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Associations of low levels of air pollution with cardiometabolic outcomes and the role of diet quality in individuals with obesity

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ABSTRACT

Background: Exposure to air pollution is associated with adverse cardiometabolic health effects and increased mortality, even at low concentrations. Some of the biological mechanisms through which air pollution can affect cardiometabolic health overlap with health outcomes associated with diet quality and changes in diet.
Objective: The objective of this study is to investigate associations of air pollutants at average concentrations below the World Health Organization, 2021 air quality guidelines with cardiometabolic outcomes. Furthermore, potential interaction between air pollutants and diet quality will be assessed.
Methods: 82 individuals with obesity participated in a combined weight loss and weight loss maintenance study for a total of 33 weeks. A secondary analysis was conducted incorporating air pollution measurements. Data were analysed with linear mixed-effects models.
Results: A total of 17 significant associations were observed for single pollutants with 10 cardiometabolic outcomes, predominantly related to blood lipids, hormones, and glucose regulation. Diet quality, as measured by the Baltic Sea Diet score, did not appear to mediate the association of air pollution with cardiometabolic outcomes, however, diet quality was observed to significantly modify the association of $PM_{2.5}$ with total cholesterol, and the associations of NO and O_3 with ghrelin.
Discussion: These findings suggest that exposure to ambient air pollutants, especially particulate matter, at levels below World Health Organization, 2021 air quality guidelines, were associated with changes in cardiometabolic risk factors. Diet may be a personal-level approach for individuals to modify the impact of exposure to air pollution on cardiometabolic health.

1. Introduction

According to the *Lancet* commission on pollution and health, of all measured environmental exposures, pollution is considered to be biggest contributing factor to disease and premature death (Landrigan et al., 2018). A systematic analysis for the Global Burden of Disease 2019 study identified air pollution amongst the top-five level 2 risk factors for both males and females when quantifying global attributable mortality and disability-adjusted life-years (Murray et al., 2020). The main system affected by air pollution appears to be the cardiovascular system (Murray et al., 2020); exposure to air pollution is associated with numerous negative cardiometabolic outcomes, including blood lipids (Gaio et al., 2019; Shanley et al., 2016; Yang et al., 2018a), insulin resistance (Hwang et al., 2022; Zhang et al., 2021b; Zhao et al., 2022), blood pressure (Chuang et al., 2011; Yang et al., 2018b), and inflammation (Chuang et al., 2011; Xu et al., 2022; Zhao et al., 2022). Some of the associations of air pollution with cardiometabolic outcomes are observed to be more pronounced in individuals living with overweight/obesity (Kim et al., 2019; Yang et al., 2018a).

Ambient air pollution is a heterogenous mixture of particles and gases, with pollutants such as particulate matter, carbon monoxide (CO),

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Abbreviations

BMI	body mass index
CO	carbon monoxide
HDL	high-density lipoprotein
HSF	higher-satiety food
CRP	high-sensitivity C-reactive protein
LDL	low-density lipoprotein
LSF	lower-satiety food
NO	nitrogen oxide
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
$PM_{2.5}$	particulate matter with aerodynamic diameter ≤2.5 μm
PM_{10}	particulate matter with aerodynamic diameter ≤10 μm

ozone (O_3) and nitrogen dioxide (NO_2) amongst those considered to be of public health concern. While risk attributed to exposure to air pollution as a whole has decreased, ambient particulate matter pollution experienced one of the largest increases in risk exposure – this is despite the fact that the only ambient air pollutants included in the aforementioned Global Burden of Disease study were particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and O_3 (Murray et al., 2020). According to the World Health Organisation, in 2019, more than 90% of the world's population was living in places where $PM_{2.5}$ levels exceeded 2005 air quality guidelines (World Health Organization, 2021). This elevated exposure is particularly concerning given that pooled analyses of European cohorts have found exposure to air pollution at levels below World Health Organisation guideline limits to be associated with mortality (Strak et al., 2021) and cardiovascular disease incidence (Wolf et al., 2021), with some studies observing supralinear responses with $PM_{2.5}$ (the most well-documented air pollutant) (Di et al., 2017a; Schwartz et al., 2018; Villeneuve et al., 2015; Wang et al., 2017). The mechanisms through which air pollutants exert their physiological effects, and how this impacts cardiometabolic health, are yet to be fully elucidated, but can be broadly encapsulated into initiating and effector mechanisms, as illustrated by (Rajagopalan et al., 2018). Some of the biological mechanisms through which air pollution can affect cardiometabolic health overlap with health outcomes associated with diet quality and changes in diet, such as reduced inflammation (Fung et al., 2005) and oxidative stress (Dai et al., 2008), and improved endothelial function (Fung et al., 2005; Sijtsma et al., 2014), amongst other cardiometabolic risk factors (Aljahdali et al., 2022). Diet is another external exposure that has been associated with cardiometabolic health, and has been implicated in over 50% of all cardiovascular-related deaths (Afshin et al., 2019). Furthermore, it has been recently reported that an improvement in diet quality is associated with decreased risk of cardiovascular disease of between 7 and 15% (Petersen and Kris-Etherton, 2021), with diets of the highest quality being associated with a decreased risk of cardiovascular disease incidence or mortality of up to 20% (Morze et al., 2020). Despite this, the interaction between diet and air pollution and the effect on human health is a novel concept and studies directly investigating the impact of diet and nutrition in relation to the effect of environmental exposures on cardiometabolic health are limited. While diet may just be another exposure that exerts its effects through similar mechanisms as air pollution, it is possible that diet mediates the relationship between exposure to air pollution and adverse cardiometabolic health effects i.e., that exposure to air pollution could influence food choices which result in altered diet quality, or that diet modifies the strength of the associations, in that a higher diet quality could act in a protective manner against exposure to air pollution.

In 2021, the World Health Organisation updated their air quality guidelines, with new recommendations of further decreases for 6 pollutants – particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}), $PM_{2.5}$, O_3, NO_2, sulfur dioxide and CO. The WHO proposed that the disease burden attributed to $PM_{2.5}$ could be greatly reduced if current air pollution levels are reduced in accordance with the World Health Organisation's 2021 air quality guidelines (World Health Organization, 2021). The objective of this study was to investigate exposure to low levels of air pollution, below the newly-updated World Health Organisation air quality guidelines, and their associations with cardiometabolic outcomes in individuals with obesity, and to explore if diet mediated or modified these associations. This was a secondary analysis among individuals living with obesity, who first lost their weight and then achieved similar levels of success with weight-maintenance after following a isocaloric diet differing in macronutrient composition and diet quality (Karhunen et al., 2012).

2. Methods

2.1. Participants

A total of 99 individuals were recruited into the original study via local newspaper advertisements and amongst participants from studies previously conducted at the University of Eastern Finland (Karhunen et al., 2012). Individuals were eligible if they had a Body Mass Index (BMI) of between 30 and 40 kg/m^2 and were between 30 and 65 years of age. Exclusion criteria were pregnancy, type 1 or 2 diabetes, abnormal liver, thyroid or kidney function, polycystic ovary syndrome, less than 6 months since a coronary event or operation, myocardial infarction or susceptibility to arrhythmia, presence of a diagnosed eating disorder, neuroleptic or oral cortisone medication, excess alcohol consumption (>24 portions (men) or >16 portions (women) per week), or any other diseases, medications or life situations that would prevent the individual from successfully completing the study. The procedures involving human subjects were approved by the Ethics Committee of the District Hospital Region of Northern Savo (ethics no. 46/2008) and for the amendment of the project for international collaboration within LongITools-project (ethics no. 974/2020). All the participants have provided informed written consent. In addition, the trial is registered at isrctn.com with the identifier 67529475.

2.2. Protocol

Study design and study-specific details have been described elsewhere (Karhunen et al., 2012; Näätänen et al., 2021). In brief, the study was divided into two phases; a weight loss phase and a weight loss-maintenance phase. First, all participants underwent a weight loss phase for 7 weeks, where they adhered to a very-low calorie diet. This was achieved via consumption of commercial products (Nutrifast, Leiras Finland), which provided 600 kilocalories per day, and *ad libitum* intake of low-energy vegetables and beverages. The weight loss period was followed by a 2-week transition period, upon which participants were stratified by age and sex, and randomly assigned to an isocaloric diet, containing either higher-satiety foods (HSF) or lower-satiety foods (LSF), for 24 weeks. The compositions of the food differed accordingly, i.e., HSF included more dietary protein and fibre and less dietary fat and carbohydrate as compared to LSF. Intervention food products contributed roughly 30% of the individuals' required energy intake calculated based on maintaining their current weight and were provided once every 2 weeks, with the remainder of the diet comprised of freely selected foods. Other than the intervention food products, both groups received the same treatment; instructions on intervention food products to be consumed daily, suggestions on freely selected foods to be eaten *ad libitum*, with participants advised to maintain weight following the weight loss intervention and to keep physical activity consistent during the remainder of the study. As reported previously, there were no differences in body weight and weight loss between the HSF and LSF groups (Karhunen et al., 2012; Näätänen et al., 2021). For this analysis,

the study will be considered in its entirety (investigating the weight loss and weight loss-maintenance periods together) to maximise the number of timepoints incorporated into the analyses.

2.3. Study measurements

2.3.1. Diet

Diet was assessed five times during the study: once prior to the weight loss intervention, and four times during the weight loss-maintenance phase (at 6, 12, 18 and 24 weeks after beginning weight loss-maintenance), with food intake measured via 4-day food records.

2.3.2. Biochemistry

Blood samples for leptin, insulin, ghrelin, peptide YY, glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and free fatty acids were collected in the morning in a fasted state at baseline (prior to weight loss intervention), and during weight loss-maintenance at weeks 0, 12 and 24. High-sensitivity C-reactive protein (CRP), interleukin-6 (IL6), interleukin-1 receptor antagonist protein (IL1ra) and high molecular weight adiponectin (adiponectin) were measured at baseline and at weeks 0 and 24 of the weight loss-maintenance phase. Measurements for fasting glucose, insulin, leptin, ghrelin, and peptide YY have been described previously (Näätänen et al., 2021), while measurements for free fatty acids, CRP, cytokines, adiponectin, triglycerides, and cholesterol are described in detail in Supplement A - Methods.

2.3.3. Anthropometry and clinical measures

Measurements for body composition and anthropometric measurements has been described previously (Näätänen et al., 2021). Systolic blood pressure and diastolic blood pressure measurements were taken from the right arm using an automatic, oscillometric blood pressure and pulse monitor (Automatic M6 AC, OMRON Healthcare Europe, Hoofddorp, Netherlands) with an accuracy of ±3 mmHg. The measurement protocol allowed participants to rest in a seated position for 10–15 min followed by two measurements with at least 1 min between measurements. The average of the two measurements for systolic blood pressure and diastolic blood pressure were used in the analysis.

2.3.4. Calculations

BMI was calculated as: weight (kg)/[height (m)] (Keys et al., 1972). Fat mass and fat-free mass indexes (FMI, FFMI) were calculated as fat mass (kg)/[height (m)] and fat-free mass (kg)/[height (m)], respectively (VanItallie et al., 1990). The insulinogenic index was calculated as the ratio of the change in insulin and glucose responses from 0 to 30 min.

The homeostasis model assessment of insulin resistance (HOMA-IR) was determined using the following formula: fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5 (Matthews et al., 1985).

Diet quality was calculated based on the Baltic Sea Diet Score, which consists of nine categories (six which represent food groups, and three that account for specific nutrients), with a higher score indicative of better adherence to a healthy Nordic diet, and is representative of a traditional diet in Finland (Kanerva et al., 2014). However, due to differences in food records, a modified diet score was created based on food records in this study, which was made up of 8 categories (compared to the original Baltic Sea Diet Score, it did not incorporate a measure for the ratio of polyunsaturated fatty acids to saturated fatty acids + *trans*-fatty acids). The score was calculated based on terciles of consumption for each of the categories, with a score of 1 indicating the "least healthy" option, and a score of 3 indicating the "most healthy" option, except for alcohol, which was given a score of 1 or 2 based on whether the individual was above or below cut-offs for moderate consumption according to recommendations in Nordic countries (defined as 20g or less per day for men and 10g or less per day for women) (Kanerva et al., 2014). The maximum score (highest diet quality) possible was 23, while the minimum score (lowest diet quality) was 9.

2.4. Air pollution data

Air pollution data were measured by the city of Kuopio as part of their continuous air quality monitoring. The data and details on the measurements are available from the open data repository of Finnish Meteorological Institute (https://en.ilmatieteenlaitos.fi/open-data). The main pollutants monitored within the period of this study (2008–2009) were CO, nitrogen oxide (NO), NO_2, nitrogen oxides (NO_x), O_3, and particulate matter ($PM_{2.5}$ and PM_{10}). The data were monitored in multiple measurement sites in the city area and the concentrations applied here are spatial averages of all measurement sites over a 24-h period on the day of an individuals' study measurements. The averaging is a necessity as it was not possible to assign specific concentrations for all study subjects based on their home address and daily activities. The spatial averaging was, in turn, possible, as Kuopio area is rather homogeneous in terms of air pollution.

2.5. Statistical methods

All statistical analyses were performed using R software (R Core Team, 2021; https://www.R-project.org) and RStudio, Integrated Development Environment for R, version 2022.7.1.554 (RStudio, Boston, MA, USA). Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables and counts (%) for categorical variables. Data were analysed with linear mixed-effects models, using the *lmer* package in R (Bates et al., 2015), to investigate differences across various outcomes between the HSF group and the LSF group for the full study duration, using an intention-to-treat principle. *P* values for linear models were calculated using *lmerTest* package in R (Kuznetsova et al., 2017) while model assumptions were checked using *performance* (Lüdecke et al., 2021).

Models were built forward from the basic-fit model using treatment effect (*time, measured in weeks, x study group interaction)*. Model adequacy of each stage of the model was assessed via Bayesian information criterion, a lower value indicating better model fit. Along with the main treatment effect, the full model was further adjusted for sex, age at baseline, weight, smoking, temperature, sunshine duration, and a pollutant of interest as fixed effects, with participant included as random effect (intercept). Full models were repeated for each outcome for each air pollutant measured to assess single-pollutant effects. Models were then further adjusted for diet quality to determine the effect of diet on the relationship between the exposure and the outcome, whether it mediated or moderated the effect of the exposure on the outcome. The *interactions* R package was used to plot effect modification of diet quality on the single pollutant exposure (Long, 2021). Sensitivity analyses were completed for hypertension, exercise, and education, and precipitation level, which can lead to a washout effect and reduce particulate matter concentrations. A p value of <0.05 for a two-tailed test was used to indicate statistical significance.

3. Results

3.1. Characteristics of participants

Of the 99 individuals who were recruited into the study, 82 participants completed the entire study (both weight loss and weight loss-maintenance phases). Baseline characteristics of the 82 participants analysed in this study, along with single pollutant measurements, are presented in Table 1. Mean daily values of all pollutants are below the new 2021 World Health Organisation air quality guidelines (World Health Organization, 2021). Correlation between pollutants is presented in Supplement A Table S1. There were no significant differences between HSF and LSF groups upon completion of the weight loss protocol, nor upon completion of the weight loss-maintenance intervention (see Supplement A Tables S2–S3). Compliance during the weight loss-maintenance phase did not significantly differ between groups

Table 1
Baseline characteristics of participants.

Characteristic	Total (n = 82)[a]	HSF (*n* = 40)[a]	LSF (*n* = 42)[a]	*p*-value[b]
Age	49.33 ± 9.26	49.10 ± 9.07	49.55 ± 9.54	0.82
Sex				0.53
Female	61 (74.39%)	31 (77.50%)	30 (71.43%)	
Male	21 (25.61%)	9 (22.50%)	12 (28.57%)	
BMI (kg/m^2)	34.16 ± 2.52	34.32 ± 2.71	34.02 ± 2.34	0.71
Smoking				0.95
Current Smoker	9 (10.98%)	5 (12.50%)	4 (9.52%)	
Never Smoked	41 (50%)	20 (50.00%)	21 (50.00%)	
Quit Smoking	32 (39.02%)	15 (37.50%)	17 (40.48%)	
NO (μg/m^3)	8.37 ± 7.63	8.95 ± 8.45	7.82 ± 6.82	0.67
NO_2 (μg/m^3)	15.43 ± 5.70	15.74 ± 6.04	15.13 ± 5.41	0.68
NO_x (μg/m^3)	23.80 ± 12.96	24.69 ± 14.12	22.95 ± 11.86	0.57
PM_{10} (μg/m^3)	11.12 ± 4.11	10.92 ± 4.37	11.30 ± 3.90	0.55
$PM_{2.5}$ (μg/m^3)	7.41 ± 3.14	7.22 ± 3.36	7.58 ± 2.94	0.42
O_3 (μg/m^3)	32.85 ± 9.40	32.47 ± 9.75	33.22 ± 9.17	0.66
CO (mg/m^3)	0.09 ± 0.07	0.09 ± 0.08	0.08 ± 0.07	0.33
Temperature (°C)	9.42 ± 3.09	9.27 ± 2.89	9.56 ± 3.29	0.82
Baltic Sea Diet Score	15.51 ± 2.32	15.95 ± 2.18	15.10 ± 2.40	0.21

The Baltic Sea Diet Score (ranging from the lowest-diet quality score of 9 to the highest-diet quality score of 23) was computed by summing up terciles scores for 8 dietary categories (fruits & berries, vegetables, cereals, low-fat milk, fish, meat products, total fat, and alcohol).
LSF: Low-satiety food, HSF: High-satiety food, BMI: Body mass index, NO: Nitrogen oxide, NO_2: Nitrogen dioxide, NO_x: Nitrogen oxides, PM_{10}: Particulate matter with aerodynamic diameter ≤10 μm, $PM_{2.5}$: Particulate matter with aerodynamic diameter ≤2.5 μm, O_3: Ozone, CO: Carbon monoxide.
[a] n (%); Mean ± SD.
[b] Wilcoxon rank sum test, Pearson's Chi-squared test.

(Karhunen et al., 2012). There were no significant differences between participants across diet quality terciles (presented in Supplement A Table S4).

3.2. Associations of exposure to low-dose air pollution with cardiometabolic outcomes

In total, there were 17 significant associations for individual pollutants with cardiometabolic outcomes (Table 2). No pollutant was significantly associated with markers of inflammation (Supplement A Table S5) or blood pressure (Supplement A Table S9). Exposure to PM_{10}, $PM_{2.5}$ and O_3 were all positively associated with total cholesterol. Exposure to $PM_{2.5}$ and O_3 were positively associated with LDL-cholesterol. Exposure to PM_{10} and $PM_{2.5}$ were positively associated with triglycerides. Air pollutants were significantly associated with several of the hormones measured in this study: exposure to PM_{10} and $PM_{2.5}$ were positively associated with insulin and HOMA-IR, exposure to $PM_{2.5}$ was positively associated with leptin, and exposure to CO was negatively associated with peptide YY. CO was negatively associated with waist circumference, which was the only significant association observed between an air pollutant and anthropometric measurement. All results, including non-significant findings, are presented in Supplement A Tables S5–S10.

3.3. Diet quality as a mediator for the associations of air pollutants with cardiometabolic outcomes

After the main model was further adjusted for diet quality, the significance of the association for O_3 with total cholesterol was reduced to $p = 0.055$ (Table 2). However, upon comparison of the main model and the model additionally adjusted for diet quality, diet quality does not appear to significantly mediate the association of O_3 with total cholesterol (β_{diff} = 0.0002, 95% CI [−0.012, 0.012]). All other previously significant associations remained below a *p*-value of 0.05, with diet quality explaining less than 10% for each of the significant associations between single pollutants and cardiometabolic outcomes. Three cardiometabolic outcomes (insulin, triglycerides, and leptin) that did not previously meet the threshold for significance were observed to be below $p = 0.05$ after adjusting for diet quality. However, upon inspection of their 95% confidence intervals, diet quality was not deemed to significantly mediate the association of NO_2 with insulin ($\beta_{diff} = -0.018$, 95% CI [−0.160, 0.123], $p = 0.042$), NO_2 with triglycerides ($\beta_{diff} = -0.001$, 95% CI [−0.013, 0.011], $p = 0.049$) or PM_{10} with leptin ($\beta_{diff} = -0.005$, 95% CI [−0.168, 0.158], $p = 0.049$) (Supplement A Tables S7 and S8).

Table 2
Significant associations of low-dose air pollution with cardiometabolic outcomes, and mediation by diet quality.

Variable	Main Model		+ Diet Quality	
	β (95%CI)	*p* value	β (95%CI)	*p* value
Glucose (mmol/L)				
CO	−0.658 (−1.264, −0.051)	0.034	−0.680 (−1.308, −0.052)	0.034
Insulin (mU/L)				
PM_{10}	0.083 (0.019, 0.147)	0.012	0.081 (0.017, 0.146)	0.014
$PM_{2.5}$	0.226 (0.088, 0.365)	0.001	0.215 (0.073, 0.357)	0.003
HOMA-IR				
PM_{10}	0.027 (0.005, 0.048)	0.014	0.026 (0.005, 0.047)	0.017
$PM_{2.5}$	0.071 (0.025, 0.116)	0.003	0.066 (0.019, 0.113)	0.006
Leptin (ng/mL)				
$PM_{2.5}$	0.237 (0.060, 0.415)	0.009	0.246 (0.065, 0.427)	0.008
Peptide YY (pg/mL)				
CO	−35.080 (−66.804, −3.356)	0.030	−37.174 (−70.099, −4.250)	0.027
Total Cholesterol (mmol/L)				
PM_{10}	0.012 (0.002, 0.021)	0.021	0.011 (0.001, 0.021)	0.031
$PM_{2.5}$	0.030 (0.008, 0.052)	0.004	0.030 (0.008, 0.052)	0.007
O_3	0.006 (0.000, 0.012)	0.045	0.006 (−0.000, 0.012)	0.055
LDL Cholesterol (mmol/L)				
$PM_{2.5}$	0.027 (0.008, 0.045)	0.005	0.025 (0.006, 0.044)	0.009
O_3	0.006 (0.001, 0.012)	0.016	0.006 (0.001, 0.011)	0.022
Triglycerides (mmol/L)				
PM_{10}	0.007 (0.001, 0.012)	0.015	0.007 (0.001, 0.012)	0.018
$PM_{2.5}$	0.019 (0.008, 0.031)	0.001	0.018 (0.006, 0.030)	0.003
Free fatty acids (mmol/L)				
PM_{10}	−0.003 (−0.006, −0.000)	0.035	−0.003 (−0.007, −0.000)	0.032
$PM_{2.5}$	−0.011 (−0.018, −0.004)	0.002	−0.011 (−0.018, −0.005)	0.001
Waist circumference (cm)				
CO	−3.884 (−7.248, −0.520)	0.024	−4.213 (−7.688, −0.738)	0.017

Regression coefficient β (95% CI) values are shown for estimated changes in presented outcomes for exposure to each listed pollutant. *P* values for the main model are received from linear mixed-effects models adjusted for sex, age at baseline, weight, smoking, temperature, and length of day. The diet quality model further adjusted the main model for diet quality as measured by the Baltic Sea Diet score. All biochemical measures were taken in the fasted state.
Data were available for all participants (n = 82). Inflammatory markers were measured at three timepoints (baseline of weight-loss intervention, and Weeks 0 and 24 of the weight-loss maintenance phase). All other outcomes were measured at four timepoints (baseline of weight-loss intervention, and Weeks 0, 12 and 24 of the weight-loss maintenance phase).
The Baltic Sea Diet Score (ranging from the lowest-diet quality score of 9 to the highest-diet quality score of 23) was computed by summing up terciles scores for 8 dietary categories (fruits & berries, vegetables, cereals, low-fat milk, fish, meat products, total fat, and alcohol).
LDL: Low-density lipoprotein, NO: Nitrogen oxide, NO_2: Nitrogen dioxide, NO_x: Nitrogen oxides, PM_{10}: Particulate matter with aerodynamic diameter ≤10 μm, $PM_{2.5}$: Particulate matter with aerodynamic diameter ≤2.5 μm, O_3: Ozone, CO: Carbon monoxide.

3.4. Diet quality as a modifier for the associations of air pollutants with cardiometabolic outcomes

Three associations of single air pollutants with cardiometabolic outcomes were significantly modified by diet quality. Diet quality significantly modified the associations of NO with ghrelin and O_3 with ghrelin (Supplement A Table S13), and of $PM_{2.5}$ with total cholesterol (Supplement A Table S14), as illustrated in Fig. 1A, **1B**, and **1C**, respectively. Circulating levels of total cholesterol associated with $PM_{2.5}$ were lower in individuals with a higher diet quality ($p = 0.028$); individuals with a higher diet quality were observed to have 0.011 mmol/L 95% CI (−0.020, −0.001) lower circulating levels of total cholesterol for every one-unit increase in $PM_{2.5}$ concentration compared to those with lower diet quality. Circulating levels of ghrelin associated with NO ($p = 0.008$) and O_3 ($p = 0.017$) were higher and lower, respectively, in individuals with a higher diet quality. Individuals with a higher diet quality were observed to have 1.574 pg/mL 95% CI (0.414, 2.734) higher levels of ghrelin for every one-unit increase in NO, while individuals with higher diet quality were observed to have 0.335 pg/mL 95% CI (−0.608, −0.061) lower levels of ghrelin for every one-unit increase in O_3, when compared to individuals with lower diet quality.

3.5. Sensitivity analyses

The results remained largely unchanged after performing sensitivity analyses for the main model, the findings of which are presented in **Supplement B**. The association of PM_{10} with glucose was strengthened after controlling for exercise ($p = 0.044$), while the association of O_3 with total cholesterol was weakened after controlling for precipitation ($p = 0.059$).

4. Discussion

We conducted an analysis to determine if exposure to air pollution at levels below the updated World Health Organization, 2021 air quality guidelines were associated with cardiometabolic outcomes in individuals who were undergoing a combined weight loss and weight loss-maintenance intervention. A total of 17 significant associations were observed for single pollutants with 10 cardiometabolic outcomes, predominantly related to blood lipids, hormones, and glucose regulation. Diet quality, as measured by the Baltic Sea Diet Score, did not appear to mediate the association of air pollution with cardiometabolic outcomes, however, diet quality was observed to significantly modify the association of $PM_{2.5}$ with total cholesterol, and the associations of NO and O_3 with ghrelin.

Average daily pollutant concentrations in this study were below the updated World Health Organization, 2021 air quality guidelines, with most pollutant concentrations less than half of the recommended concentration. Despite this, numerous associations for exposure to single pollutants with cardiometabolic outcomes were observed even at these very low levels. Previous studies of European and North American cohorts have also found that exposure to air pollution at levels below then-current guidelines is associated with adverse effects and mortality (Di et al., 2017b; Strak et al., 2021). Of the 17 significant associations observed in this study, exposure to particulate matter was associated with 12 cardiometabolic outcomes (five associations with PM_{10} and seven with $PM_{2.5}$), while exposure to O_3 and CO was associated with two and three cardiometabolic outcomes, respectively. While much of the literature on the adverse health effects observed with exposure to ambient air pollution focuses on particulate matter (Murray et al., 2020), air pollution is a heterogenous mixture of gaseous and particulate constituents. Furthermore, there are numerous primary and secondary toxic particulates contained within particulate matter that vary in time and location. As such, many different outcomes have been previously

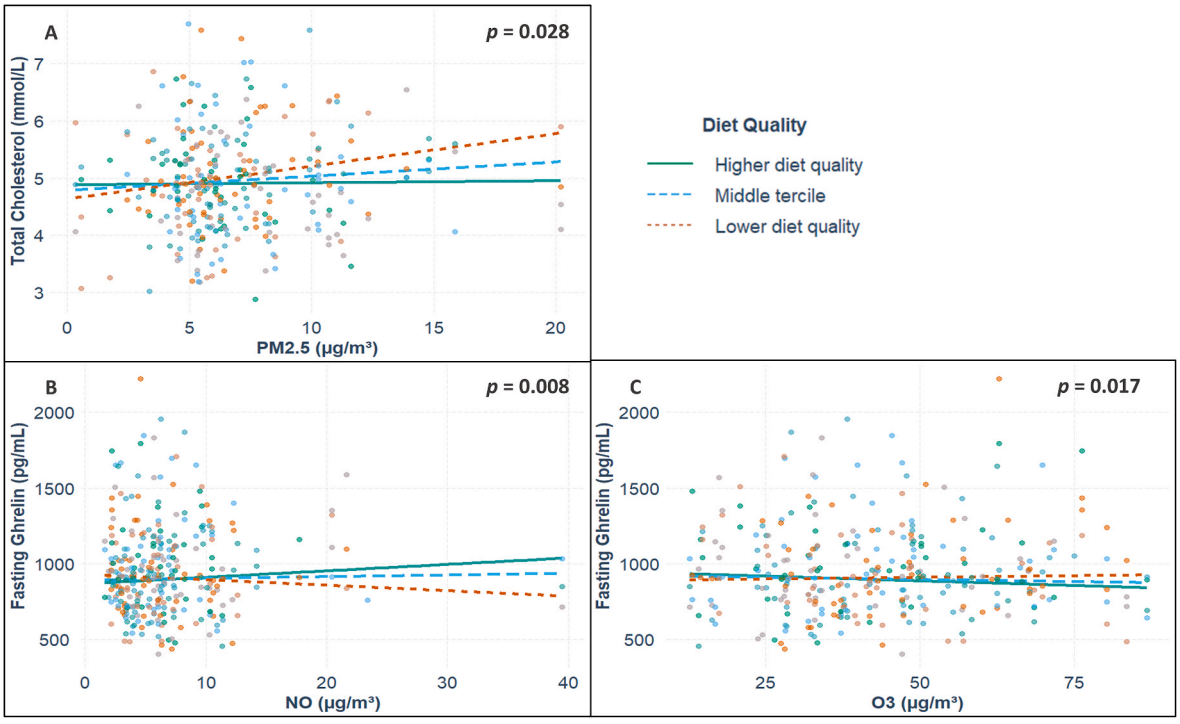

Fig. 1. Diet quality as a modifier of the association of single air pollutants with cardiometabolic outcomes
The Baltic Sea Diet Score (ranging from the lowest-diet quality score of 9 to the highest-diet quality score of 23) was computed by summing up terciles scores for 8 dietary categories.
Medians for diet quality terciles: Lower = 13, Middle = 16 and Upper = 18.
NO: Nitrogen oxide, NOx: Nitrogen oxides, O3: Ozone, $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤2.5 μm.

associated with exposure to air pollution (Kampa and Castanas, 2008; Rajagopalan and Brook, 2012). Oxidative stress and inflammation are generally considered the primary initiating mechanisms of adverse health effects with exposure to air pollution, while there are suggestions that pollutants may translocate across the lung barrier and be directly deposited at remote deposit sites where they can induce localised effects (Al-Kindi et al., 2020; Rajagopalan et al., 2018). However, in our study, no pollutant was associated with a marker of inflammation, with pollutant exposure predominantly associated with lipids and hormones. While inflammation is considered to be one of the main mechanisms through which air pollutants exert adverse health effects, the literature is still equivocal, with findings differing across exposure duration (short-term vs. long-term), geography and pollutant type (gaseous vs. particulate) (Liu et al., 2019; Xu et al., 2022). In recent years, emerging evidence has also implicated the activation of the autonomic nervous system and dysregulation of the hypothalamus-pituitary-adrenal axis upon exposure to pollutants as potential drivers of adverse cardiometabolic health effects (Kodavanti, 2016; Snow et al., 2018), with chronic activation and dysregulation of the stress response system also a characteristic of cardiometabolic diseases.

Exposure to particulate matter was associated with several lipids in our study: PM_{10} and $PM_{2.5}$ were both positively associated with cholesterol (total, LDL) and triglycerides, and negatively associated with free fatty acids. We did not observe any significant change in HDL cholesterol; evidence of the effect of particulate matter on HDL cholesterol ambiguous, with positive (McGuinn et al., 2019), negative (Yang et al., 2018a; Zhang et al., 2021a), and null (Chuang et al., 2011; Hu et al., 2022; Li et al., 2021) associations all reported. In contrast, findings for the impact of particulate matter, especially $PM_{2.5}$, on total cholesterol and LDL cholesterol are typically consistent, with exposure to $PM_{2.5}$ positively associated with both (Chuang et al., 2011; Hu et al., 2022; McGuinn et al., 2019; Yang et al., 2018a; Zhang et al., 2021a). The novel aspect of our study is that the majority of these other studies investigated exposure to much higher levels of $PM_{2.5}$, more than ten times higher in some instances, whereas increased levels of cholesterol with exposure to $PM_{2.5}$ found in this study were observed with levels below the newly-updated air quality guidelines from the World Health Organisation. We observed that exposure to O_3 was also positively associated with total cholesterol and LDL cholesterol. Literature on the effect of O_3 on cholesterol is equivocal, with both positive (Chuang et al., 2011)[10] and negative (Yang et al., 2018a; Zhang et al., 2021a) associations reported. The mechanisms behind the effect of O_3 on serum lipids are not fully understood - O_3 is a strong oxidant and can induce oxidative stress and inflammatory responses (Zhang et al., 2019), and inflammation can cause alterations in cholesterol levels and increases in triglycerides (Feingold and Grunfeld, 2000). Increased circulating total cholesterol and LDL cholesterol, and low levels of HDL cholesterol, have been consistently associated with increased risk of cardiovascular disease mortality (Jung et al., 2022), while elevated concentrations of triglycerides are also associated with an increased risk of cardiovascular disease (Sarwar et al., 2007; Toth et al., 2018) and may be a marker of insulin resistance (Ma et al., 2020). Given that several pollutants ($PM_{2.5}$, PM_{10}, and O_3) were positively associated with total and LDL cholesterol, while $PM_{2.5}$ and PM_{10} were also positively associated with triglycerides, it is possible exposure to pollutants at low concentrations, even below the updated WHO air quality guidelines, may still be associated with increased risk of cardiometabolic disease.

In addition to associations with serum lipids, we observed a negative association for exposure to CO with fasting glucose. No other pollutants were associated with fasting glucose in our study, although other studies have reported positive associations for fasting glucose with exposure to $PM_{2.5}$ (Chuang et al., 2011; Zhao et al., 2022), PM_{10} and O_3 (Chuang et al., 2011). Furthermore, an association for exposure to CO with fasting glucose has not been reported in other studies that also investigated this relationship, despite the fact that they had much higher measured levels of CO exposure (Chuang et al., 2011; Sade et al., 2015). We also observed that exposure to $PM_{2.5}$, along with PM_{10}, was positively associated with insulin and HOMA-IR, which is concordant with other studies (Hwang et al., 2022; Zhang et al., 2021b; Zhao et al., 2022). In a cohort of Korean adults, exposure to CO was also positively associated with HOMA-IR, which we did not observe (Hwang et al., 2022). A 2009 mathematical analysis suggested that insulin resistance is likely to be the largest singular cause of coronary artery disease. Findings from this simulation study indicated that, if the development of insulin resistance was prevented in young adults, approximately 42% of myocardial infarctions that were predicted to occur during a follow-up period of 60 years could be prevented (Eddy et al., 2009). Exposure to particulate matter and increased insulin resistance may be age-dependent and/or require accumulated exposure – in our study, participants were living with obesity at baseline (while 56.1% of participants reduced their weight status to overweight following the weight loss phase) and had an average age of 50 years, while the referenced studies that observed similar findings reported a lower mean BMI (considered overweight) and a median age above 50 (Zhang et al., 2021b) and a mean age of 64 (Zhao et al., 2022). However, exposure to $PM_{2.5}$ and PM_{10} was not significantly associated with HOMA-IR when assessing both short-term and long-term exposure to particulate matter in the Meta-AIR study (Kim et al., 2019), where they investigated young adults with obesity aged 17–22 years, even though their exposure levels were higher than what was observed in our study.

Along with insulin, exposure to air pollution was associated with two other hormones in our study: exposure to CO was negatively associated with fasting peptide YY, while exposure to $PM_{2.5}$ was positively associated with fasting leptin. Emerging evidence suggests exposure to air pollution dysregulates the hypothalamic-pituitary-adrenal axis, possibly via inflammation, and this may have a downstream effect on appetite and satiety (Al-Kindi et al., 2020; Rajagopalan and Brook, 2012). To the best of our knowledge, our finding of an association of an air pollutant with peptide YY is novel, with no study conducted in humans reporting on exposure to air pollution and associations with peptide YY. While limited, several human studies have reported on the association of air pollutants with leptin levels and have also observed positive associations, albeit with different pollutants. One study that investigated chronic exposure to ambient air pollution in elderly found that black carbon was positively associated with leptin (Wang et al., 2014), while exposure to NO_2 was positively associated with leptin in a German adult population (Wolf et al., 2016). Another study, this time conducted in children, concluded that exposure to air pollution may dysregulate food regulatory/reward hormones (Calderón-Garcidueñas et al., 2015). Animal studies on exposure to pollution observed increased consumption of highly palatable food (da Silveira et al., 2018), while short-term exposure to $PM_{2.5}$ has been observed to induce hypothalamic inflammation in mice, with leptin resistance and hyperphagia seen with long-term exposure (Campolim et al., 2020). Given the involvement of peptide YY and leptin in regulating appetite and energy homeostasis (Arora and Anubhuti, 2006), perturbation of these appetite-related hormones, along with others, could contribute toward uncontrolled reward-related eating and play a role in the development of obesity. While the evidence from individual studies on the association of air pollution with body weight status remains mixed (An et al., 2018), multiple recent meta-analyses have observed that exposure to air pollution is associated with increased risk of childhood obesity (Huang et al., 2022; Parasin et al., 2021) and adult obesity (Huang et al., 2020), with the risk of obesity observed to be greater in children than in adults (Lin et al., 2022).

The associations for exposure to air pollution with cardiometabolic outcomes discussed previously may also be affected by diet. For example, diet quality is inversely associated with glucose, insulin, total cholesterol, and triglycerides, as observed in the large Multi-ethnic Cohort study (Guillermo et al., 2020), while peptide YY, ghrelin and leptin are all appetite-related hormones. Despite the potential physiological overlap in response to exposure to air pollution and diet, studies

investigating the interaction between these two exposures are limited, with the majority of the literature on the potential role of nutrition on air pollution-mediated adverse health effects limited to specific nutrients, with vitamins, fish oil and sulforaphane (a sulfur-rich compound found in cruciferous vegetables, such as broccoli sprouts) the most commonly investigated (Barthelemy et al., 2020; Tong, 2016). One way in which these two exposures could interact is with diet as a mediator of air pollution i.e., that exposure to air pollution could influence food choices which result in altered diet quality, and this may be one mechanism in which exposure to air pollution exerts adverse effects on cardiometabolic health. While exposure to air pollution was associated with appetite-regulating hormones in our study, diet quality did not appear to mediate the effects of single pollutants on any of the significant associations with outcomes related to inflammation, lipid metabolism and glucose regulation.

Diet may also act as an effect modifier of exposure to air pollution. As mentioned previously, diet quality and improvements in diet are inversely associated with cardiovascular disease incidence and mortality (Morze et al., 2020; Petersen and Kris-Etherton, 2021). It is possible that high diet quality may confer a protective effect against air pollution while similarly, low diet quality may have a synergistic effect with air pollution in stressing the body and causing adverse health effects. Lifestyle changes, including a healthy diet, are one proposed personal-level intervention that individuals could adopt to reduce susceptibility to air pollution (Rajagopalan et al., 2018). In recent years, a study by Lim et al. investigated the effect of the Mediterranean diet on the association between long-term exposure to air pollution and risk of cardiovascular disease mortality, and found that the Mediterranean diet modified the effect of air pollution, as those with a higher diet score had significantly lower mortality (Lim et al., 2019). In our study, we used a modified Baltic Sea Diet Score, a Nordic counterpart to the Mediterranean Diet Score. While modified variations of the Baltic Sea Diet Score have been used previously (Eloranta et al., 2016; Isanejad et al., 2018; Tertsunen et al., 2022), the modified score used in this study is not identical to any of the other modified scores, all of which also slightly differ from each other based on available measures in the respective studies. Even though levels of air pollutants measured in this study were quite low, we observed several instances of diet quality modifying the association of air pollutants with cardiometabolic outcomes.

We observed that diet quality modified the association of $PM_{2.5}$ with total cholesterol over time; individuals with a lower diet quality were observed to have higher concentrations of total cholesterol, whereas a higher diet quality appeared to mitigate the association of $PM_{2.5}$ with total cholesterol. As discussed previously, circulating levels of total cholesterol were observed to be positively associated with cardiovascular disease mortality. It is possible that improving diet quality may reduce the susceptibility of individuals to adverse health effects associated with exposure to $PM_{2.5}$ and increased concentrations of cholesterol. While we did not see a direct association between any air pollutant and ghrelin, diet quality appeared to modify the association of two pollutants (NO and O_3) with ghrelin. Ghrelin, an appetite-related hormone, has been observed to be significantly higher in individuals without metabolic syndrome compared to those with metabolic syndrome (Heshmat et al., 2016). In addition, plasma ghrelin levels have been repeatedly observed to be decreased in individuals living with obesity compared to normal-weight individuals (Shiiya et al., 2002; Tschöp et al., 2001). Furthermore, ghrelin has been observed to be inversely associated with fasting glucose and LDL cholesterol (Heshmat et al., 2016), and with insulin resistance and mean arterial pressure (Schutte et al., 2010). There are minimal studies that report on the effect of exposure to air pollution with circulating ghrelin, with one study conducted in normal weight children observing that exposure to higher levels of air pollution was associated with decreases in ghrelin (Calderón-Garcidueñas et al., 2015), while another study found no differences in serum ghrelin in adult municipal policemen exposed to a high-traffic urban area in Italy compared to those who were unexposed (Molfino et al., 2020). In our study, individuals with higher diet quality were observed to have higher circulating concentrations of plasma ghrelin with exposure to NO, while in individuals with lower diet quality, ghrelin levels appeared to marginally decrease. This differed for O_3, where individuals with higher diet quality were observed to have lower ghrelin concentration with exposure to O_3. While it may be biologically plausible that NO and O_3 exert different effects on ghrelin, it should also be noted O_3 and NO are negatively correlated (Han et al., 2011; Paraschiv et al., 2020) and thus some effects in the models may also be inverse if the pollutants are indicators for the effect of overall pollution as opposed to being direct causes.

Our study has several strengths. First, we examined the association between ambient air pollutants (NO, NO_2, NO_x, PM_{10}, $PM_{2.5}$, O_3, and CO) and the impact on clinical outcomes implicated in the development of cardiometabolic diseases, at levels below the updated WHO 2021 air quality guidelines. Furthermore, this study explored the interaction of diet on the relationship between air pollution and cardiometabolic outcomes, providing novel insights. The randomised controlled trial allowed for the intervention to be more tightly controlled and monitored compared to an observational study design and reduces potential sources of bias. Coupled with this, the use of a longitudinal design allows for changes to be assessed over time, and the use of linear mixed-effect models allows for these changes to be assessed accounting for individual differences. While not a true reflection of long-term exposure to ambient air pollution, the study duration (~33 weeks) allowed for the impact of individual pollutants to be assessed beyond just acute effects. There were also quite a few limitations with this study. Firstly, air pollution in this region of Finland is quite homogenous and, while air pollution measurements were actual values taken from monitoring stations, there is a risk of exposure misclassification due to personal exposure levels not being assessed. Furthermore, this study investigated single-pollutant models; while this is useful to understand the effect of individual pollutants, air pollution is a mixture of various compounds, and this mixture may exert its effects differently than any single pollutant. Due to the low levels of pollutant exposure and the small sample size, we did not adjust for multiple testing and so cannot ignore the possibility of false positives obtained in our analysis. Furthermore, while several variables were adjusted for, it is not possible to rule out residual confounding, especially because of potentially improved health status following a successful weight loss intervention.

In conclusion, our study suggests that exposure to average levels of ambient air pollution below newly updated World Health Organisation air quality guidelines, especially particulate matter, was associated with changes in cardiometabolic risk factors in individuals living with obesity/overweight. Diet quality did not mediate the association of air pollution with cardiometabolic outcomes however, diet quality may modify the impact of exposure to air pollution, even at low pollutant concentrations. These findings may provide novel insights into individual measures to mitigate the negative impact of air pollution on personal health. However, it requires further investigation to determine if diet may be a plausible approach to manage adverse health effects associated with exposure to air pollution. Further research is also required to determine if diet quality has the potential to modify the effects of exposure to air pollution in other populations, such as children and young adults, or individuals deemed to be living with a normal weight.

Credit author statement

DRH, MK and SM conceptualised the study. AK, SP and LK provided scientific advice for completion of the study. DRH and SM planned and DRH performed the statistical analyses. DRH, AK, SM and MK interpreted the results. DRH drafted the manuscript. All authors critically revised the manuscript for its intellectual content and approved the final version of the manuscript. LK is the principal investigator of the original intervention.

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Declaration of competing interest

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

Data availability

Data will be made available on request.

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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.2023.117637.

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