Health & Place 93 (2025) 103453

Contents lists available at ScienceDirect

Health and Place

journal homepage: www.elsevier.com/locate/healthplace

Air pollution exposure and incidence of cardiometabolic diseases: Exploring the modifying role of dietary antioxidant intake in adults

Shradha Mishra [a,b], Ilonca Vaartjes [b], Yvonne T. van der Schouw [b], Esmée M. Bijnens [a,c], Jolanda M.A. Boer [d], George S. Downward [b,e], Roel C.H. Vermeulen [b,e], W. Monique M. Verschuren [b,d], Tim S. Nawrot [a,f], Erik J. Timmermans [b,*]

[a] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[b] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Environmental Sciences, Faculty of Science, Open University, Heerlen, the Netherlands
[d] Centre for Prevention, Lifestyle and Health, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
[e] Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, Utrecht, the Netherlands
[f] Department of Public Health & Primary Care, Occupational & Environmental Medicine, Leuven University, Leuven, Belgium

ARTICLE INFO

Keywords:
Air pollution
Cardiovascular disease
Diabetes mellitus
Dietary antioxidants
Cardiometabolic disease

ABSTRACT

While the antioxidative potential of certain vitamins and minerals in cardio-protection has garnered increasing interest, their ability to attenuate associations between air pollution exposure and cardiometabolic diseases (CMDs) remains unexplored. This study examined the associations of air pollution (particulate matter including ultrafine particles (UFP), and nitrogen oxides, including NO_2 and NO_x) and six dietary antioxidants with incident non-fatal CMDs in 30,519 EPIC-NL study participants. Data on CMD incidence (total cardiovascular disease (CVD), acute myocardial infarction (AMI), coronary heart disease (CHD) and heart failure (HF)) and Type 2 Diabetes Mellitus (T2DM) diagnoses were obtained from medical registries. Annual average ambient concentrations of air pollutants at the participants' baseline residential addresses were predicted using land use regression models. Dietary intake of antioxidants was assessed via a food frequency questionnaire. Multivariable Cox regression models were used to explore associations. Exposures to NO_2 and UFP were associated with elevated HF risk (Hazard Ratio (HR) (95 % CI): 1.24 (1.00, 1.54) and 1.69 (1.04, 2.76), respectively). Higher beta-carotene intake was associated with reduced risk of total CVD and CHD incidence (HR (95 % CI): 0.94 (0.89, 0.99) and 0.92 (0.84, 0.99), respectively), whereas, in general, antioxidant intake was positively associated with incident T2DM. Interaction analyses indicated some variability in CMD risk by antioxidant intake, but none of these interactions remained significant after correcting for multiple comparisons. These findings indicate that the associations of air pollution with incident CMD do not differ by dietary antioxidant intake.

1. Introduction

The adverse impact of air pollution exposure on the development and progression of various cardiometabolic diseases (CMDs), including Type 2 Diabetes Mellitus (T2DM) and cardiovascular diseases (CVDs) such as acute myocardial infarct (AMI), coronary heart disease (CHD) and heart failure (HF), are well-established, with systemic inflammation and oxidative stress proposed as the main underlying mechanisms (Pearson, 2011; Walton-Moss et al., 2014; Janjua et al., 2021; Patel et al., 2010; Callahan et al., 2022). Given the predominance of air pollution in urban settings, understanding these associations is particularly crucial for informing urban health policies and mitigation strategies, since the urban context introduces unique exposure patterns, making it essential to explore potential interventions at various policy levels. Consequently, there is an increasing emphasis on the identification and implementation of interventions at both individual as well as community policy levels that could potentially mitigate the adverse cardiometabolic health effects associated with these factors (Pearson, 2011; Walton-Moss et al., 2014; Janjua et al., 2021).

Certain dietary micronutrient vitamins and minerals are known to

This article is part of a special issue entitled: Urban Health Research published in Health and Place.

* Corresponding author. Internal mail no. Str. 6.131. P.O. Box 85500. 3508 GA Utrecht, the Netherlands.
E-mail address: e.j.timmermans-5@umcutrecht.nl (E.J. Timmermans).

https://doi.org/10.1016/j.healthplace.2025.103453
Received 30 September 2024; Received in revised form 28 February 2025; Accepted 17 March 2025
Available online 23 March 2025

have antioxidative properties, due to their ability to scavenge free radicals and oxidative species, thus shielding sensitive biological targets from oxidative damage (Patel et al., 2010; Callahan et al., 2022; Halliwell and Gutteridge, 2015). This suggests a role for dietary antioxidants within the context of mitigation of CMD risks from air pollutants (Sesso et al., 2008; Jenkins et al., 2020; Nascimento et al., 2018; da Silva et al., 2021). However, despite the abundance of studies investigating the effect of common antioxidants, especially vitamins C and E, beta-carotene and selenium, on various cardiometabolic events, conditions and mortality rates, their findings remain largely inconsistent (Aune et al., 2018; Gale et al., 1995; Sahyoun et al., 1996; Lawlor et al., 2005; Aucott et al., 2007). While some studies show inverse associations between antioxidant intake and cardiometabolic risk, others report no significant associations and some positive associations have also been suggested (Bjelakovic et al., 2007; Lonn et al., 2005; Miller et al., 2005; Myung et al., 2013). Moreover, the focus of such epidemiological studies has primarily centered on the independent effect of individual antioxidants, with relatively less exploration into the combined antioxidant activity of specific phytochemicals, vitamins, and minerals (Parohan et al., 2019; Mozaffari et al., 2018). Furthermore, only a limited number of studies have investigated the individual effects of multiple antioxidants on cardiometabolic outcomes within the same study framework (Klipstein-Grobusch et al., 1999; Rimm et al., 1993; Kushi et al., 1996; Mirmiran et al., 2022; Montonen et al., 2004). Additionally, the epidemiological evidence regarding the potential of primary antioxidants, including vitamins A, C, and E, to modulate the toxic cellular and systemic effects induced by air pollutants remains scarce and limited to respiratory outcomes and T2DM incidence, leaving their overall cardiometabolic effects largely unexplored (Li et al., 2022; Shin and Kim, 2023; Hatch, 1995). Such emerging evidence suggests the plausibility of dietary antioxidants, especially those linked with circulating inflammatory biomarkers like interleukin β and tumor necrosis factor α, to modify the risk of air pollution-related adverse cardiometabolic risk (Wu et al., 2023).

Downward et al. (2018) previously compared and elucidated the effects of ultrafine particles (UFP) and various conventional air pollutants on the incidence of fatal as well as non-fatal cardiovascular and cerebrovascular outcomes in adults residing in (major) urban areas in the Netherlands using the EPIC-NL study. Their study offered evidence regarding the detrimental impact of UFP exposure on cardiovascular health. The present study extends those analyses, and aims to examine the associations of air pollution and dietary antioxidants, individually and as a composite score, with non-fatal CMD incidence in the same population. Furthermore, this study aims to assess whether dietary antioxidants attenuate the risk of CMD incidence, attributable to air pollution exposure.

2. Materials and methods

2.1. Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a multicenter research endeavor devised to investigate the relationship between nutrition, lifestyle, environmental and genetic factors and the etiology of cancer, as well as other chronic diseases (Barricarte et al., 2002; Bingham and Riboli, 2004). The Dutch contributions to the EPIC study (i.e., EPIC-NL) comprised two cohorts: Prospect, comprising 17,357 women aged 49–70 years, residing in or around the city of Utrecht, and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) comprising 22,654 men and women, aged 20–59 years, residing in the cities of Amsterdam, Doetinchem and Maastricht. Recruitment for both cohorts occurred concurrently between 1993 and 1997, with participants providing written informed consent for study enrollment. The EPIC-NL study was conducted according to the guidelines in the Declaration of Helsinki, and all procedures involving the participants were approved by the institutional review board of the University Medical Center Utrecht (Prospect) and the medical ethical committee of TNO Nutrition and Food Research (MORGEN).

Following the withdrawal of consent for participation by one participant, the total EPIC-NL study population consists of 40,010 participants, of which 96.7 % (n = 38,707) participants consented to follow-up. After the exclusion of participants with prevalent CVD or T2DM at the time of study recruitment, missing information on covariates, exposure or outcome measurements, vital status, and withdrawal or lack of informed consent to follow-up, a total of 30,519 participants were included in the present study. Fig. 1 presents the study sample selection.

2.2. Outcome assessment

2.2.1. Incidence of cardiometabolic diseases

The outcomes of interest for this study were defined as the first occurrence of any and specific non-fatal CVD and T2DM, within those EPIC-NL participants who did not have any documented history of these diseases at the time of study enrollment. Outcomes were defined using the ninth revision of the International Classification of Diseases, clinical modification (ICD-9) and grouped according to general diagnoses, including any (i.e., total) CVD, AMI, CHD, and HF, as well as T2DM. The ICD-9 codes associated with these outcomes are available in Supplementary Table S1.

EPIC-NL participants were followed for the occurrence of non-fatal cardiovascular events by linkage with several local and national medical registries. Information on vital status was obtained through linkage with municipal population registries. Morbidity data were provided by the Dutch Hospital Discharge Register (HDR). These linkages were conducted based on a validated, probabilistic method, using birth date, sex, postal code and general practitioner records (Herings et al., 1992; Struijk et al., 2014). Complete data on endpoints were available until December 31, 2010 and the validity of diagnoses from these sources has been assessed and reported previously (Merry et al., 2009a).

Three sources of ascertaining incident T2DM were used in this study: self-report, linkages with HDR, and urinary glucose strip test (Prospect participants only) (Beulens et al., 2005, 2009; Scheffers et al., 2020). Verification of potential T2DM cases detected by any of these methods was carried out with information from participants' general practitioner or pharmacist. Verification information was available for 89 % of the potential diabetes cases, and 72 % of these cases were verified as T2DM and subsequently used for the analysis, as previously described by Sluijs et al. (2010).

2.3. Exposure assessment

2.3.1. Air pollution

The measurements and linkage of air pollution exposure measures, including conventional air pollutants and UFP to EPIC-NL participants have been described in detail previously (Downward et al., 2018). Ambient concentrations of conventional air pollutants (in $\mu g/m^3$), including particulate matter with diameters <2.5 μm ($PM_{2.5}$), <10 μm (PM_{10}), nitrogen oxides (NO_x), and nitrogen dioxide (NO_2), were predicted using land use regression (LUR) models. These models were originally developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, which is a multicenter study across Europe, designed to investigate the impact of air pollution exposure on health by utilizing data from existing cohorts studies (Beelen et al., 2015). Briefly, air pollutant measurements were conducted at 40 sites for PM and 80 sites for nitrogen oxides, accompanied by the use of Geographic Information Systems to evaluate potential predictors of spatial variation, across Belgium and the Netherlands during three 14-day periods (per site) in 2009 (Eeftens et al., 2012; Beelen et al., 2013). These models were then used to estimate annual average ambient pollutant concentrations at participants' baseline addresses. The median

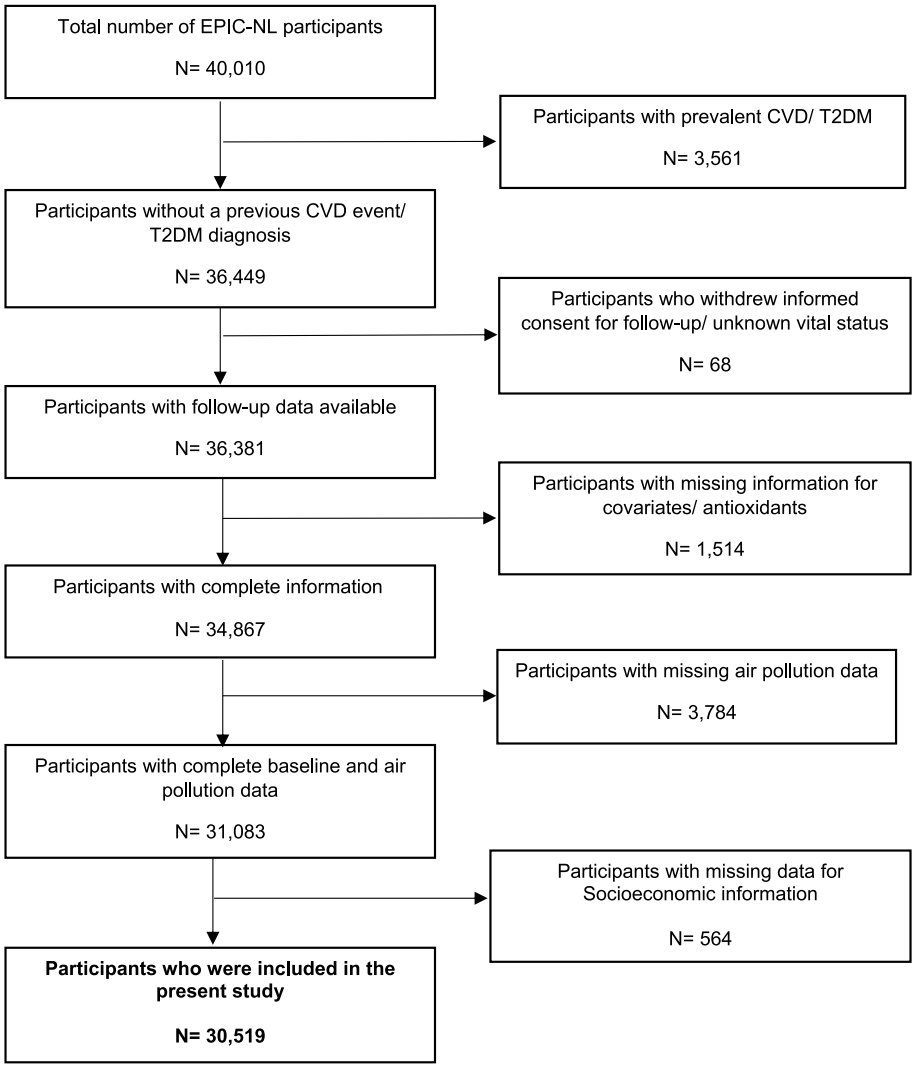

Fig. 1. Flow diagram presenting the selection of study participants.

variance explained by these models was 67 % for $PM_{2.5}$, 68 % for PM_{10}, 86 % for NO_2, and 87 % for NO_x (Eeftens et al., 2012; Beelen et al., 2013).

Exposure concentration of UFP (in particles/cm^3) was assessed using LUR models developed during a monitoring campaign between January 2014 and February 2015 by Van Nunen et al. (2017). Measurements of UFP were collected for 30-min periods at 242 sites in Amsterdam, Maastricht, and Utrecht, covering the major metropolitan areas contributing to the EPIC-NL cohort. Each monitoring site was visited thrice to account for seasonal variation, and the predictors used included traffic, population, industry, sea, airports, restaurants, and green spaces. With a median spatial variation of 50 %, these models were subsequently used to predict ambient UFP concentrations at the baseline addresses of participants (Downward et al., 2018).

2.4. Assessment of dietary antioxidants

2.4.1. Individual dietary antioxidants

The validated semi-quantitative Dutch EPIC food frequency questionnaire (FFQ) was used to assess the food consumption of 77 main food categories enabling estimation of 178 food items during the year preceding study enrolment in both cohorts of EPIC-NL (Beulens et al., 2009; Ocké et al., 1997a, 1997b). The individual daily dietary intake of six primary antioxidants, including retinol, beta-carotene, selenium (measured as μg/day), and vitamins C, E, and zinc (measured as mg/day) was estimated based on the average daily consumption among the study participants (Beulens et al., 2009).

2.4.2. Composite Dietary Antioxidant Index

The cumulative intake of the six individual dietary antioxidants was assessed using the Composite Dietary Antioxidant Index (CDAI). This study employed a modified version of the CDAI, developed originally by Wright et al. (2004), to examine the synergistic effects of six antioxidants (Maugeri et al., 2019). This formula incorporates the six antioxidants mainly associated with oxidative processes and has been validated previously in a prospective cohort study by using anti-inflammatory markers (Luu et al., 2015). The CDAI was estimated by standardizing the values of the dietary antioxidants. This involved subtracting the mean from the individual dietary intake of each antioxidant and dividing by the standard deviation. The standardized intake values were then summed using the following formula:

$$CDAI = \sum_{i=1}^{6} \left(\frac{xi - \mu i}{Si} \right)$$

In this formula, xi represents the individual daily intake of dietary antioxidants (i.e., retinol, beta-carotene, vitamins C and E, zinc and selenium), and μi and Si represent the mean and standard deviation values of antioxidant i for the study population, respectively.

2.5. Description of covariates

In the present study, the analyses were adjusted for various covariates whose selection was informed by existing literature and methodologies adopted by comparable studies (Li et al., 2022; Downward et al., 2018; Colizzi et al., 2023). Baseline data on demographic characteristics, lifestyle, presence of chronic diseases and/or potential risk factors were collected using a general questionnaire (Beulens et al., 2009). These included age at recruitment (in years), sex (male or female), level of education (low, middle or high), smoking status (current, former, or never), alcohol consumption (>1 drink/week, <1 drink/-week, quit or never consumed), and physical activity. Physical activity was determined by the calculation of the Cambridge Physical Activity Index which has been previously validated (Haftenberger et al., 2002; Wareham et al., 2003). This index combined occupational activity along with outdoor activities during summer (including cycling and walking) and was divided into four categories: inactive, moderately inactive, moderately active and active. Quality of diet, indicated by total dietary fiber intake (in grams) and total dietary energy intake (in kilocalories), was assessed via the FFQ (Ocké et al., 1997b). Additionally, participants underwent physical assessments, including height and weight measurements. Body Mass Index (BMI) was calculated in kg/m^2 for each participant by dividing their weight by height squared.

In addition to these individual-level covariates, the analyses in the present study were also adjusted for area-level socioeconomic information, as indicated by the percentage of low-income individuals living in the participants' neighborhood (Downward et al., 2018).

2.6. Statistical analysis

Characteristics of the study sample and the area-level exposure measures were presented using descriptive statistics. Multivariable Cox proportional hazard regression models were used to examine the associations of ambient air pollution exposure concentrations with the incidence of any non-fatal CVD events, including specific non-fatal CVD events, (i.e., AMI, CHD and HF) as well as the first diagnosis of T2DM, for the duration of the study follow-up. In line with previous research, these associations are presented for a 5 $\mu g/m^3$ increment in concentrations of $PM_{2.5}$, 10 $\mu g/m^3$ increments of PM_{10}, and NO_2, a 20 $\mu g/m^3$ increment of NO_x, and per 10,000 particles/cm^3 for UFP exposures (Downward et al., 2018). Air pollution exposure was analyzed as a continuous variable and the survival time scale was defined as the number of years until December 31, 2010, for the occurrence of a first non-fatal CVD event. The associations of individual dietary antioxidant intake and CDAI with the incidence of each of the five outcomes were also determined similarly and are presented per 1 unit increase in dietary antioxidant intake.

Next, effect modifications by dietary intake of each of the six antioxidants were investigated by introducing interaction terms to the Cox proportional hazard regression models. These interaction terms included each of the five air pollutants along with an indicator of dietary antioxidant intake, first assessed individually, then cumulatively. Each of the six antioxidants was split at its median to compare the effects between high and low antioxidant intake groups of participants. The CDAI scores were divided into tertiles, with using the lowest tertile as reference category.

All statistical explorations followed the same level of increasing adjustments for relevant covariates and potential confounders. Model 1 adjusted for demographic factors, including age at recruitment, sex and educational level. Model 2 additionally adjusted for lifestyle factors, including alcohol consumption, smoking status, physical activity, diet quality and BMI. Finally, Model 3 additionally adjusted for area-level socioeconomic information. Each interaction term, together with its two main terms, were statistically tested in a fully adjusted model. P-values <0.05 were considered statistically significant in all statistical analyses. Furthermore, the Bonferroni correction was applied while testing interaction terms to account for the risk of Type 1 errors due to multiple comparisons and ensure the reliability and robustness of any significant interactions observed. A total of 175 interaction terms (i.e., 5 air pollution measures x 7 dietary antioxidant intake measures x 5 CMD outcome measures) were tested additionally at a corrected significance level of $p < 0.0003$ (i.e., $0.05/175 = 0.0003$). No additional corrections were applied when assessing the associations between air pollution, dietary antioxidant intake, and CMD outcomes, as these analyses were hypothesis-driven rather than exploratory. Statistical analyses were conducted with the statistical software IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, New York, United States of America).

3. Results

The baseline characteristics of the study population are presented in Table 1. The mean age of the included participants was 50.1 years with a

Table 1
Baseline characteristics of the study sample (n = 30,519) and area-level exposure measures.

Characteristics	Mean ± SD or n (%)
Age in years at recruitment	50.1 ± 11.3
Sex	
Male	7293 (23.9)
Female	23,226 (76.1)
Level of education	
Low	18,173 (59.5)
Medium	6331 (20.7)
High	6015 (19.8)
Smoking status	
Current	9222 (30.2)
Never	11,574 (37.9)
Former	9723 (31.9)
Alcohol consumption	
Never	2017 (6.6)
Quit	317 (1.0)
Yes, <1 drink/week	9159 (30.1)
Yes, >1 drink/week	19,026 (62.3)
Physical activity[b]	
Inactive	2197 (7.2)
Moderately inactive	7533 (24.7)
Moderately active	7912 (25.9)
Active	12,877 (42.2)
Total dietary fiber intake (g)	23.4 ± 4.8
Total dietary energy intake (kcal)	2040.2 ± 626.4
BMI (kg/m^2)	25.7 ± 4.0
Percentage of individuals with low income in the neighborhood	38.9 ± 7.9
Estimated annual pollutant exposure at baseline[c]	
$PM_{2.5}$	16.9 ± 0.6
PM_{10}	25.4 ± 1.5
NO_2	25.3 ± 6.2
NO_x	38.1 ± 11.4
UFP (particles/cm^3)	11,215 ± 2356
Individual antioxidants intake (mg)	
Retinol	0.7 ± 0.5
Beta-carotene	1.6 ± 0.6
Vitamin C	109.9 ± 45.4
Vitamin E	12.2 ± 3.3
Zinc	10.0 ± 1.7
Selenium	0.04 ± 0.007
CDAI	
T1 (−15.45 to −1.31)	10,163 (33.3)
T2 (−1.30 to 1.29)	10,163 (33.3)
T3 (1.30–26.92)	10,193 (33.4)

[a]Abbreviations: BMI= Body Mass Index, CDAI= Composite Dietary Antioxidant Index, cm = Centimeter, g = Gram, kcal = Kilocalories, kg = Kilogram, m = Kilometer, m = Meter, mg = Milligram, NO_2= Nitrogen dioxide, NO_x = Nitrogen oxides, n = number, $PM_{2.5}$ = Particulate matter with diameter <2.5 μm, PM_{10} = Particulate matter with diameter <10 μm, SD= Standard deviation, UFP= Ultrafine particles.
[b]Categorized according to the Cambridge Physical Activity Index.
[c]Measurements are in $\mu g/m^3$ unless specified otherwise.

standard deviation of 11.3. Females formed the majority of the study population (76.1 %), attributable to the fact that the Prospect cohort exclusively comprised females. Of the total study population without any prevalent CMDs, 3386 (11.1 %) had an incident CVD event (any) while 787 (2.6 %) developed T2DM. Among the participants who had an incident CVD event, the largest number of cases were recorded for CHD (n = 1904) followed by AMI (n = 527) and HF (n = 259) (Supplementary Table S2).

3.1. Associations between air pollution exposure and incident cardiometabolic diseases

Fig. 2 shows the associations of air pollution exposures with total incident CVD. After adjustment for all covariates (Table 2, Model 3), it was found that ambient NO_2 and UFP exposure were positively associated with HF incidence (Hazard Ratio (HR) (95 % CI): 1.24 (1.00, 1.54) and 1.69 (1.04, 2.76), respectively). No other statistically significant associations were observed between air pollution exposures and the incidence of CMDs in the fully adjusted models (Table 2, Model 3).

3.2. Associations between dietary antioxidant intake and incident cardiometabolic diseases

Table 3 shows the associations of dietary antioxidant intake with incident CMDs. In the fully adjusted models (Table 3, Model 3), beta-carotene was significantly associated with a reduced incidence of total CVDs and incident CHD (HR (95 % CI): 0.94 (0.89, 0.99) and 0.92 (0.84, 0.99), respectively. The fully adjusted models did not indicate significant associations between other dietary antioxidants or CDAI and AMI or HF incidence. Dietary retinol, vitamin E, zinc, and selenium, as well as CDAI, were significantly positively associated with the incidence of T2DM (HR (95 % CI): 1.13 (1.03, 1.23), 1.03 (1.01, 1.04), 1.07 (1.03, 1.10), 1.02 (1.01, 1.03), and 1.05 (1.03, 1.07), respectively) (Table 3, Model 3).

3.3. Modifying effects of dietary antioxidants in the association between air pollution and cardiometabolic diseases

Interaction terms between the five air pollutants, six dietary antioxidants, and the CDAI were tested for effect modification across five cardiometabolic outcomes, both at a significance threshold of 0.05 and a corrected threshold of 0.0003. None of the antioxidants interacted significantly with any air pollutant under the Bonferroni correction (i.e., adjusted significance threshold: $p < 0.0003$), indicating that the associations of air pollution with incident CMD do not differ by dietary antioxidant intake.

At the uncorrected 0.05 level, a few significant interactions were observed. Results from the exploratory stratified analyses for the association between air pollution exposure and incident CMDs are presented in Supplementary Table S2 and Supplementary Fig. S1. Stratified analyses revealed that for total CVD incidence, higher $PM_{2.5}$ exposure was non-significantly associated with increased risk in individuals with low zinc intake (HR (95 % CI): 1.10 (0.79, 1.53)), in comparison to those with higher zinc intake (HR (95 % CI): 0.70 (0.49, 1.02)). In terms of HF, significant interactions were observed between PM and nitrogen oxides and dietary vitamins C and E. Specifically, at low vitamin C intake, $PM_{2.5}$ exposure was linked to a markedly lower HF risk (HR (95 % CI): 0.09 (0.01, 0.59)), while no significant positive association was observed at higher vitamin C intake (HR (95 % CI): 1.18 (0.26, 5.38)). This trend was reversed for vitamin E, wherein for PM_{10} exposure, low intake was associated with a significantly higher HF risk (HR (95 % CI): 4.24 (1.37, 13.15)), while no significant protective effect was seen in individuals with higher vitamin E intake (HR (95 % CI): 0.69 (0.17, 2.74)). Additionally, for NO_2 exposure, significantly higher HF risk was observed in individuals with low vitamin E intake (HR (95 % CI): 1.56 (1.18, 2.08)), with a non-significant reduction in risk for those with high intake (HR (95 % CI): 0.93 (0.67, 1.29)). Similarly, NO_x exposure showed significantly higher HF risk at low vitamin E intake (HR (95 % CI): 1.41 (1.06, 1.88)) and a reduced, non-significant trend for high intake (HR (95 % CI): 0.85 (0.60, 1.21)). Conversely, and albeit non-significantly, trends for T2DM indicated that low vitamin E intake was associated with a reduced risk following UFP exposures (HR (95 % CI): 0.72 (0.50, 10.4)), whereas high vitamin E intake appeared to increase T2DM risk (HR (95 % CI): 1.23 (0.90, 1.70)).

4. Discussion

This study examined the role of dietary antioxidants in modifying the occurrence of CMDs in response to air pollution exposure within the general adult population in the Netherlands. The analyses revealed that higher ambient NO_2 and UFP exposure was associated with increased HF incidence. Dietary intake of beta-carotene was linked to a reduced incidence of total CVD, particularly CHD incidence. Conversely, higher antioxidant intake was positively associated with T2DM incidence. After correcting for multiple testing, no significant interactions were observed between the air pollutants and antioxidants, suggesting the absence of any effect modification on cardiometabolic risk.

The main strengths of this study are its large sample size, prospective

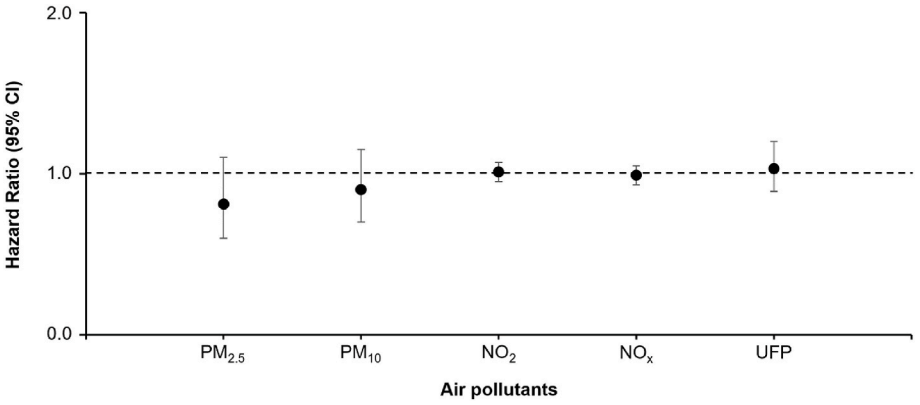

Fig. 2. Associations between exposure to the five air pollutants and total cardiovascular disease incidence. [a-b]

[a] Abbreviations: CVD= Cardiovascular diseases (including cardiac arrest, cerebrovascular disease, coronary heart disease, heart failure, peripheral vascular diseases, pulmonary embolism, and diseases of arteries, arterioles and capillaries); PM_{10} = Particulate matter with diameter <10 μm, $PM_{2.5}$ = Particulate matter with diameter <2.5 μm, NO_2= Nitrogen dioxide, NO_x = Nitrogen oxides, UFP= Ultrafine particles.

[b] The presented associations are adjusted for age at recruitment, sex, educational level, smoking status, alcohol consumption, physical activity, total dietary fiber intake, total dietary energy intake, Body Mass Index, and area-level socioeconomic information.

Table 2
Associations of annual air pollution exposure with incidence of cardiovascular disease events and Type 2 Diabetes Mellitus in single pollutant models.[a-d].

	Model 1	Model 2	Model 3
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Total CVD*			
$PM_{2.5}$	0.87 (0.64, 1.17)	0.81 (0.60, 1.10)	0.81 (0.60, 1.10)
PM_{10}	1.02 (0.80, 1.30)	0.87 (0.68, 1.11)	0.90 (0.70, 1.15)
NO_2	1.03 (0.98, 1.10)	1.01 (0.94, 1.06)	1.01 (0.95, 1.07)
NO_x	1.01 (0.95, 1.07)	0.98 (0.92, 1.04)	0.99 (0.93, 1.05)
UFP	1.14 (0.99, 1.32)	1.03 (0.89, 1.19)	1.03 (0.89, 1.20)
AMI			
$PM_{2.5}$	0.68 (0.31, 1.49)	0.63 (0.29, 1.38)	0.62 (0.28, 1.36)
PM_{10}	1.13 (0.63, 2.04)	0.88 (0.48, 1.59)	0.94 (0.51, 1.72)
NO_2	1.13 (0.98, 1.29)	1.06 (0.93, 1.22)	1.09 (0.95, 1.25)
NO_x	1.09 (0.94, 1.26)	1.04 (0.89, 1.21)	1.05 (0.90, 1.23)
UFP	1.36 (0.96, 1.92)	1.15 (0.81, 1.64)	1.16 (0.81, 1.66)
CHD			
$PM_{2.5}$	0.74 (0.49, 1.12)	0.70 (0.46, 1.06)	0.70 (0.46, 1.05)
PM_{10}	0.95 (0.69, 1.31)	0.84 (0.60, 1.16)	0.89 (0.64, 1.23)
NO_2	1.03 (0.96, 1.11)	1.00 (0.93, 1.08)	1.02 (0.95, 1.10)
NO_x	1.00 (0.92, 1.09)	0.98 (0.90, 1.06)	0.99 (0.91, 1.07)
UFP	1.09 (0.90, 1.32)	0.99 (0.82, 1.20)	1.00 (0.82, 1.21)
HF			
$PM_{2.5}$	0.38 (0.11, 1.27)	0.38 (0.11, 1.26)	0.38 (0.11, 1.26)
PM_{10}	1.93 (0.82, 4.52)	1.87 (0.79, 4.41)	1.97 (0.83, 4.70)
NO_2	1.21 (0.98, 1.49)	1.22 (0.99, 1.50)	**1.24 (1.00, 1.54)**
NO_x	1.12 (0.90, 1.39)	1.12 (0.90, 1.40)	1.14 (0.91, 1.42)
UFP	**1.75 (1.08, 2.82)**	**1.70 (1.05, 2.77)**	**1.69 (1.04, 2.76)**
T2DM			
$PM_{2.5}$	0.64 (0.39, 1.06)	0.63 (0.38, 1.05)	0.63 (0.38, 1.05)
PM_{10}	0.91 (0.61, 1.36)	0.87 (0.58, 1.31)	0.89 (0.59, 1.33)
NO_2	1.05 (0.95, 1.15)	1.05 (0.96, 1.16)	1.06 (0.96, 1.17)
NO_x	1.01 (0.92, 1.12)	1.01 (0.91, 1.12)	1.01 (0.92, 1.12)
UFP	1.02 (0.81, 1.29)	0.98 (0.77, 1.24)	0.98 (0.77, 1.24)

[a] Abbreviations: AMI= Acute Myocardial Infarct, CHD= Coronary Heart Disease, CI= Confidence interval, CVD= Cardiovascular diseases, HF= Heart failure, HR= Hazard Ratio, PM_{10} = Particulate matter with diameter <10 μm, $PM_{2.5}$ = Particulate matter with diameter <2.5 μm, NO_2= Nitrogen dioxide, NO_x = Nitrogen oxides, T2DM = Type 2 Diabetes Mellitus, UFP= Ultrafine particles.

[b] The associations in Model 1 are adjusted for age, sex, and educational level. The associations in Model 2 are additionally adjusted for smoking status, alcohol consumption, physical activity, total dietary fiber intake, total dietary energy intake, and Body Mass Index. The associations in Model 3 are additionally adjusted for area-level socioeconomic information.

[c] The associations presented in bold are statistically significant (i.e. p-value<0.05).

[d] Associations for $PM_{2.5}$ are presented for a 5 $\mu g/m^3$ increment, PM_{10} and NO_2 for a 10 $\mu g/m^3$ increment, NO_x for a 20 $\mu g/m^3$ increment, and UFP are presented for a 10,000 particles/cm^3 increment.

[*] Including cardiac arrest, cerebrovascular disease, CHD, HF, peripheral vascular diseases, pulmonary embolism, and diseases of arteries, arterioles and capillaries.

Table 3
Associations of dietary antioxidants with incidence of cardiovascular disease events and Type 2 Diabetes Mellitus.[a-c].

	Model 1	Model 2	Model 3
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Total CVD*			
Retinol	**1.10 (1.03, 1.16)**	1.02 (0.96, 1.09)	1.02 (0.96, 1.09)
Beta-carotene	**0.90 (0.85, 0.96)**	**0.94 (0.88, 1.00)**	**0.94 (0.89, 0.99)**
Vitamin C	**1.00 (1.00, 1.00)**	**1.00 (1.00, 1.00)**	1.00 (1.00, 1.00)
Vitamin E	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Zinc	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
Selenium	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)
CDAI	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
AMI			
Retinol	1.11 (0.95, 1.28)	1.00 (0.85, 1.17)	1.00 (0.85, 1.17)
Beta-carotene	**0.82 (0.70, 0.96)**	0.86 (0.73, 1.01)	0.87 (0.73, 1.02)
Vitamin C	**1.00 (1.00, 1.00)**	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Vitamin E	1.01 (0.98, 1.03)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)
Zinc	0.99 (0.94, 1.04)	1.00 (0.95, 1.05)	1.01 (0.95, 1.05)
Selenium	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
CDAI	0.99 (0.97, 1.02)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
CHD			
Retinol	**1.09 (1.01, 1.18)**	1.03 (0.95, 1.12)	1.03 (0.95, 1.12)
Beta-carotene	**0.90 (0.83, 0.97)**	**0.91 (0.84, 0.99)**	**0.92 (0.84, 0.99)**
Vitamin C	**0.99 (0.98, 1.00)**	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Vitamin E	1.01 (0.99, 1.03)	1.01 (1.00, 1.03)	1.00 (1.01, 1.00)
Zinc	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Selenium	**1.01 (1.00, 1.01)**	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
CDAI	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)
HF			
Retinol	1.13 (0.91, 1.40)	1.03 (0.82, 1.30)	1.03 (0.81, 1.30)
Beta-carotene	1.02 (0.84, 1.24)	1.04 (0.85, 1.28)	1.05 (0.86, 1.29)
Vitamin C	1.00 (1.00, 1.00)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)
Vitamin E	1.00 (0.96, 1.03)	0.99 (0.96, 1.03)	1.00 (0.96, 1.03)
Zinc	1.02 (0.95, 1.10)	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)
Selenium	**1.02 (1.01, 1.04)**	1.02 (0.99, 1.03)	1.02 (1.00, 1.03)
CDAI	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)
T2DM			
Retinol	**1.24 (1.15, 1.35)**	**1.13 (1.03, 1.23)**	**1.13 (1.03, 1.23)**
Beta-carotene	1.05 (0.97, 1.14)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)
Vitamin C	1.00 (1.00, 1.00)	**1.00 (1.00, 1.00)**	1.00 (1.00, 1.00)
Vitamin E	**1.03 (1.01, 1.04)**	**1.03 (1.01, 1.04)**	**1.03 (1.01, 1.04)**
Zinc	**1.12 (1.09 1.16)**	**1.07 (1.03, 1.10)**	**1.07 (1.03, 1.10)**
Selenium	**1.03 (1.03, 1.04)**	**1.02 (1.01, 1.03)**	**1.02 (1.01, 1.03)**
CDAI	**1.07 (1.06, 1.09)**	**1.05 (1.03, 1.07)**	**1.05 (1.03, 1.07)**

[a] Abbreviations: AMI= Acute Myocardial Infarct, CDAI= Composite Dietary Antioxidant Index, CHD= Coronary Heart Disease, CI= Confidence interval, CVD= Cardiovascular diseases, HF= Heart failure, HR= Hazard Ratio, T2DM = Type 2 Diabetes Mellitus.

[b] The associations in Model 1 are adjusted for age, sex, and educational level. The associations in Model 2 are additionally adjusted for smoking status, alcohol consumption, physical activity, total dietary fiber intake, total dietary energy intake, and Body Mass Index. The associations in Model 3 are additionally adjusted for area-level socioeconomic information.

[c] The associations presented in bold are statistically significant (i.e. p-value<0.05).

[*] Including cardiac arrest, cerebrovascular disease, CHD, HF, peripheral vascular diseases, pulmonary embolism, and diseases of arteries, arterioles and capillaries.

design, and the added value of a long follow-up period of over twelve years. Notably, it is the first epidemiological endeavor to assess both the individual and collective impacts of six primary antioxidants on CMD risk in a sizable study population exposed to air pollution. This is also the first study to examine the associations between CDAI scores and the incidence of T2DM in the general population. Moreover, all CVD outcomes were ascertained via linkage to national registries, ensuring valid and reliable outcome classification and completeness of follow-up data (Colizzi et al., 2023; Merry et al., 2009b). Finally, adjustment for area-level socioeconomic information allowed for the control of residual confounding factors that could influence individuals' exposure to air pollution and dietary patterns (van den Brekel et al., 2024; Hulshof et al., 2003).

Overall, non-significant associations emerged between exposures to the five air pollutants and CMD incidence, with expected associations observed only in the case of HF incidence for NO_2 and UFP exposures. These associations were consistent with the findings previously shown by Downward et al. (2018) in the same population, who also reported some similar unexpected directions and non-significant associations. While these observations were unanticipated, considering that air pollution exposure is generally an established risk factor for CVD, previous studies have also reported variances in the associations between varying levels of these air pollutants and the incidence of acute CVD events in European countries (Cesaroni et al., 2014). The other non-significant, almost close to unity observations were consistent with previous findings from a large English cohort, where positive associations were also indicated only for HF incidence due to exposure to air pollution (Atkinson et al., 2013). Additionally, an analysis of 22 European cohorts revealed close to unity associations between conventional

air pollutants and mortality from overall as well as specific CVDs (Beelen et al., 2014). However, despite isolated instances of such variability in the associations between air pollution exposure and cardiovascular outcomes, the majority of evidence firmly establishes air pollution as a significant risk factor for cardiovascular morbidity and mortality (Chen and Hoek, 2020; Liu et al., 2023). Our findings regarding T2DM incidence aligned with those reported by Park et al. (2015) who also found no significant impact of long-term exposure to PM and nitrogen oxides on T2DM incidence. This adds to the complexity of existing epidemiological evidence and challenges the prevailing notion that air pollution may act as an independent risk factor for T2DM development (Park and Wang, 2014; Rajagopalan and Brook, 2012). A potential limitation arises here from the usage of historical exposure data, measured and modeled decades after their period of assignment. While using currently derived models to predict exposures 10 years prior may still be efficient, validation of the pertinent period between exposures and outcomes remains challenging (Downward et al., 2018; Montagne et al., 2015).

Next, the associations between individual dietary antioxidants and incident CVD events were found to be generally non-significant and close to unity. Contrary to recent suggestions, we found no significant associations between CDAI and any incident CVD events (Zhang et al., 2023; Yang et al., 2023; Wang and Yi, 2022; Ma et al., 2023). These findings second the results from the meta-analyses conducted by Aune et al. (2018) who also reported no evidence for the protective effects of antioxidants on overall CVD. Additionally, retinol, vitamin E, zinc, selenium and CDAI were shown to increase the risk of T2DM development in the study population. The overall positive trend in associations between dietary antioxidants and T2DM incidence was consistent with observations of Zhang et al. (2024) and Liao et al. (2020) who found that serum concentrations of selenium were positively associated with T2DM risk in their study populations. Previously, serum concentrations of retinol have also been shown to be positively associated with impaired glucose tolerance by Tavridou et al. (1997). So far, meta-analytical evidence regarding the associations between antioxidants and cardiometabolic health indicators and outcomes remains heterogenous and scant (Ye and Song, 2008; Seung-Kwon et al., 2013; Vivekananthan et al., 2003; Jayedi et al., 2019).

However, an important consideration here is that antioxidant intake was assessed from dietary data obtained via a single FFQ administered at baseline. Although found to be reasonably adequate for estimating overall intake of various food groups and nutrients, the FFQ demonstrated lower relative validity of vegetables and fish intake; which may have diluted some associations since these foods are considered rich sources of beta-carotene and vitamin E[45]. Furthermore, while the FFQ was found to be adequate for estimating dietary retinol among EPIC-NL participants, results for other micronutrients indicated poor reliability, especially for beta-carotene and vitamin C for men and vitamin E for women (Ocké et al., 1997b). Additionally, potential changes in participants' diets following recruitment pose uncertainty regarding the effects on study outcomes.

After applying Bonferroni correction for multiple comparisons, none of the interaction terms for CDAI and individual antioxidants with the air pollutants remained below the adjusted significance threshold, suggesting no modifying effects of dietary antioxidants on the impact of air pollution on CMD risk. In contrast, the uncorrected analyses revealed a few statistically significant interactions and further stratification revealed mixed, sometimes contradictory associations. In these uncorrected stratified analyses, higher zinc and vitamin E intake seemed to mitigate the adverse effects of PM and nitrogen oxides on total CVD and HF risk. These findings contrasted with the associations observed in the context of UFP and $PM_{2.5}$ exposures where higher vitamin E and C intake was linked with elevated T2DM and HF risk respectively. Only one previous study has examined the modifying effect of individuals' Mediterranean Diet scores (aMED) (considered to be enriched with antioxidant compounds) on the associations of exposure to $PM_{2.5}$ and NO_2 with cardiovascular-related mortality risk (Lim et al., 2019). The study found that participants with higher aMED quintiles had a reduced risk of cardiovascular-related mortality due to air pollution exposure (Lim et al., 2019). So far, no other studies have examined the potential interactions between general dietary patterns and air pollution exposures in the context of cardiovascular outcomes, while only two have explored this in the context of T2DM. One study compared the impact of residential $PM_{2.5}$, PM_{10}, NO_2, and NO_x exposures on T2DM incidence between individuals with sufficient and insufficient intake of dietary antioxidant vitamins (based on the British adult recommended nutrient intake reference values) and concluded that sufficient intake of vitamins C and E could mitigate the adverse effects of air pollution on diabetes development (Li et al., 2022). A more recent study indicated no significant interactions between exposure to $PM_{2.5}$ and 22 dietary nutrients in the context of T2DM incidence among Korean adults, but found stronger associations with NO_2 exposures among participants with lower retinol intake (Shin and Kim, 2023). A limitation in this context is the temporal gap between dietary assessments and exposure estimates, which may introduce uncertainty in capturing the true interaction between nutrient intake and exposure to specific air pollutants.

In this study, it is also crucial to consider the risk of chance or inflated findings, particularly in uncorrected exploratory analyses where some associations may lack biological plausibility. While multiple testing corrections were not applied to the hypothesis-driven analyses, raising the possibility of Type I errors, applying stringent corrections in such cases could obscure true associations. The trade-off between statistical conservatism and hypothesis-driven approaches should be considered when evaluating the findings. Additionally, despite accounting for a wide range of covariates, the possibility of residual confounding from unmeasured variables (e.g., individual supplement use) cannot be ruled out, further reflecting underlying complexities in exposure-response relationships. This study underscores the need for future research to advance the current understanding of the intricate interplay between dietary antioxidants, air pollution exposure, and CMD incidence. Future studies could replicate and extend these findings in large, diverse population-based cohorts exposed to varying levels of air pollution and dietary patterns. This is important for generalizing and reproducing the study findings, as the present study population was predominantly female and of Dutch descent. Longitudinal studies with frequent dietary assessments and more detailed and updated exposure measurements would provide valuable insights into the relationships between dietary antioxidants, air pollution exposure, and CMD incidence. Mechanistic studies are needed to further unravel the underlying biological mechanisms responsible for these findings. Additionally, comprehensive systematic and meta-analytical research could offer further clarity on the nature of the relationship between dietary antioxidants and CMDs, particularly as existing studies have predominantly focused on the antioxidative potential of these micronutrients through interventions such as supplementation (Bjelakovic et al., 2007; Lonn et al., 2005; Miller et al., 2005). Finally, exploring the impact of supplementations alongside dietary changes on CMD risk in the context of air pollution exposure might inform preventive strategies tailored toward vulnerable populations.

5. Conclusion

This study highlights the complex and nuanced interplay between dietary antioxidants and air pollution exposure in relation to CMD incidence. Overall, the findings revealed largely non-significant associations between air pollution and CMDs, with significant positive associations only observed for NO_2 and UFP exposures with HF incidence. Beta-carotene was associated with a reduced risk of total CVD, while higher levels of antioxidant intake were generally linked to an increased incidence of T2DM. After accounting for multiple comparisons, no statistically significant interactions between antioxidants and air pollutants emerged, indicating that the associations of air pollution with CMD outcomes do not differ by dietary antioxidant intake. Further research is

warranted to confirm the generalizability of these observations and provide further elucidations regarding the possible causal factors and mechanisms, particularly those driving the indicated positive associations between dietary antioxidants and T2DM incidence. These findings could be of particular relevance in urban settings, where high air pollution exposure necessitates targeted policy measures for mitigating its adverse health impacts.

CRediT authorship contribution statement

Shradha Mishra: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Ilonca Vaartjes:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Yvonne T. van der Schouw:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **Esmée M. Bijnens:** Writing – review & editing, Conceptualization. **Jolanda M.A. Boer:** Writing – review & editing, Project administration, Data curation. **George S. Downward:** Writing – review & editing, Methodology, Data curation. **Roel C.H. Vermeulen:** Writing – review & editing, Project administration, Data curation. **W. Monique M. Verschuren:** Writing – review & editing, Project administration, Data curation. **Tim S. Nawrot:** Writing – review & editing, Supervision. **Erik J. Timmermans:** Writing – review & editing, Supervision, Conceptualization.

Funding

The EPIC-NL study was funded by "Europe against Cancer" Program of the European Commission (DG SANCO); the Dutch Ministry of Public Health, Welfare and Sports (VWS); the Netherlands Organization for Health Research and Development (ZonMw); and the World Cancer Research Fund (WCRF).

The present study has received funding from the European Union's Horizon 2020 research and innovation program 'SURREAL' under grant agreement No 956780. TSN holds funding by Methusalem. IV and EJT are supported by an NWO Gravitation Grant (Exposome-NL, 024.004.017).

The funding bodies had no role in the study design, the collection, analysis and interpretation of the data, in writing of the manuscript and in the decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.healthplace.2025.103453.

Data availability

The data of EPIC-NL are available on request, provided that an agreement is made up with the steering group of EPIC-NL.

References

Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2013. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24 (1).

Aucott, L.S., Jia, X., McNeill, G., 2007. Nutritional status and subsequent all-cause mortality in men and women aged 75 years or over living in the community. Br. J. Nutr. 98 (3), 593–599.

Aune, D., Keum, N., Giovannucci, E., et al., 2018. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. Am. J. Clin. Nutr. 108 (5), 1069–1091.

Barricarte, A., Berglund, G., Boeing, H., et al., 2002. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 5 (6b), 1113–1124.

Beelen, R., Hoek, G., Vienneau, D., et al., 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. Atmos. Environ. 72, 10–23.

Beelen, R., Stafoggia, M., Raaschou-Nielsen, O., et al., 2014. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. Epidemiology 25 (3).

Beelen, R., Hoek, G., Raaschou-Nielsen, O., et al., 2015. Natural-cause mortality and long-term exposure to particle components: an analysis of 19 European cohorts within the multi-center ESCAPE project. Environ. Health Perspect. 123 (6), 525–533.

Beulens, J.W., Stolk, R.P., Van Der Schouw, Y.T., Grobbee, D.E., Hendriks, H.F., Bots, M. L., 2005. Alcohol consumption and risk of type 2 diabetes among older women. Diabetes Care 28 (12), 2933–2938.

Beulens, J.W.J., Monninkhof, E.M., Verschuren, W.M.M., et al., 2009. Cohort profile: the EPIC-NL study. Int. J. Epidemiol. 39 (5), 1170–1178.

Bingham, S., Riboli, E., 2004. Diet and cancer — the European prospective investigation into cancer and nutrition. Nat. Rev. Cancer 4 (3), 206–215.

Bjelakovic, G., Nikolova, D., Gluud, L.L., Simonetti, R.G., Gluud, C., 2007. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 297 (8), 842–857.

Callahan, A., Leonard, H., Powell, T., 2022. Nutrition: Science and Everyday Application, second ed. Open Oregon Educational Resources, Pressbooks, Oregon, United States.

Cesaroni, G., Forastiere, F., Stafoggia, M., et al., 2014. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. Br. Med. J. 348, f7412.

Chen, J., Hoek, G., 2020. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. Environ. Int. 143, 105974.

Colizzi, C., Harbers, M.C., Vellinga, R.E., et al., 2023. Adherence to the EAT-lancet healthy reference diet in relation to risk of cardiovascular events and environmental impact: results from the EPIC-NL cohort. J. Am. Heart Assoc. 12 (8), e026318.

da Silva, A., Caldas, A.P.S., Pinto, S.L., et al., 2021. Dietary total antioxidant capacity is inversely associated with cardiovascular events and cardiometabolic risk factors: a cross-sectional study. Nutrition 89, 111140.

Downward, G.S., van Nunen, E., Kerckhoffs, J., et al., 2018. Long-term exposure to ultrafine particles and incidence of cardiovascular and cerebrovascular disease in a prospective study of a Dutch cohort. Environ. Health Perspect. 126 (12), 127007.

Eeftens, M., Beelen, R., de Hoogh, K., et al., 2012. Development of land use regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. Environ. Sci. Technol. 46 (20), 11195–11205.

Gale, C.R., Martyn, C.N., Winter, P.D., Cooper, C., 1995. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. Br. Med. J. 310 (6994), 1563–1566.

Haftenberger, M., Schuit, A., Tormo, M., et al., 2002. Physical activity of subjects aged 50–64 years involved in the European prospective investigation into cancer and nutrition (EPIC). Public Health Nutr. 5 (6b), 1163–1177.

Halliwell, B., Gutteridge, J.M., 2015. Free Radicals in Biology and Medicine. Oxford university press, USA.

Hatch, G.E., 1995. Asthma, inhaled oxidants, and dietary antioxidants. Am. J. Clin. Nutr. 61 (3), 625S–630S.

Herings, R., Bakker, A., Stricker, B., Nap, G., 1992. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. Journal of epidemiology and community health 46 (2), 136.

Hulshof, K.F.A.M., Brussaard, J.H., Kruizinga, A.G., Telman, J., Löwik, M.R.H., 2003. Socio-economic status, dietary intake and 10 y trends: the Dutch National Food Consumption Survey. Eur. J. Clin. Nutr. 57 (1), 128–137.

Janjua, S., Powell, P., Atkinson, R., Stovold, E., Fortescue, R., 2021. Individual-level interventions to reduce personal exposure to outdoor air pollution and their effects on people with long-term respiratory conditions. Cochrane Database Syst. Rev. 8 (8), Cd013441.

Jayedi, A., Rashidy-Pour, A., Parohan, M., Zargar, M.S., Shab-Bidar, S., 2019. Dietary and circulating vitamin C, vitamin E, β-carotene and risk of total cardiovascular mortality: a systematic review and dose–response meta-analysis of prospective observational studies. Public Health Nutr. 22 (10), 1872–1887.

Jenkins, D.J.A., Kitts, D., Giovannucci, E.L., et al., 2020. Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. Am. J. Clin. Nutr. 112 (6), 1642–1652.

Klipstein-Grobusch, K., Geleijnse, J.M., den Breeijen, J.H., et al., 1999. Dietary antioxidants and risk of myocardial infarction in the elderly: the Rotterdam Study. Am. J. Clin. Nutr. 69 (2), 261–266.

Kushi, L.H., Folsom, A.R., Prineas, R.J., Mink, P.J., Wu, Y., Bostick, R.M., 1996. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N. Engl. J. Med. 334 (18), 1156–1162.

Lawlor, D., Ebrahim, S., Kundu, D., Bruckdorfer, K., Whincup, P., Smith, G.D., 2005. Vitamin C is not associated with coronary heart disease risk once life course socioeconomic position is taken into account: prospective findings from the British Women's Heart and Health Study. Heart 91 (8), 1086.

Li, H., Cai, M., Li, H., et al., 2022. Is dietary intake of antioxidant vitamins associated with reduced adverse effects of air pollution on diabetes? Findings from a large cohort study. Ecotoxicol. Environ. Saf. 246, 114182.

Liao, X.-L., Wang, Z.-H., Liang, X.-N., et al., 2020. The association of circulating selenium concentrations with diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity 13 (null), 4755–4761.

Lim, C.C., Hayes, R.B., Ahn, J., et al., 2019. Mediterranean diet and the association between air pollution and cardiovascular disease mortality risk. Circulation 139 (15), 1766–1775.

Liu, M., Meijer, P., Lam, T.M., et al., 2023. The built environment and cardiovascular disease: an umbrella review and meta-meta-analysis. Eur J Prev Cardiol 30 (16), 1801–1827.

Lonn, E., Bosch, J., Yusuf, S., et al., 2005. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 293 (11), 1338–1347.
Luu, H.N., Wen, W., Li, H., et al., 2015. Are dietary antioxidant intake indices correlated to oxidative stress and inflammatory marker levels? Antioxidants Redox Signal. 22 (11), 951–959.
Ma, R., Zhou, X., Zhang, G., et al., 2023. Association between composite dietary antioxidant index and coronary heart disease among US adults: a cross-sectional analysis. BMC Public Health 23 (1), 2426.
Maugeri, A., Hruskova, J., Jakubik, J., et al., 2019. Dietary antioxidant intake decreases carotid intima media thickness in women but not in men: a cross-sectional assessment in the Kardiovize study. Free Radic. Biol. Med. 131, 274–281.
Merry, A.H., Boer, J.M., Schouten, L.J., et al., 2009a. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in The Netherlands using the cardiovascular registry Maastricht cohort study. Eur. J. Epidemiol. 24 (5), 237–247.
Merry, A.H., Boer, J.M., Schouten, L.J., et al., 2009b. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in The Netherlands using the cardiovascular registry Maastricht cohort study. European journal of epidemiology 24, 237–247.
Miller 3rd, E.R., Pastor-Barriuso, R., Dalal, D., Riemersma, R.A., Appel, L.J., Guallar, E., 2005. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann. Intern. Med. 142 (1), 37–46.
Mirmiran, P., Hosseini-Esfahani, F., Esfandiar, Z., Hosseinpour-Niazi, S., Azizi, F., 2022. Associations between dietary antioxidant intakes and cardiovascular disease. Sci. Rep. 12 (1), 1504.
Montagne, D.R., Hoek, G., Klompmaker, J.O., Wang, M., Meliefste, K., Brunekreef, B., 2015. Land use regression models for ultrafine particles and black carbon based on short-term monitoring predict past spatial variation. Environ. Sci. Technol. 49 (14), 8712–8720.
Montonen, J., Knekt, P., Jarvinen, R., Reunanen, A., 2004. Dietary antioxidant intake and risk of type 2 diabetes. Diabetes Care 27 (2), 362–366.
Mozaffari, H., Daneshzad, E., Surkan, P.J., Azadbakht, L., 2018. Dietary total antioxidant capacity and cardiovascular disease risk factors: a systematic review of observational studies. J. Am. Coll. Nutr. 37 (6), 533–545.
Myung, S.-K., Ju, W., Cho, B., et al., 2013. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. Br. Med. J. 346.
Nascimento, L.M., Gomes, K.R.O., Mascarenhas, M.D.M., Miranda, C.E.S., AraÚJo, TMEd, Frota, KdMG., 2018. Association between the consumption of antioxidant nutrients with lipid alterations and cardiometabolic risk in adolescents. Rev. Nutr. 31.
Ocké, M.C., Bueno-de-Mesquita, H.B., Goddijn, H.E., et al., 1997a. The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int. J. Epidemiol. 26 (Suppl. 1), S37–S48.
Ocké, M.C., Bueno-de-Mesquita, H.B., Pols, M.A., Smit, H.A., van Staveren, W.A., Kromhout, D., 1997b. The Dutch EPIC food frequency questionnaire. II. Relative validity and reproducibility for nutrients. Int. J. Epidemiol. 26 (Suppl. 1), S49–S58.
Park, S.K., Wang, W., 2014. Ambient air pollution and type 2 diabetes: a systematic review of epidemiologic research. Curr Environ Health Rep 1 (3), 275–286.
Park, S.K., Adar, S.D., O'Neill, M.S., et al., 2015. Long-term exposure to air pollution and type 2 diabetes mellitus in a multiethnic cohort. Am. J. Epidemiol. 181 (5), 327–336.
Parohan, M., Anjom-Shoae, J., Nasiri, M., Khodadost, M., Khatibi, S.R., Sadeghi, O., 2019. Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. Eur. J. Nutr. 58 (6), 2175–2189.
Patel, V.K., Kpatel, C., Patel, H.U., Patel, C., 2010. Vitamins, minerals and carotenoids as a antioxidants. Asian J. Res. Chem. 3 (2), 255–260.
Pearson, T.A., 2011. Public policy approaches to the prevention of heart disease and stroke. Circulation 124 (23), 2560–2571.
Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 61 (12), 3037–3045.
Rimm, E.B., Stampfer, M.J., Ascherio, A., Giovannucci, E., Colditz, G.A., Willett, W.C., 1993. Vitamin E consumption and the risk of coronary heart disease in men. N. Engl. J. Med. 328 (20), 1450–1456.
Sahyoun, N.R., Jacques, P.F., Russell, R.M., 1996. Carotenoids, vitamins C and E, and mortality in an eiderly population. American journal of epidemiology 144 (5), 501–511.
Scheffers, F.R., Wijga, A.H., Verschuren, W.M.M., et al., 2020. Pure fruit juice and fruit consumption are not associated with incidence of type 2Diabetes after adjustment for overall DietaryQuality in the European ProspectiveInvestigation into cancer andNutrition–Netherlands (EPIC-NL) study. J. Nutr. 150 (6), 1470–1477.
Sesso, H.D., Buring, J.E., Christen, W.G., et al., 2008. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA 300 (18), 2123–2133.
Seung-Kwon, M., Woong, J., Belong, C., et al., 2013. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ Br. Med. J. (Clin. Res. Ed.) 346, f10.
Shin, M.-K., Kim, K.-N., 2023. Association between long-term air pollution exposure and development of diabetes among community-dwelling adults: modification of the associations by dietary nutrients. Environ. Int. 174, 107908.
Sluijs, I., van, A.D., Beulens, J.W., et al., 2010. Ascertainment and verification of diabetes in the EPIC-NL study. Neth. J. Med. 68 (1), 333–339.
Struijk, E.A., May, A.M., Wezenbeek, N.L.W., et al., 2014. Adherence to dietary guidelines and cardiovascular disease risk in the EPIC-NL cohort. Int. J. Cardiol. 176 (2), 354–359.
Tavridou, A., Unwin, N.C., Laker, M.F., White, M., Alberti, K.G.M.M., 1997. Serum concentrations of vitamins A and E in impaired glucose tolerance. Clin. Chim. Acta 266 (2), 129–140.
van den Brekel, L., Lenters, V., Mackenbach, J.D., et al., 2024. Ethnic and socioeconomic inequalities in air pollution exposure: a cross-sectional analysis of nationwide individual-level data from The Netherlands. Lancet Planet. Health 8 (1), e18–e29.
van Nunen, E., Vermeulen, R., Tsai, M.Y., et al., 2017. Land use regression models for ultrafine particles in six European areas. Environ. Sci. Technol. 51 (6), 3336–3345.
Vivekananthan, D.P., Penn, M.S., Sapp, S.K., Hsu, A., Topol, E.J., 2003. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet 361 (9374), 2017–2023.
Walton-Moss, B., Samuel, L., Nguyen, T.H., Commodore-Mensah, Y., Hayat, M.J., Szanton, S.L., 2014. Community-based cardiovascular health interventions in vulnerable populations: a systematic review. J. Cardiovasc. Nurs. 29 (4), 293–307.
Wang, L., Yi, Z., 2022. Association of the Composite dietary antioxidant index with all-cause and cardiovascular mortality: a prospective cohort study. Front. Cardiovasc. Med. 9.
Wareham, N.J., Jakes, R.W., Rennie, K.L., et al., 2003. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 6 (4), 407–413.
Wright, M.E., Mayne, S.T., Stolzenberg-Solomon, R.Z., et al., 2004. Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. Am. J. Epidemiol. 160 (1), 68–76.
Wu, D., Wang, H., Wang, W., et al., 2023. Association between composite dietary antioxidant index and handgrip strength in American adults: data from National Health and Nutrition Examination Survey (NHANES, 2011-2014). Front. Nutr. 10, 1147869.
Yang, C., Yang, Q., Peng, X., Li, X., Rao, G., 2023. Associations of composite dietary antioxidant index with cardiovascular disease mortality among patients with type 2 diabetes. Diabetol. Metab. Syndr. 15 (1), 131.
Ye, Z., Song, H., 2008. Antioxidant vitamins intake and the risk of coronary heart disease: meta-analysis of cohort studies. Eur. J. Cardiovasc. Prev. Rehabil. 15 (1), 26–34.
Zhang, J., Lu, X., Wu, R., et al., 2023. Associations between composite dietary antioxidant index and estimated 10-year atherosclerotic cardiovascular disease risk among U.S. adults. Front. Nutr. 10.
Zhang, C., Zeng, Q., Liu, X., et al., 2024. Association of blood selenium levels with diabetes and heart failure in American general adults: a cross-sectional study of NHANES 2011–2020 pre. Biol. Trace Elem. Res. 202 (8), 3413–3424.