.26)	1.16 (0.27)	1.17 (0.27)	1.17 (0.27)
NO_3^-*	3.46 (0.98)	3.35 (0.96)	3.41 (0.98)	3.44 (0.99)	3.41 (0.98)
NH_4^+*	0.79 (0.24)	0.83 (0.27)	0.85 (0.28)	0.86 (0.28)	0.83 (0.27)
SIA*	5.43 (1.31)	5.33 (1.33)	5.42 (1.36)	5.47 (1.37)	5.41 (1.34)
SOA*	0.44 (0.28)	0.38 (0.26)	0.37 (0.27)	0.38 (0.28)	0.39 (0.28)
$PM_{2.5}$*	8.84 (2.05)	8.87 (2.16)	9.04 (2.27)	9.16 (2.30)	8.98 (2.20)
PM_{10}*	13.83 (3.34)	14.22 (3.50)	14.44 (3.74)	14.61 (3.83)	14.28 (3.62)

*$p < 0.005$ with comparison across quartiles by Chi2 tests for the categorical variables and Kruskal–Wallis tests for continuous variables.
[a] Population density calculated in a 1000 m radius of the participants residential location.

found for 30 and 60-day exposure, but not in shorter windows (Diez Roux et al., 2006). Short (1 week) exposure windows are often not found to be associated with increased CRP (Hennig et al., 2014; Dabass et al., 2016; Steinvil et al., 2008). A study in midlife US females found no association between O_3 or $PM_{2.5}$ and CRP with a 30 days exposure window although increased CRP was observed for 6 months O_3 and 1 year $PM_{2.5}$ (Green et al., 2015). An additional consideration is the donation restrictions in place after travel to a range of destinations making it more likely for the donors to have been at home within the exposure period. Our analysis of a 7-day exposure window generally reflected the main analysis although without significant effects of NO_x, NO_2, and SO_4^{2-}.

NO_x, NO_2, CO, SO_2, mineral dust, BC, sea salt, SO_4^{2-}, SIA, NH_4^+, and PM were associated with higher CRP, while SOA, O_3 and NH_3 were associated with lower CRP. Several of the pollutants primarily associated with combustion processes, traffic, and industry, such as NO_x, NO_2, CO, SO_2 and $PPM_{2.5}$, were associated with higher CRP. Associations between the typical industry and traffic emissions and CRP levels have been reported in other studies (Hennig et al., 2014; Green et al., 2015; Diez Roux et al., 2006).

Concentrations NH_3 are higher in rural areas of Denmark and are typically seen in relation to agricultural activities and NH_3 was associated with lower CRP. NH_4^+ exposure was associated with higher CRP although it is mostly formed from livestock NH_3 emissions from agriculture in reaction with SO_2 or NO_2 usually from combustion processes. O_3 is also higher in the countryside as it reacts with NO_x gasses and other compounds found in higher concentrations in cities with more traffic. O_3 was associated with lower CRP as would be expected because of the inverse relationship with other pollutants that were associated with higher CRP. The same inverse relationship likely also applied to the association of NH_3 with lower CRP. SOA is in the modelled exposure

Table 3
Odds ratios (ORs) and 95% Confidence Intervals (CIs) for higher C-reactive protein (CRP) according to the level of air pollutants during 30 days prior to sample date. Exposure is scaled deciles (top vs bottom).

Air pollutant	Basic model[a]	Adjusted model[b]	Fully adjusted model[c]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gases			
NO_x	1.16 (1.06–1.27)	1.57 (1.39–1.76)	1.33 (1.18–1.50)
NO_2	1.13 (1.03–1.24)	1.52 (1.35–1.71)	1.32 (1.16–1.49)
O_3	0.63 (0.58–0.69)	0.54 (0.49–0.59)	0.61 (0.55–0.68)
CO	1.44 (1.32–1.58)	1.81 (1.64–2.01)	1.67 (1.41–1.97)
SO_2	1.42 (1.29–1.55)	1.71 (1.55–1.90)	1.48 (1.32–1.66)
NH_3	0.89 (0.81–0.97)	0.76 (0.69–0.84)	0.81 (0.73–0.89)
Primary particles			
Mineral dust	1.37 (1.25–1.50)	1.60 (1.45–1.76)	1.26 (1.08–1.48)
BC	1.36 (1.25–1.49)	1.69 (1.52–1.87)	1.37 (1.17–1.59)
OC	1.38 (1.26–1.51)	1.49 (1.36–1.64)	1.12 (0.96–1.30)
$PPM_{2.5}$	1.36 (1.25–1.49)	1.55 (1.41–1.71)	1.19 (1.02–1.40)
Sea salt	1.33 (1.22–1.45)	1.40 (1.28–1.54)	1.44 (1.32–1.58)
Secondary particles			
SO_4^{2-}	1.09 (1.00–1.20)	1.06 (0.97–1.17)	1.18 (1.07–1.29)
NO_3^-	1.02 (0.93–1.11)	0.95 (0.86–1.04)	1.04 (0.95–1.15)
NH_4^+	1.53 (1.40–1.68)	1.45 (1.33–1.59)	1.29 (1.13–1.47)
SIA	1.12 (1.03–1.23)	1.06 (0.96–1.16)	1.11 (1.01–1.21)
SOA	0.59 (0.54–0.65)	0.56 (0.51–0.62)	0.59 (0.52–0.69)
Total particles			
$PM_{2.5}$	1.33 (1.22–1.46)	1.33 (1.21–1.45)	1.20 (1.08–1.32)
PM_{10}	1.52 (1.39–1.66)	1.64 (1.49–1.80)	1.43 (1.28–1.60)

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, body mass index (BMI), smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.
[c] Adjusted for age, sex, season of sampling, BMI, smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.

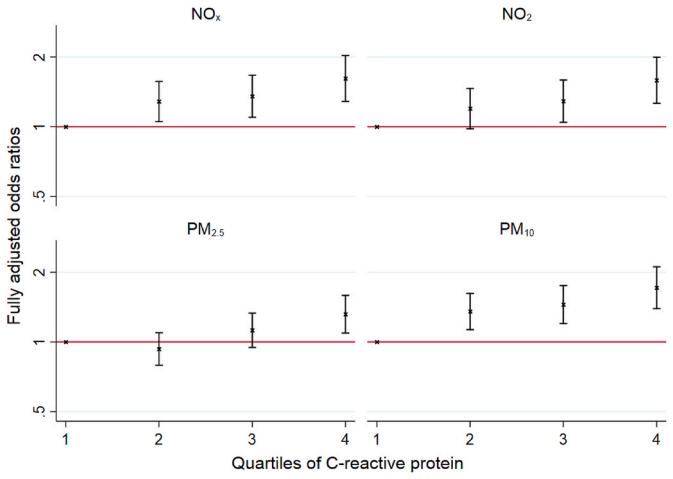

Fig. 1. Odds ratios and 95% confidence intervals for C-reactive protein (CRP) levels in quartile 2, 3, and 4 compared to CRP levels in quartile 1 according to level of air pollutant exposure as scaled deciles (highest vs lowest decile. NO_x 11.3 vs 23.5, NO_2 10.2 vs 20.1, $PM_{2.5}$ 6.56 vs 12.20, PM_{10} 11.3 vs 20.7 all as $\mu g/m^3$) during the 30 days prior to sampling. Odds ratios are adjusted for age, sex, season of sampling, BMI, smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status, and income), and population density.

data formed from natural emissions of volatile organic compounds (VOCs) from vegetation and to a limited extent from anthropogenic activities (e.g. residential wood combustion) and the modelling has its uncertainties (Zare et al., 2012, 2014; Srivastava et al., 2022). There is an east-west gradient of the modelled SOA concentration across Denmark (due to biogenic VOC emissions in e.g., Finland contributing to

Table 4
Odds ratios (ORs) and 95% Confidence Intervals (CIs) for C-reactive protein (CRP) 3 mg/L or higher according to the levels of air pollutants during 30 days prior to sample date.

Air pollutants	CRP below 3 mg/L (n = 14,156)	CRP 3 mg/L and above (n = 1125)	Basic model[a]	Adjusted model[b]	Fully adjusted model[c]
	Mean (SD)	Mean (SD)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gases					
NO_x	17.82 (4.83)	18.04 (5.25)	1.26 (1.04–1.54)	1.56 (1.22–1.99)	1.33 (1.03–1.72)
NO_2	15.53 (3.82)	15.67 (4.13)	1.27 (1.04–1.54)	1.58 (1.24–2.03)	1.37 (1.06–1.78)
O_3	61.08 (9.97)	60.02 (10.99)	0.79 (0.65–0.95)	0.69 (0.57–0.85)	0.81 (0.65–1.02)
CO	152.98 (35.59)	157.86 (40.40)	1.46 (1.20–1.77)	1.69 (1.37–2.10)	1.43 (0.99–2.07)
SO_2	2.46 (1.42)	2.58 (1.54)	1.48 (1.22–1.79)	1.64 (1.32–2.03)	1.39 (1.08–1.79)
NH_3	1.34 (0.91)	1.33 (0.96)	0.76 (0.62–0.92)	0.64 (0.52–0.79)	0.65 (0.52–0.80)
Primary particles					
Mineral dust	0.73 (0.44)	0.80 (0.50)	1.55 (1.28–1.87)	1.74 (1.42–2.14)	1.63 (1.16–2.30)
BC	0.57 (0.29)	0.61 (0.33)	1.50 (1.24–1.82)	1.74 (1.41–2.15)	1.52 (1.10–2.09)
OC	1.26 (0.85)	1.42 (0.96)	1.63 (1.34–1.97)	1.73 (1.41–2.11)	1.65 (1.18–2.30)
$PPM_{2.5}$	2.56 (1.57)	2.83 (1.79)	1.56 (1.29–1.89)	1.72 (1.40–2.11)	1.58 (1.13–2.22)
Sea salt	0.60 (0.14)	0.60 (0.14)	0.97 (0.80–1.17)	0.98 (0.80–1.20)	1.01 (0.83–1.23)
Secondary particles					
SO_4^{2-}	1.16 (0.26)	1.18 (0.28)	1.14 (0.94–1.37)	1.06 (0.87–1.29)	1.14 (0.93–1.40)
NO_3^-	3.41 (0.98)	3.42 (0.97)	1.04 (0.86–1.26)	0.94 (0.77–1.14)	1.01 (0.82–1.24)
NH_4^+	0.83 (0.27)	0.86 (0.29)	1.47 (1.21–1.78)	1.34 (1.10–1.64)	1.01 (0.76–1.35)
SIA	5.41 (1.34)	5.46 (1.35)	1.15 (0.95–1.39)	1.03 (0.85–1.26)	1.06 (0.86–1.30)
SOA	0.39 (0.27)	0.37 (0.29)	0.68 (0.56–0.82)	0.65 (0.53–0.79)	0.82 (0.60–1.13)
Total particles					
$PM_{2.5}$	8.96 (2.18)	9.26 (2.37)	1.46 (1.21–1.77)	1.37 (1.12–1.68)	1.22 (0.98–1.52)
PM_{10}	14.24 (3.59)	14.78 (3.96)	1.49 (1.23–1.80)	1.50 (1.23–1.83)	1.25 (0.98–1.59)

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, body mass index (BMI), smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.
[c] Adjusted for age, sex, season of sampling, BMI, smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.

SOA formation), meaning that SOA is typically higher in the Capital Region. The SOA levels in Denmark are, however, generally low. The limited geographical distribution and known uncertainties in SOA modelling makes us wary of drawing conclusions on this pollutant based on this study alone. Sea salt, a naturally occurring component of mainly PM_{10}, is especially high along the less densely populated west coast of Denmark and thus, this study may miss the most heavily exposed residents. Sea salt was associated with higher CRP despite it having an association with proximity to the ocean, which would normally mean cleaner air. Both Copenhagen and Aarhus are harbour towns in proximity to notable shipping routes and proximity to the sea in these cities may be associated with greater NO_x and NO_2 exposure. Additionally, the difference in sea salt exposure between quartiles was very small. Future studies with a more geographically dispersed cohort are required to

Table 5
Odds ratios (ORs) and 95% Confidence Intervals (CIs) for higher C-reactive protein (CRP) quartile according to the level of air pollutants during the 30 days prior to sample date.

Air pollutant[a]	Basic model[b]	Adjusted model[c]	Fully adjusted model[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gases			
NO_x	1.11 (1.05–1.18)	1.35 (1.26–1.46)	1.21 (1.11–1.30)
NO_2	1.12 (1.04–1.21)	1.45 (1.32–1.60)	1.28 (1.15–1.41)
O_3	0.85 (0.83–0.88)	0.81 (0.79–0.84)	0.84 (0.81–0.87)
CO	1.04 (1.03–1.05)	1.06 (1.05–1.07)	1.06 (1.05–1.08)
SO_2	1.07 (1.05–1.09)	1.09 (1.07–1.11)	1.06 (1.03–1.08)
NH_3	1.02 (0.99–1.05)	0.98 (0.95–1.01)	0.96 (0.93–1.00)
Primary particles			
Mineral dust	1.03 (1.03–1.04)	1.04 (1.03–1.05)	1.04 (1.03–1.05)
BC	1.05 (1.04–1.06)	1.06 (1.05–1.08)	1.05 (1.04–1.07)
OC	1.20 (1.16–1.24)	1.23 (1.19–1.28)	1.24 (1.17–1.31)
$PPM_{2.5}$	1.10 (1.08–1.12)	1.12 (1.10–1.14)	1.12 (1.08–1.15)
Sea salt	1.06 (1.04–1.08)	1.07 (1.05–1.10)	1.07 (1.05–1.10)
Secondary particles			
SO_4^{2-}	1.09 (0.97–1.21)	1.05 (0.94–1.17)	1.19 (1.06–1.34)
NO_3^-	0.99 (0.96–1.02)	0.97 (0.94–1.00)	1.01 (0.98–1.05)
NH_4^+	1.06 (1.05–1.07)	1.06 (1.05–1.07)	1.06 (1.05–1.08)
SIA	1.13 (1.01–1.25)	1.04 (0.93–1.16)	1.13 (1.01–1.27)
SOA	0.95 (0.94–0.96)	0.94 (0.93–0.95)	0.96 (0.95–0.98)
Total particles			
$PM_{2.5}$	1.30 (1.22–1.39)	1.32 (1.23–1.41)	1.24 (1.15–1.34)
PM_{10}	1.56 (1.44–1.69)	1.65 (1.52–1.80)	1.60 (1.44–1.78)

[a] NO_x, NO_2, O_3, CO, PM_{10}: 10 μg/m^3, SIA, $PM_{2.5}$: 5 μg/m^3,SO_2, NH_3, OC, $PPM_{2.5}$, SO_4^{2-}, NO_3^-: 1 μg/m^3, mineral dust, BC, sea salt, NH_4^+, SOA: 0.1 μg/m^3.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, body mass index (BMI), smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.
[d] Adjusted for age, sex, season of sampling, BMI, smoking, somatic illness (as measured by the Charlson comorbidity index), socioeconomic variables (educational level, employment status and income), and population density.

better understand the association with sea salt. Recent years have seen a general decrease in air pollution and the number of street segments in Copenhagen with model calculated exceedances have decreased by a third between 2010 and 2016 (Ellermann et al., 2017). This may influence future studies with more recent data. NO_x, NO_2 and NH_3 showed no difference in exposure level between CPR quartiles, but despite this we still found significant effects of exposure for these pollutants in the analysis even in the basic model.

For air pollutants such as CO, SO_2, mineral dust, BC, OC, $PPM_{2.5}$, NH_4^+, SIA, and $PM_{2.5}$, associated with higher CRP, an association with lower CRP was observed in some of the first exposure deciles compared to the lowest decile while the association with higher CRP was only observed in the highest deciles. The differences in exposure were generally limited but there may be some residual confounding for those living in the least polluted areas compared to those living in the other lightly polluted areas. Although the background pollution is low there may be occupational exposures or behavioural factors that could explain the associations with lower CRP.

High population density, low income, and lower education levels may be associated with living in more polluted areas (close to heavily trafficked roads) and possibly with types of work with a greater pollution exposure. Associations between income levels and pollution levels have been reported in Norway (Audun Hoemsnes Moss, 2019). We know individuals with shorter educations and lower income to be underrepresented among Danish blood donors compared to the general population and the prevalence of blood donors to be greater in urban areas (Burgdorf et al., 2017). Age, education, and income have previously been described as influencers of air pollution exposure (Liang et al., 2019; Raaschou-Nielsen et al., 2022).

Our results are consistent with previous findings of CRP being associated with air pollution exposure (Dutta et al., 2012; Pilz et al., 2018; Hennig et al., 2014; Zhang et al., 2017), especially for pollutants related to industry, combustion, and traffic. The large number of measurements and detailed adjustments and modelling may explain why the present study found associations when other studies did not (Forbes et al., 2009; Dabass et al., 2016; Steinvil et al., 2008; Li et al., 2012). A medium sized study with Swedish and Italian participants examined 28 cytokines and long term NO_x exposure and found associations in Italy but not in Sweden (Mostafavi et al., 2015). Further studies with a wide range of different inflammation markers are required for a better understanding of the inflammatory effects of air pollution exposure in a setting with low to moderate concentrations of air pollution. The inflammation associated with air pollution exposure may be conveyed through oxidative stress induced by inhaled air pollutants. Additionally, the small size of $PM_{2.5}$ particles allows them to penetrate deep into the lung, where alveolar macrophages may phagocytise them and release proinflammatory factors (Hiraiwa and van Eeden, 2013; Hogg and van Eeden, 2009). The persistent inflammation caused by air pollution exposure may help explain some of the diseases also associated with air pollution, such as asthma, allergies, and COPD (DeVries et al., 2017; Gehring et al., 2020; Li et al., 2022).

4.1. Strengths and limitations

The use of linked data from detailed Danish population-based registers is a considerable strength of the present study, allowing adjustment for a wide range of possible confounding factors (i.e. socioeconomic variables and Charlson comorbidity index), which have been collected independently of the study hypothesis. Furthermore, we were able to remove participants who used oral contraceptives, as these are known to have increased CRP (Sørensen et al., 2014). Another advantage is the complete residential address information for all Danish residents, which when linked with daily concentrations of air pollutants, yielded an exposure measure prior to CRP measurement for all participants living in Denmark. The Danish air pollution model system is continually being evaluated with measurements from the Danish monitoring stations, and has proven to reproduce measured values with high accuracy (Brandt et al., 2003; Brandt, 2001). Since blood donors are generally healthy, the influence on CRP levels from factors such as atherosclerosis or medication may be reduced.

Our study also has several limitations. We only included participants from the DBDS, selecting a generally healthy study population, and at the time the DBDS only included blood donors at donation sites in Copenhagen and Aarhus, the two largest cities in Denmark. We further restricted to participants with information on BMI and smoking, assuming data to be missing at random as previous DBDS studies have not found patterns in the missing questionnaires (Dinh et al., 2019; Sørensen et al., 2014). Despite adjustment for a range of potential confounding factors, including issues regarding lifestyle and socioeconomic differences, the possibility of some residual confounding cannot be eliminated. Conversely, we cannot eliminate the possibility of some over adjustment in the models. There may have been minor variations in sample handling time before freezing across donation sites, but we know there was a good correlation (r2: 0.98) for thawed samples validated against fresh serum (Sørensen et al., 2014). The use of ambient air concentrations at residential addresses to define exposure to air pollutants does not account for the hours spent at work and daily commute to/from work. Commuting may be a large source of daily exposure (Liang et al., 2019) and many types of work, such as construction, do not take place at the registered place of work. Our exposure estimates are for outdoor air pollution, but we know that we spend most of our time indoors, and indoor estimates are greatly influenced by factors, which cannot be easily modelled, such as ventilation, insulation, cleaning, and cooking habits. The modelled background air pollution level may be closer to the level inside participant's homes than the pollution level at street level. The modelled 1 km × 1 km grid data is likely a better estimate for individual exposure than using data from measuring stations

alone. Most samples were collected in the spring and summer months but air pollution is generally higher during winter (Ellermann et al., 2017). This could induce bias but also an adjustment for calendar time as week or month is likely an overadjustment that masks the effects of air pollution with the given exposure windows. Thus, we included season of sampling in the fully adjusted model as this goes beyond the exposure windows. Finally, in some analyses, the parallel regressions/proportional odds assumption was violated for some air pollutants. Nevertheless, results were reflected by the analysis of LGI and were generally consistent across the various analyses and stratifications and is an argument for the validity of the models. Additionally, the analysis with a seven-day exposure window reflected the results of the 30-day exposure window.

5. Conclusion

This large study among healthy individuals found that even small differences in air pollution exposure are associated with increased levels of CRP. This indicates that low to moderate levels of air pollution may have a significant impact on health. Notably, the air pollution components associated with traffic and industry were associated with higher CRP levels while O_3 and NH_3, which are associated with more rural areas and agriculture, were associated with lower CRP levels.

Author contributions

Bertram Kjerulff: Conceptualisation, methodology, resources, data curation, writing – original draft, project administration, visualisation. Henriette Thisted Horsdal: Methodology, formal analysis, data curation, writing – review and editing, visualisation. Kathrine Kaspersen: conceptualisation, methodology, resources, writing – review and editing. Susan Mikkelsen: Resources, data curation writing – review and editing. Khoa Manh Dinh: Resources, data curation, writing – review and editing. Margit Hørup Larsen: Investigation, validation, resources, writing – review and editing. Sisse Rye Ostrowski: Resources, writing – review and editing. Henrik Ullum: Investigation conceptualisation, writing – review and editing. Erik Sørensen: Investigation, validation, writing – review and editing. Ole Birger Pedersen: Conceptualisation, resurces, writing – review and editing. Mie Topholm Bruun: Resources, writing – review and editing. Kaspar René Nielsen: Resources, writing – review and editing. Jørgen Brandt: Methodology, data curation, writing – review and editing. Camilla Geels: Methodology, data curation, writing – review and editing. Lise M. Frohn: Methodology, data curation, writing – review and editing. Jesper H. Christensen: Methodology, data curation, writing – review and editing. Torben Sigsgaard: conceptualisation, writing – review and editing, supervision, funding acquisition. Clive Eric Sabel: writing – review and editing, supervision, funding acquisition. Carsten Bøcker Pedersen: conceptualisation, methodology, writing – review and editing, supervision, project administration, funding acquisition. Christian Erikstrup: conceptualisation, writing – review and editing, supervision, project administration, funding acquisition.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Co-author is chairman of Zealand Regional Committee on Health Research Ethics - Ole Birger Pedersen.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116426.

References

Adami, G., Viapiana, O., Rossini, M., Orsolini, G., Bertoldo, E., Giollo, A., et al., 2021. Association between environmental air pollution and rheumatoid arthritis flares. Rheumatology 60 (10), 4591–4597.

Audun Hoemsnes Moss, 2019. Norwegian Inequality in Two Dimensions : Air Pollution and Income [Internet]. Norwegian University of Life Sciences [cited 2022 Nov 16]. Available from: https://nmbu.brage.unit.no/nmbu-xmlui/handle/11250/2600168.

Brandt, J., 2001. Operational air pollution forecasts from European to local scale. Atmos. Environ. 35, 91–98.

Brandt, J., Christensen, J.H., Frohn, L.M., Berkowicz, R., 2003. Air pollution forecasting from regional to urban street scale—implementation and validation for two cities in Denmark. Phys. Chem. Earth, Parts A/B/C 28 (8), 335–344.

Brandt, J., Silver, J.D., Frohn, L.M., Geels, C., Gross, A., Hansen, A.B., et al., 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos. Environ. 53, 156–176.

Burgdorf, K.S., Simonsen, J., Sundby, A., Rostgaard, K., Pedersen, O.B., Sørensen, E., et al., 2017. Socio-demographic characteristics of Danish blood donors. In: Bönig, H. (Ed.), PLoS One 12 (2), e0169112.

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chron. Dis. 40 (5), 373–383.

Dabass, A., Talbott, E.O., Venkat, A., Rager, J., Marsh, G.M., Sharma, R.K., et al., 2016. Association of exposure to particulate matter (PM2.5) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001–2008). Int. J. Hyg Environ. Health 219 (3), 301–310.

DeVries, R., Kriebel, D., Sama, S., 2017. Outdoor air pollution and COPD-related emergency department visits, hospital admissions, and mortality: a meta-analysis. COPD 14 (1), 113–121.

Diez Roux, A.V., Auchincloss, A.H., Astor, B., Barr, R.G., Cushman, M., Dvonch, T., et al., 2006. Recent exposure to particulate matter and C-reactive protein concentration in the multi-ethnic study of atherosclerosis. Am. J. Epidemiol. 164 (5), 437–448.

Dinh, K.M., Kaspersen, K.A., Mikkelsen, S., Pedersen, O.B., Petersen, M.S., Thørner, L.W., et al., 2019. Low-grade inflammation is negatively associated with physical health-related quality of life in healthy individuals: results from the Danish blood donor study (DBDS). PLoS One 14 (3), e0214468.

Dutta, A., Ray, M.R., Banerjee, A., 2012. Systemic inflammatory changes and increased oxidative stress in rural Indian women cooking with biomass fuels. Toxicol. Appl. Pharmacol. 261 (3), 255–262.

Ellermann, T., Nygaard, J., Nøjgaard, J.K., Nordstrøm, C., Brandt, J., Christensen, J., Ketzel, M., Massling, A., Bossi, R., Jensen, S.S., 2017. THE Danish AIR QUALITY MONITORING PROGRAMME Annual Summary for 2016 [Internet]. Aarhus University, DCE – Danish Centre for Environment and Energy (Scientific Report from DCE – Danish Centre for Environment and Energy No. 234.). Available from: https://envs.au.dk/en/research-areas/air-pollution-emissions-and-effects/air-pollution-effects/effect-on-nature-and-aquatic-environment/reports/.

Erikstrup, C., Sørensen, E., Nielsen, K.R., Bruun, M.T., Petersen, M.S., Rostgaard, K., et al., 2022. Cohort profile: the Danish blood donor study. Int. J. Epidemiol. dyac194.

Forbes, L.J.L., Patel, M.D., Rudnicka, A.R., Cook, D.G., Bush, T., Stedman, J.R., et al., 2009. Chronic exposure to outdoor air pollution and markers of systemic inflammation. Epidemiology 20 (2), 245–253.

Frohn, L.M., Geels, C., Andersen, C., Andersson, C., Bennet, C., Christensen, J.H., et al., 2022. Evaluation of multidecadal high-resolution atmospheric chemistry-transport modelling for exposure assessments in the continental Nordic countries. Atmos. Environ. 290, 119334.

Gehring, U., Wijga, A.H., Koppelman, G.H., Vonk, J.M., Smit, H.A., Brunekreef, B., 2020. Air pollution and the development of asthma from birth until young adulthood. Eur. Respir. J. 56 (1), 2000147.

Gogna, P., King, W.D., Villeneuve, P.J., Kumarathasan, P., Johnson, M., Lanphear, B., et al., 2021. Ambient air pollution and inflammatory effects in a Canadian pregnancy cohort. Environmental Epidemiology 5 (5), e168.
Green, R., Broadwin, R., Malig, B., Basu, R., Gold, E.B., Qi, L., et al., 2015. Long-and Short-Term Exposure To Air Pollution and Inflammatory/Hemostatic Markers in Midlife Women: Epidemiology 1.
Hennig, F., Fuks, K., Moebus, S., Weinmayr, G., Memmesheimer, M., Jakobs, H., et al., 2014. Association between source-specific particulate matter air pollution and hs-CRP: local traffic and industrial emissions. Environ. Health Perspect. 122 (7), 703–710.
Hiraiwa, K., van Eeden, S.F., 2013. Contribution of lung macrophages to the inflammatory responses induced by exposure to air pollutants. Mediat. Inflamm. 2013, 619523.
Hogg, J.C., van Eeden, S., 2009. Pulmonary and systemic response to atmospheric pollution. Respirology 14 (3), 336–346.
Jensen, V.M., Rasmussen, A.W., 2011. Danish education registers. Scand. J. Publ. Health 39 (7 Suppl. l), 91–94.
Kurt, O.K., Zhang, J., Pinkerton, K.E., 2016. Pulmonary health effects of air pollution. Curr. Opin. Pulm. Med. 22 (2), 138–143.
Li, Y., Rittenhouse-Olson, K., Scheider, W.L., Mu, L., 2012. Effect of particulate matter air pollution on C-reactive protein: a review of epidemiologic studies. Rev. Environ. Health 27 (2–3), 133–149.
Li, S., Wu, W., Wang, G., Zhang, X., Guo, Q., Wang, B., et al., 2022. Association between exposure to air pollution and risk of allergic rhinitis: a systematic review and meta-analysis. Environ. Res. 205, 112472.
Liang, L., Gong, P., Cong, N., Li, Z., Zhao, Y., Chen, Y., 2019. Assessment of personal exposure to particulate air pollution: the first result of City Health Outlook (CHO) project. BMC Publ. Health 19 (1), 711.
Libby, P., Ridker, P.M., Maseri, A., 2002. Inflammation and atherosclerosis. Circulation 105 (9), 1135–1143.
Lynge, E., Sandegaard, J.L., Rebolj, M., 2011. The Danish national patient register. Scand. J. Publ. Health 39 (7 Suppl. l), 30–33.
Mostafavi, N., Vlaanderen, J., Chadeau-Hyam, M., Beelen, R., Modig, L., Palli, D., et al., 2015. Inflammatory markers in relation to long-term air pollution. Environ. Int. 81, 1–7.
Pedersen, C.B., 2011. The Danish Civil registration system. Scand. J. Publ. Health 39 (7_ Suppl. l), 22–25.
Petersson, F., Baadsgaard, M., Thygesen, L.C., 2011. Danish registers on personal labour market affiliation. Scand. J. Publ. Health 39 (7 Suppl. l), 95–98.
Pilz, V., Wolf, K., Breitner, S., Rückerl, R., Koenig, W., Rathmann, W., et al., 2018. C-reactive protein (CRP) and long-term air pollution with a focus on ultrafine particles. Int. J. Hyg Environ. Health 221 (3), 510–518.
Raaschou-Nielsen, O., Thorsteinson, E., Antonsen, S., Holst, G.J., Sigsgaard, T., Geels, C., et al., 2020. Long-term exposure to air pollution and mortality in the Danish population a nationwide study. EClinicalMedicine 28, 100605.
Raaschou-Nielsen, O., Taj, T., Poulsen, A.H., Hvidtfeldt, U.A., Ketzel, M., Christensen, J. H., et al., 2022. Air pollution at the residence of Danish adults, by socio-demographic characteristics, morbidity, and address level characteristics. Environ. Res. 208, 112714.
Raaschou-Nielsen, O., Antonsen, S., Agerbo, E., Hvidtfeldt, U.A., Geels, C., Frohn, L.M., et al., 2023. PM2.5 air pollution components and mortality in Denmark. Environ. Int. 171, 107685.
Rosvall, M., Engstrom, G., Janzon, L., Berglund, G., Hedblad, B., 2007. The role of low grade inflammation as measured by C-reactive protein levels in the explanation of socioeconomic differences in carotid atherosclerosis. Eur. J. Publ. Health 17 (4), 340–347.
Shah, A.S.V., Langrish, J.P., Nair, H., McAllister, D.A., Hunter, A.L., Donaldson, K., et al., 2013. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 382 (9897), 1039–1048.
Sørensen, C.J., Pedersen, O.B., Petersen, M.S., Sørensen, E., Kotzé, S., Thørner, L.W., et al., 2014. Combined oral contraception and obesity are strong predictors of low-grade inflammation in healthy individuals: results from the Danish Blood Donor Study (DBDS). PLoS One 9 (2), e88196.
Srivastava, D., Vu, T.V., Tong, S., Shi, Z., Harrison, R.M., 2022. Formation of secondary organic aerosols from anthropogenic precursors in laboratory studies. npj Clim Atmos Sci 5 (1), 22.
Steinvil, A., Kordova-Biezuner, L., Shapira, I., Berliner, S., Rogowski, O., 2008. Short-term exposure to air pollution and inflammation-sensitive biomarkers. Environ. Res. 106 (1), 51–61.
Tanaka, T., Asai, M., Yanagita, Y., Nishinakagawa, T., Miyamoto, N., Kotaki, K., et al., 2013. Longitudinal study of respiratory function and symptoms in a non-smoking group of long-term officially-acknowledged victims of pollution-related illness. BMC Publ. Health 13 (1), 766.
WHO. Ambient air pollution [Internet]. [cited 2022 Feb 22]. Available from:: https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/ambient-air-pollution.
Wu, W., Jin, Y., Carlsten, C., 2018. Inflammatory health effects of indoor and outdoor particulate matter. J. Allergy Clin. Immunol. 141 (3), 833–844.
Zare, A., Christensen, J.H., Irannejad, P., Brandt, J., 2012. Evaluation of two isoprene emission models for use in a long-range air pollution model. Atmos. Chem. Phys. 12 (16), 7399–7412.
Zare, A., Christensen, J.H., Gross, A., Irannejad, P., Glasius, M., Brandt, J., 2014. Quantifying the contributions of natural emissions to ozone and total fine PM concentrations in the Northern Hemisphere. Atmos. Chem. Phys. 14 (6), 2735–2756.
Zhang, Z., Chang, L.Y., Lau, A.K.H., Chan, T.C., Chieh Chuang, Y., Chan, J., et al., 2017. Satellite-based estimates of long-term exposure to fine particulate matter are associated with C-reactive protein in 30 034 Taiwanese adults. Int. J. Epidemiol. 46 (4), 1126–1136.