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Ambient air pollution and lipid profile: Systematic review and meta-analysis☆

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ABSTRACT

Ambient air pollution (AAP) is recognized a cardiovascular risk factor and lipid profile dysregulation seems to be one of the potential mediators involved. However, results from epidemiologic research on the association between exposure to AAP and altered lipid profile have been inconsistent. This study aims to systematically review and meta-analyse epidemiologic evidence on the association between exposure to ambient air pollutants (particulate matter, nitrogen oxides, sulphur dioxide, ozone, carbon monoxide, back carbon) and lipid profile parameters (Total cholesterol; High-Density Lipoprotein Cholesterol; Low-Density Lipoprotein Cholesterol; TG-Triglycerides) or dyslipidaemia.

Systematic electronic literature search was performed in PubMed, Web of Science and Scopus databases (last search on 24th May 2019) using keywords related to the exposure (ambient air pollutants) and to the outcomes (lipid profile parameters/dyslipidaemia). Qualitative and quantitative information of the studies were extracted and fixed or random-effects models were used to obtain a pooled effect estimate per each pollutant/outcome combination.

22 studies were qualitatively analysed and, from those, 3 studies were quantitatively analysed. Particulate matters were the most studied pollutants and a considerable heterogeneity in air pollution assessment methods and outcomes definitions was detected. Age, obesity related measures, tobacco consumption, sex and socioeconomic factors were the most frequent considered variables for confounding adjustment in the models. In a long-term exposure scenario, we found a 3.14% (1.36%–4.95%) increase in TG levels per 10 $\mu g/m^3$ PM_{10} increment and a 4.24% (1.37%–7.19%) increase in TG levels per 10 $\mu g/m^3$ NO_2 increment. No significant associations were detected for the remaining pollutant/outcome combinations.

Despite the few studies included in the meta-analysis, our study suggests some epidemiologic evidence supporting the association between PM_{10} and NO_2 exposures and increased TG levels. Due to the very low level of evidence, more studies are needed to clarify the role of lipid profile dysregulation as a mediator on the AAP adverse cardiovascular effects.

1. Introduction

Ambient air pollution (AAP) is a major global environmental problem posing numerous management challenges. In the last decades, increasing industrialization and urbanization has resulted in higher levels of air pollution worldwide making air quality management a priority due to its influence on human health. Nevertheless, a large proportion of the population is still exposed to air pollutants levels above recommended standards despite air quality policies implemented in many countries and according to the World Health Organization (WHO), in 2016, 91% of the world's population was living in places where the WHO air quality guidelines levels were not met (WHO, 2018).

Although it may seem intuitive that exposure to air pollutants affects mostly the respiratory system, there is evidence that the majority of its adverse effects are on the cardiovascular system (Brook, 2008; Simkhovich et al., 2008; Meo and Suraya, 2015). Worldwide, 3.7 million deaths were attributable to AAP in 2012,

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with ischaemic heart disease and stroke accounting for 80% of premature deaths, followed by lung diseases and lung cancer (WHO, 2016).

The pathophysiologic mechanisms linking AAP and cardiovascular events are still an area of research and scientific debate. However, lipid metabolism alteration through oxidative stress and subsequent systemic inflammatory response seems to be one of the potential mediators of the adverse cardiovascular effects of air pollution (Brook et al., 2010; Araujo, 2010; Li et al., 2013). It is plausible that lipid profile parameters, namely Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C) and Triglycerides (TG) levels are affected by exposure to air pollutants which will, in turn, contribute to trigger cardiovascular events.

In the past years, some epidemiological studies explored the association between AAP exposure and lipid profile parameters or dyslipidaemia (Yeatts et al., 2007; Chuang et al., 2010; Bind et al., 2016; Sade et al., 2016; Shanley et al., 2016; Cai et al., 2017; Yang et al., 2018a) but the results are not consistent and some studies failed to demonstrate the deleterious effect of AAP on the lipid profile parameters, namely on TC and HDL (Fioravanti et al., 2018). Moreover, a recent study suggest that among the several cardiometabolic risk factors, dyslipidaemias may be the most sensitive to air pollution exposure (Yang et al., 2019).

Until now, to the best of our knowledge, no systematic review exploring the link between exposure to AAP and lipid profile parameters or dyslipidaemia has been published. This study aimed to systematically review and meta-analyse the association between exposure to ambient air pollutants (particulate matter – PM_{10}, $PM_{2.5}$ and ultrafine particles, nitrogen oxides– NO_x, nitrogen dioxide – NO_2, sulphur dioxide – SO_2, ozone – O_3, carbon monoxide – CO, Black carbon– BC) and levels of blood lipid parameters (TC, HDL-C, LDL-C and TG) or dyslipidaemia conditions. Our hypothesis is that an increase in levels of ambient air pollutants is associated with an increase in levels of TC, LDL-C and TG, a decrease in levels of HDL-C and an increase in the prevalence of dyslipidaemia.

2. Methods

2.1. Search strategy

The systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). Full search criteria are presented in Table S1 (Supplementary material). In short, three bibliographic databases (PubMed, Web of Science and Scopus) were considered to the literature search using the combinations of the keywords related to the exposure (air pollution, air pollutant*, particulate matter, PM_{10}, $PM_{2.5}$, ultrafine particles, ozone, sulphur dioxide, nitrogen oxides, carbon monoxide, black carbon) and the outcomes (lipid profile, high density lipoprotein cholesterol, HDL, low density lipoprotein cholesterol, LDL, cholesterol, triglycerides, dyslipid*, hypercholesterol*, hypertriglycerid*). Moreover, the reference lists of all included studies as well as their citation lists were also screened. All observational studies (cohort, cross sectional and case-control studies) published until the date of the search (24th May 2019) were considered. Two of the authors (VG and RR) independently searched the articles and downloaded them into EndNote Web® reference management software to remove duplicated references. The title and abstracts of the remaining articles were screened for eligibility and the full texts of the potential eligible articles were further analysed. In case of disagreement between the two authors, a third author (BN) resolved any discrepancies.

2.2. Eligibility criteria

Studies were included if they met all of the following criteria: (a) Considering at least one of the following air pollutants exposure: PM_{10}, $PM_{2.5}$, ultrafine particles, NO_X NO_2, SO_2, O_3, CO; BC (b) Reporting the association of exposure to the air pollutants with at least one lipid parameter values (TC, HDL-C, LDL-C, TG) or with any dyslipidaemia condition related with these lipid parameters (high TC; low HDL-C, high LDL-C, high TG); (c) reporting a quantitative measure of the association.

Due to the wide range of definitions and cut-offs used to define dyslipidaemia conditions (Reiner et al., 2011; NCEP-ATP III Expert Panel, 2002; JCDCG, 2007) no specific definition was assumed as an inclusion criteria and all of the studies reporting any type of dyslipidaemia (high TC; low HDL-C, high LDL-C, high TG or dyslipidaemia diagnosed by a physician) were considered. Only original research published in English as a full publication in a peer reviewed journal were included.

2.3. Data extraction and synthesis

The following data were extracted into the final list of studies for qualitative synthesis: author, publication year, country, study period, study population, study design, sample size, type of pollutant, exposure period, exposure assessment method, type of outcome, fasting state of participants for blood collection, association assessment method, effect estimate definition, effect estimate (EE) values and their 95% confidence intervals (95% CI) and confounding adjustment variables.

Only single-pollutant model estimates were extracted even when both single pollutant and multi-pollutant models were available. Effect estimates from the fully adjusted models were those extracted and extra estimates from sensitivity analysis were not considered.

Exposure times up to 30 days were considered as short-term exposure and exposure times more than 30 days were considered as long-term exposure (EPA, 2011). In the case of articles reporting multiple lags estimates to assess short-term exposures, the lag estimate considered in this review was chosen based on the following priority order criteria already considered in previous systematic reviews by the following: (1) the lag that the author focused on or stated as a priority; (2) the lag that showed the highest significance level (positive or negative); or (3) the lag with the largest effect estimate (positive or negative) (Atkinson et al., 2012; Yang et al., 2018b). The same priority order criteria were applied when articles presented more than one effect estimate to assess long-term exposure: (1) the time period that the author focused on or stated as a priority; (2) the time period that showed the highest significance level (positive or negative); or (3) the time period with the largest effect estimate (positive or negative).

Data extraction was performed independently by two of the authors and disagreements were resolved by a third one. In the case of studies with missing information it was tried to contact their authors by email.

2.4. Quality assessment

The quality of each study was independently assessed by two investigators (VG and RR) using the Joanna Briggs Institute (JBI) checklists for cohort studies and cross-sectional studies (Moola et al., 2017). In the case of the cohort studies, their quality was graded as poor (0–4), intermediate (5–8) or high (9–11). Similarly, in the case of the cross sectional studies, their quality was graded as poor (0–3), intermediate (4–6) or high (7–8) according to the JBI checklist items. Any disagreement was resolved by consensus after

discussion between the two investigators. Moreover, the approach of GRADE to rating quality of evidence was used to assess the quality of evidence from the meta-analysis. Accordingly, the level of evidence was downgraded according to the risk of bias of the included studies, inconsistency, indirectness, imprecision and publication bias (Balshem et al., 2011). Because all meta-analysis were based on observational studies, the produced evidence was immediately classified as "low level evidence" and there were no reasons to upgrade the level of evidence.

2.5. Statistical analysis

Beyond the PRISMA guidelines (Moher et al., 2009), meta-analysis of selected studies followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). Meta-analysis were only performed if two or more studies were comparable in terms of study population group, pollutant, outcome, exposure period and effect estimate.

Effect estimates (EE) of each air pollutant concentrations expressed as parts per billion (ppb) were converted to $\mu g/m^3$ making the following assumptions: 1 ppb = 1.96 $\mu g/m^3$ for O_3; 1 ppb = 1.88 $\mu g/m^3$ for NO_2; 1 ppb = 2.62 $\mu g/m^3$ for SO_2; 1 ppb = 1.15 $\mu g/m^3$ for CO (Harrop, 2002).

According to the Cochrane handbook for systematic reviews, it is recommended that meta-analysis of EE coming from skewed data on a log scale be done on the scale of the log-transformed data (Higgins and Green, 2011). Thus, EE from each study on a log scale (presented as % change in the outcome per $\mu g/m^3$ of pollutant) were back-transformed to beta coefficients (β) assuming the following formula: $\beta = \ln[(EE/100)+1]$ (Higgins et al., 2008). This formula was applied to the EE and to both limits of the respective 95% CI values in order to obtain the standard error of β estimate. Obtained β estimate values were converted for a fixed increment in pollutant concentration (per 10 $\mu g/m^3$ of pollutant) and these estimates, and corresponding 95%CI, were used in the meta-analysis.

The β estimate standard error (SE) from the transformed 95%CI limits values of EE was obtained from the formula $SE = (\beta UL - \beta LL)/3.92$ where $\beta UL = \ln[(EE\_UL/100)+1]$, $\beta LL = \ln[(EE\_LL/100)+1]$ and EE_UL and EE_LL are respectively the upper (UL) and lower (LL) 95% confidence limits of the effect estimates (EE) (Higgins and Green,

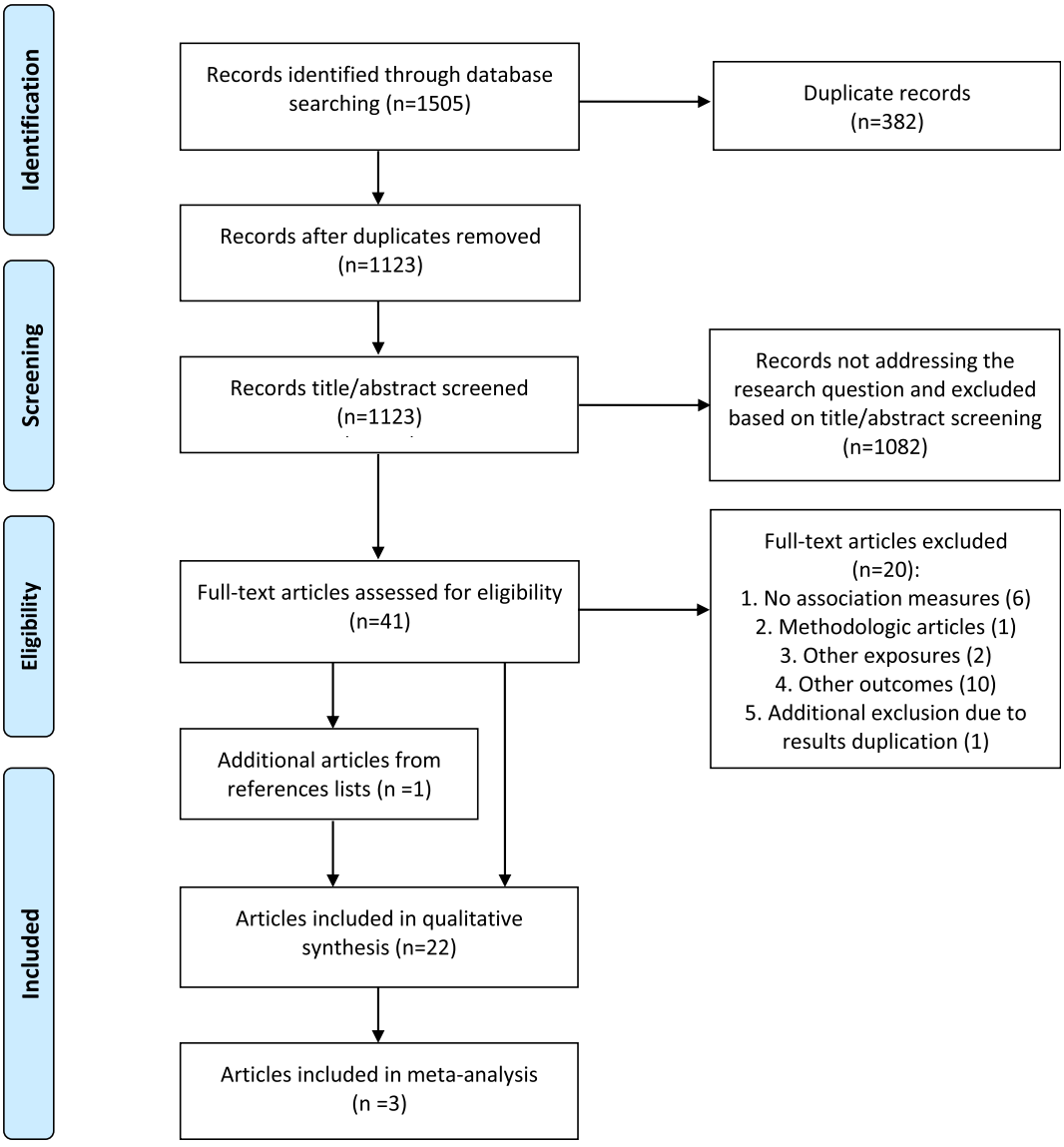

Fig. 1. Flow diagram of study selection process (Adapted from Moher et al., 2009).

Table 1
General characteristics of the studies included in the qualitative synthesis.

Author, year	Country	Study period	Study Population	Study Design	Sample size	Pollutants	Exposure Duration	Outcomes
Yeatts et al. (2007)	USA	2003–2004	Patient Adults, 21-50y	Cohort	12	$PM_{2.5}$	Short-term	TC, TG
Chuang et al. (2010)	Taiwan	2002	Adults, 16-90y	Cross-sectional	7578	PM_{10}, NO_2, SO_2, O_3, CO	Short-term	HDL-C, LDL-C, TG
Chuang et al. (2011)	Taiwan	2000	Elderly, 54-90y	Cross-sectional	1023[a]	$PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, CO	Long-term	TC, HDL-C, TG
Sorensen et al. (2015)	Denmark	1993–1997	Adults, 50-64y	Cross-sectional	36039	$PM_{2.5}$, NO_2	Long-term	TC
Eze et al. (2015)	Switzerland	2001–2002	Adults, 29–73y	Cross-sectional	3684	PM_{10}, NO_2	Long-term	Dyslipidaemia[c]
Bind et al. (2016)	USA	1995–2013	Elderly Men, 49-100y	Cohort	1112	$PM_{2.5}$	Short-term	HDL-C, LDL-C, TG
Sade et al. (2016)	Israel	2003–2012	Patient Adults, >18y	Cohort	73117[a]	$PM_{2.5}$, PM_{10}	Short/Long-term	HDL-C, TG, LDL-C
Chen et al. (2016)	USA	2002–2008	Patient Adults, 34.5 ± 8.1y	Cross-sectional	1023[a]	$PM_{2.5}$, NO_2, O_3	Short/Long-term	TC, HDL-C, LDL-C, TG
Shanley et al. (2016)	USA	1988–1994	Adults, 17-90y	Cross-sectional	11623[a]	PM_{10}	Long-term	TC, HDL-C, TG, LDL-C
Wallwork et al. (2017)	USA	2000–2011	Elderly men, 70.4 ± 6.9y	Cohort	326[a]	$PM_{2.5}$	Long-term	Dyslipidaemia[d]
Bell et al. (2017)	USA	2000–2002	Adults, 45-84y	Cross-sectional	6654	$PM_{2.5}$	Short/Long-term	HDL-C, BC
Cai et al. (2017)	Norway Netherlands	2006–2013	Adults, 47.6 ± 13.7y	Cross-sectional	114082[a]	PM_{10}, NO_2	Long-term	TC, HDL-C, TG
Poursafa et al. (2017)	Iran	2014–2016	Children and Adolescents, 6-18y	Cross-sectional	186	$PM_{2.5}$	Long-term	TC, HDL-C, LDL-C, TG
Fioravanti et al. (2018)	Italy	2011–2012	Children, 8y	Cross-sectional	410	$PM_{2.5}$, PM_{10}, NO_2	Long-term	TC, HDL-C
Wang et al. (2018)	China	2011–2015	Patient Adults, $52.2\% \geq 60$y	Cross-sectional	3912	PM_{10},NO_2, SO_2	Short-term	TC, HDL-C, TG, LDL-C
Yang et al., (2018a) [b]	China	2009	Adults,18-74y	Cross-sectional	15477	$PM_{2.5}$, PM_{10}, NO_2,SO_2 O_3	Long-term	TC, HDL-C, TG, LDL-C Dyslipidaemia[e]
Ghosh et al. (2018)	USA	2005–2014	Patient Adolescents, 14-17y	Cohort	75	$PM_{2.5}$, NO_2, O_3	Long-term	HDL-C, TG
Lee et al. (2019)	South Korea	2009–2013	Adults, 55.1 ± 7.1y	Cohort	87417[a]	$PM_{2.5}$	Long-term	Dyslipidaemia[f]
Li et al. (2019)	China	2014–2016	Adults, 23.3 ± 5.4 y	Cohort	73	$PM_{2.5}$, NO_2,SO_2, CO, BC, PNC	Short-term	HDL-C
McGuinn et al. (2019)	USA	2001–2010	Patients, 60.8 ± 12.1 y	Cross-sectional	6587	$PM_{2.5}$	Long-term	TC, HDL-C, LDL-C, TG
Shin et al. (2019)	South Korea	2012	Adults, 47.8 ± 0.06 y	Cross-sectional	100867	PM_{10}, NO_2, SO_2, O_3, CO	Long-term	Dyslipidaemia[g]
Wu et al. (2019)	USA	1999–2005	Midlife women in menopausal transition, 49±3y	Cohort	2289[a]	$PM_{2.5}$	Short/Long-term	TC, HDL-C, LDL-C, TG

Abbreviations: y-years; PM - particulate matter; PNC-Ultrafine Particulate number concentration; NO_2—nitrogen dioxide; SO_2—sulphur dioxide; O_3—ozone; CO – carbon monoxide; TC – Total cholesterol, HDL-C - High Density Lipoprotein Cholesterol, LDL-C - Low Density Lipoprotein Cholesterol; TG – Triglycerides.

[a] Sample size varies according to the analysed outcome.

[b] Another study by Yang et al. (2019) was also found but it report duplicate results regarding the outcomes High TG and High LDL-C. Consequently, we opted to report only results from Yang et al. (2018a) because they were presented adjusted for more confounding variables.

[c] Dyslipidaemia was defined according to 3 different definitions: High TG: TG ≥ 150 mg/dL or medication; Low HDL-C: HDL-C <35 mg/dL for men and HDL-C <39 mg/dL for women (WHO definition); and Low HDL-C: HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women or medication (IDF/ATP definition).

[d] Dyslipidaemia was defined according to 2 different definitions: High TG: TG ≥ 150 mg/dL or medication; and Low HDL-C: HDL-C <40 mg/dL or medication.

[e] Dyslipidaemia was defined according to 4 different definitions: High TG: TG ≥ 200mg/Dl; High TC: TC ≥ 240mg/Dl; High LDL-C: LDL-C (≥160 mg/dL); and High HDL: HDL ≤40 mg/dL.

[f] Dyslipidaemia was defined according to 2 different definitions: High TG: TG ≥ 150 mg/dL; and Low HDL-C: HDL-C <40 mg/dL for men and HDL-C <50 mg/dL for women.

[g] Dyslipidaemia diagnosed by a physician (auto reported information).

2011). Finally, the pooling estimate and 95% confidence limits estimates were transformed ($EE = 100 \times [\exp(\beta)\text{-}1]$) and presented in the forest plots as % change in the outcome per $\mu g/m^3$ of pollutant.

The heterogeneity of the included studies was evaluated by using the Cochran's Q test and I^2 statistic. Regarding the Cochran's Q test, if the *p-value* was <0.05, a random-effects model was assumed to calculate the Pooled effect estimate (PEE). Otherwise, a fixed-effect model was considered. Concerning the I^2 statistic, if the value was >50%, we considered that there is a statistically significant heterogeneity (Higgins et al., 2003). Additionally, The Egger's test for asymmetry was used to assess the publication bias (Egger et al., 1997).

Meta-analysis were performed using the package "meta" (Schwarzer, 2007) of the R software (version 3.4.3, R Development Core R Core Team, 2017) assuming 0.05 level of significance, and forest plots were constructed using the package "forestplot" (Gordon and Lumley, 2017) of the same software.

3. Results

From the 1505 records identified through database searching and after duplicates were removed, the title/abstract of 1123 records were screened. From those, 41 were full-text assessed for eligibility and 1 more article were selected from their reference lists. A total of 22 articles met the inclusion criteria and all of them were considered to have moderate/high quality based on the JBI checklists for cohort studies and cross-sectional studies (Tables S2 and S3, Supplemental material) and were included in the qualitative synthesis (Yeatts et al., 2007; Chuang et al., 2010; Chuang et al., 2011; Sørensen et al., 2015; Eze et al., 2015; Bind et al., 2016; Sade et al., 2016; Chen et al., 2016; Shanley et al., 2016; Wallwork et al., 2017; Bell et al., 2017; Cai et al., 2017; Poursafa et al., 2017; Fioravanti et al., 2018; Wang et al., 2018; Yang et al., 2018a; Ghosh et al., 2018; Lee et al., 2019; Li et al., 2019; McGuinn et al., 2019; Shin et al., 2019; Wu et al., 2019). Finally, 3 articles (Cai et al., 2017; Shanley et al., 2016; Yang et al., 2018a) covering the same population group (Adults, both sexes), pollutant (PM_{10} and NO_2), outcomes (TC, HDL-C, LDL-C and TG), period of exposure (long-term

Table 2
Description of Methods of Exposure Assessment, Fasting State of Participants, Methods of Association Assessment and Effect Estimate Definition of the studies included in the qualitative synthesis.

Author, year	Method of Exposure Assessment	Fasting State of Participants	Method of Association Assessment	Effect Estimate Definition
Yeatts et al. (2007)	Direct measurement on the local	Not reported	Mixed models	Change in outcomes (%, 95%CI) per 1 μg/m^3 increase in pollutant
Chuang et al. (2010)	Direct measurement from the nearest station within 10 km	Yes	GAM	Change in outcome (mg/dL,95%CI) per IQR (μg/m^3 to PM10 and ppb to O3) increase in pollutants
Chuang et al. (2011)	Direct measurement from the nearest station within 10 km	Yes	GAM	Change in outcome (mg/dL,95%CI) per IQR (μg/m^3 to PM_{10} and ppb to O_3) increase in pollutants
Sorensen et al. (2015)	NO_2: Dispersion model; $PM_{2.5}$: LUR model	No	GLM	Change in outcome (mg/dL,95%CI) per IQR (μg/m^3) increase in pollutant
Eze et al. (2015)	PM_{10}: Dispersion models; NO_2: hybrid model incorporating LUR	Yes	Mixed logistic regression models	OR per 10 increase in pollutants
Bind et al. (2016)	Direct measurement from a single monitor station	Not reported	Quantile regressions for longitudinal data	Differences in a given percentile of the outcome (mg/dL) per IQR (μg/m^3) increase in pollutant
Sade et al. (2016)	Spatiotemporal hybrid model (satellite and LUR)	Yes	Mixed models	Change in outcome (%,95%CI) per IQR (μg/m^3) increase in pollutant
Chen et al. (2016)	Spatial interpolation (maximum radius of 50 Km)	Yes	Variance component models	TC, HDL-C, LDL-C: Changes in the outcome (mg/dL) per 1-SD change in pollutants. TG: % change (%,95%CI) in the outcome per with 1-SD change of pollutants
Shanley et al. (2016)	Direct measurement from the nearest station within 20 miles	Yes/No	GLM	Change in outcome (%,95%CI) per IQR (μg/m^3) increase in pollutant
Wallwork et al. (2017)	Spatiotemporal hybrid model (satellite and LUR)	Yes	Cox proportional hazards models	Hazard ratio
Bell et al. (2017)	Hierarchical spatiotemporal models	Yes	GLM	Change in outcome (mg/dL) per 5 μg/m^3 increase in pollutant
Cai et al. (2017)	LUR models	Yes/No	GLM	Change in outcome (%,95%CI) per IQR (μg/m^3) increase in pollutant
Poursafa et al. (2017)	Direct measurement from 6 monitor stations	Yes	GLM	Correlation coefficient between outcome and pollutant levels
Fioravanti et al. (2018)	LUR models	Not reported	GLM	Change in outcomes (mg/dL, 95%CI) per 10 μg/m^3 increase in NO_2 and PM_{10} or 5 μg/m^3 increase in $PM_{2.5}$
Wang et al. (2018)	Direct measurement from the monitoring stations	Not reported	GLM	Changes in outcome (mg/dL,95%CI) per 10 μg/m^3 increment in pollutant
Yang et al., 2018a [a]	$PM_{2.5}$: Spatial model; PM_{10}, NO_2, SO_2, O_3: Direct measurement from 11 monitoring stations	Yes	2 level logistic regression and GLM	Change in outcomes (%, 95%CI) per 10-μg/m^3 increase of pollutants and OR
Ghosh et al. (2018)	Spatial interpolation by inverse distance-squared weighting (stations within 50 Km)	Not reported	Multilevel linear spline model	Change in outcomes (mg/dL, 95%CI) per tertile of pollutant exposure (regression coefficients)
Lee et al. (2019)	Community Multiscale Air Quality Model	Yes	Cox models	Hazard Ratio (95% CI)
Li et al. (2019)	Direct measurements from monitoring stations	Yes	Generalized estimating equation models	Change in outcome (mg/dL, 95%CI) per inter-quartile range (IQR) higher exposure.
McGuinn et al. (2019)	Hybrid prediction model	Yes	GLM	Change in outcome (%, 95%CI) per 1 μg/m^3 higher average of PM2.5
Shin et al. (2019)	Direct measurements from monitoring stations	Not reported	Multiple logistic regression models	OddsRatio (OR)
Wu et al. (2019)	Direct measurements from monitoring stations (stations within 20 Km)	Yes	Mixed models	Change in outcomes (%, 95%CI) per inter-quartile range (IQR) higher exposure

Abbreviations: LUR-Land Use regression; GLM -Generalized linear models; SD−standard deviation; GAM-generalized additive model; OR-OddsRatio; IQR-interquartile ran.
[a] Another study by Yang et al. (2019) was also found but it report duplicate results regarding the outcomes High TG and High LDL-C. Consequently, we opted to report only results from Yang et al. (2018a) because they were presented adjusted for more confounding variables.

exposure) and effect estimate definition (% changes in the outcome per μg/m^3 of pollutant) were quantitative analysed (Fig. 1).

3.1. Qualitative description of the articles

The publication year of the articles range from 2007 to 2019 and more than half were published in the last 3 years. Studies were mostly conducted in the USA (n = 8), the data collection period range from 1988 to 2016 and the majority were cross-sectional studies (n = 14). Adults of the general population were the most frequently analysed population group (n = 11) although ages considered to define adults varied in the different studies, ranging from 16 to 90 years old. Moreover, a considerably proportion of the studies explored the ambient AAP effects among specific sub population groups, namely the elderly (n = 3), midlife women in menopausal transition (n = 1), children or adolescents (n = 2) and patients with chronic diseases (n = 6). Long-term exposures to $PM_{2.5}$, PM_{10} or NO_2 were the most frequently studied exposure conditions. Regarding the outcomes, continuous variables of lipid profile parameters were more frequently considered than the

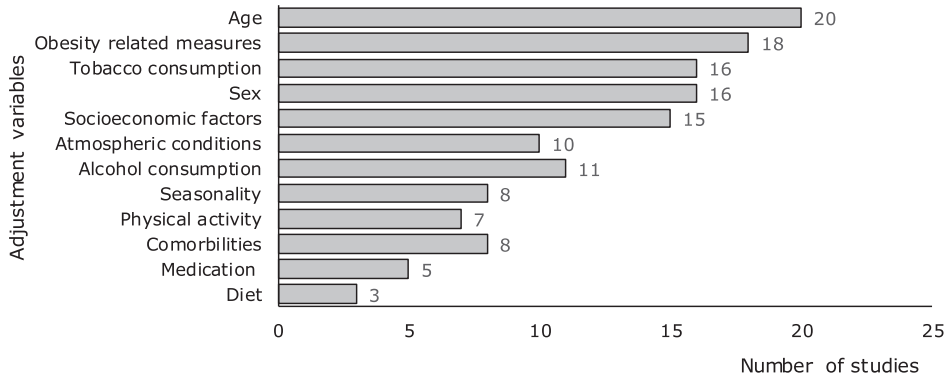

Fig. 2. Distribution of studies according to the 12 most frequently considered adjustment variables (Obesity related measures includes Body mass index, waist circumference measures or percent body fat; Socioeconomic factors includes employment status, family income, neighbourhood socio-economic index, occupation, gross domestic product, poverty-income ratio, occupation, socioeconomic status, education level, educational attainment, school attendance or Area level of Socioeconomic position).

Table 3
Effect estimate values collected from the 3 studies quantitatively analysed.

Pollutant/Outcome	Author	% change in outcome (95% CI) per Pollutant increment	% change in outcome (95% CI) per 10 μg/m^3 Pollutant increment
PM_{10}/TC	Cai et al. (2017)	−0.1(-0.3 to 0.05) per 2 μg/m^3	−0.5 (−1.5 to 0.25)
	Shanley et al. (2016)	1.43(1.21−1.66) per 11.1 μg/m^3	1.29 (1.09−1.50)
	Yang et al. (2018a)	−0.2(-0.5 to 0.1) per 10 μg/m^3	−0.2 (−0.5 to 0.1)
NO_2/TC	Cai et al. (2017)	−0.1(-0.3 to 0.1) per 7.4 μg/m^3	−0.14 (−0.41 to 0.14)
	Yang et al. (2018a)	0.7(0−1.4) per 10 μg/m^3	0.7 (0−1.4)
PM_{10}/HDL	Cai et al. (2017)	0.2(-0.1 to 0.4) per 2 μg/m^3	1.0 (−0.5 to 2.0)
	Shanley et al. (2016)	0.18(-0.32 to 0.68) per 11.1 μg/m^3	0.16 (−0.29 to 0.61)
	Yang et al. (2018a)	−0.2(-0.7 to 0.2) per 10 μg/m^3	−0.2 (−0.7 to 0.2)
NO_2/HDL	Cai et al. (2017)	0.5(0.3−0.8) per 7.4 μg/m^3	0.68 (0.41−1.08)
	Yang et al. (2018a)	−1.6(-2.3 to −1) per 10 μg/m^3	−1.6 (−2.3 to −1)
PM_{10}/LDL	Shanley et al. (2016)	1.18(0.81−1.56) per 11.1 μg/m^3	1.06 (0.73−1.41)
	Yang et al. (2018a)	−0.9(-1.3 to 0.4) per 10 μg/m^3	−0.9 (−1.3 to 0.4)
PM_{10}/TG	Cai et al. (2017)	1.9(1.5−2.4) per 2 μg/m^3	9.5 (7.5−12.0)
	Shanley et al. (2016)	2.42(1.09−3.76) per 11.1 μg/m^3	2.18 (0.98−3.39)
	Yang et al. (2018a)	4.7(3.6−5.9) per 10 μg/m^3	4.7 (3.6−5.9)
NO_2/TG	Cai et al. (2017)	2.2(1.6−2.7) per 7.4 μg/m^3	2.97 (2.16−3.65)
	Yang et al. (2018a)	6(3.5−8.6) per 10 μg/m^3	6 (3.5−8.6)

dichotomous variables regarding the dyslipidaemia condition (Yes/No). Five of the reviewed studies aimed at the association between air pollution and dyslipidaemia but they used discrepant definitions of the disease and thus were not comparable (Table 1). While some studies had direct measurements of exposure from AAP monitoring stations (n = 10), other considered more complex methods namely spatiotemporal hybrid models based on satellite information (n = 12) (Table 2). Most studies collected blood in fasting state (n = 13) but a considerable number of studies (n = 6) did not report this information. Generalized Linear models (GLM) were the most frequently used method to assess the association between pollutant exposure and lipid profile parameters (n = 9). The most common way to express the results was change in outcome (%, 95%CI) per IQR increase in pollutants (Table 2). Age, obesity related measures, tobacco consumption, sex and socioeconomic factors were the 5-most frequent considered variables for confounding adjustment in the models (Fig. 2). Additional information about the characteristics of the 16 studies included in qualitative analysis is available in Excel Table S1 (Supplemental Excel File).

In a long-term scenario, concerning studies about adults from the general population (Eze et al., 2015, Lee et al. 2019, Sørensen et al., 2015, Shanley et al., 2016, Bell et al., 2017, Cai et al., 2017, Yang et al., 2018a, Shin et al., 2019), we found that statistically significant associations were more frequently found regarding the parameters TG and TC (Table 4), but some studies also reported no significant statistically significant associations regarding these two lipid parameters (Cai et al., 2017; Yang et al., 2018a). In the elderly, in midlife women in menopausal transition and in the children/adolescents groups (Chuang et al., 2011; Wallwork et al., 2017; Wu et al., 2019), the majority of the tested associations between pollutants and lipid outcomes were not statistically significant (Table 4). Regarding the Patients group studies (Sade et al., 2016; Chen et al., 2016; Ghosh et al., 2018; McGuinn et al., 2019), a considerable number of the tested associations between pollutants and lipid outcomes were statistically significant (Table 4).

In a short-term scenario, concerning studies about adults from the general population (Chuang et al., 2010; Eze et al., 2015; Bell et al., 2017; Li et al., 2019), we found that statistically significant associations were only found concerning the HDL-C parameter (Chuang et al., 2010; Li et al., 2019) (Table 5). In the elderly, one study reported statistically significant associations between particulate matter and HDL-C, LDL-C and TG (Bind et al., 2016) (Table 5). Regarding the Patients group studies (Sade et al., 2016; Chen et al., 2016; Wang et al., 2018, Yeatts et al., 2007), the majority of the tested associations between pollutants and lipid outcomes were not statistically significant (Table 5).

Table 4
Summary of the statistical significant associations found in the included studies, in a long-term exposure scenario.

Population	Study	Pollutant	Continuous Outcome (Lipid levels)				Categorical Outcome (Yes/No)				
			TC	HDL-C	LDL-C	TG	High TC	Low HDL-C	High LDL-C	High TG	Dyslipidaemia[a]
Adults	Bell et al. (2017)	$PM_{2.5}$		NA							
		BC		**A**							
	Cai et al. (2017)	PM_{10}	NA[a]	NA[a]		**A**[a]					
		NO_2	NA[a]	**A**[a]		**A**[a]					
	Eze et al. (2015)	PM_{10}						NA		NA	
		NO_2						NA		NA	
	Lee et al. (2019)	$PM_{2.5}$						**A**		**A**	
	Shanley et al. (2016)	PM_{10}	**A**[a]	NA[a]	NA[a]	**A**[a]					
	Sorensen et al. (2015)	$PM_{2.5}$	**A**								
		NO_2	**A**								
	Yang et al. (2018a)	PM_1	**A**	**A**	**A**	NA	**A**	**A**	**A**	NA	
		$PM_{2.5}$	**A**	**A**	**A**	**A**	**A**	**A**	**A**	NA	
		PM_{10}	NA[a]	NA[a]	**A**[a]	**A**[a]	NA	NA	NA	**A**	
		NO_2	**A**[a]	**A**[a]	NA[a]	**A**[a]	**A**	NA	NA	NA	
		SO_2	NA	NA	NA	**A**	NA	NA	NA	**A**	
		O_3	**A**	**A**	**A**	**A**	NA	NA	NA	**A**	
	Shin et al. (2019)	PM_{10}									**A**
		NO_2									**A**
		SO_2									**A**
		CO									**A**
		O_3									**A**
Elderly	Chuang et al. (2011)	$PM_{2.5}$	**A**	NA		NA					
		PM_{10}	**A**	NA		NA					
		NO_2	**A**	NA		NA					
		SO_2	NA	NA		NA					
		O_3	**A**	NA		NA					
		CO	NA	NA		NA					
	Wu et al. (2019)	$PM_{2.5}$	NA	**A**	NA	NA					
	Wallwork et al. (2017)	$PM_{2.5}$						NA		NA	
Midlife women in menopausal transition	Wu et al. (2019)	$PM_{2.5}$	NA	**A**	NA	NA					
Children and adolescents	Fioravanti et al. (2018)	$PM_{2.5}$	NA	NA							
		PM_{10}	NA	NA							
		NO_2	NA	NA							
		NO_x	NA	NA							
	Poursafa et al. (2017)	$PM_{2.5}$	NA	NA	**A**	**A**					
Patients	Sade et al. (2016)	$PM_{2.5}$	**A**	**A**	**A**	**A**					
		PM_{10}	**A**	**A**	**A**	**A**					
	Chen et al. (2016)	$PM_{2.5}$	NA	NA	**A**	NA					
		NO_2	NA	**A**	NA	NA					
		O_3	NA	NA	NA	NA					
	Ghosh et al. (2018)	$PM_{2.5}$		**A**		**A**					
		NO_2		**A**		**A**					
		O_3		NA		**A**					
	McGuinn et al. (2019)	$PM_{2.5}$	**A**	**A**	**A**	**A**					

Abbreviations: PM - particulate matter; NO_2—nitrogen dioxide; NOx—nitrogen oxides; SO_2—sulphur dioxide; O_3—ozone; CO – carbon monoxide; BC-Black Carbon; TC – Total cholesterol; HDL-C - High Density Lipoprotein; Cholesterol, LDL-C - Low Density Lipoprotein Cholesterol; TG – Triglycerides; A - Statistical significant association; NA - Not statistical significant association; * Dyslipidaemia condition was defined through autorrepored information, considering dyslipidaemia diagnosed by a physician.

[a] The effect estimate correspondent to this association were included in the meta-analysis.

3.2. Quantitative analysis

From the 3 studies (Shanley et al., 2016; Cai et al., 2017; Yang et al., 2018a) selected for quantitative comparison, it was possible to extract data on 17 effect estimate values covering 7 different pollutant/outcome combinations. Each study present its estimates in different pollutant increments (Table 3).

After conversion, these effect estimates were meta-analysed in seven different analyses regarding each pollutant/outcome combination (Fig. 3). Accordingly, it showed that PM_{10} and NO_2 exposures were significantly associated with increased levels of TG, in a long-term exposure scenario. We found a 3.14% (1.36%–4.95%) increase in TG levels per 10 $\mu g/m^3$ PM_{10} increment and a 4.24% (1.37%–7.19%) increase in TG levels per 10 $\mu g/m^3$ NO_2 increment. Concerning the publication bias assessment, in the case of the meta-analysis reporting results from 3 studies, we found no indication for such source of bias (PM10/TC: p-value of Egger's test = 0.54; PM10/HDL-C: p-value of Egger's test = 0.40; PM10/TG: p-value of Egger's test = 0.63). In the case of the meta-analysis reporting results from 2 studies, publication bias was not assessed as there were inadequate numbers of included studies to apply the test. No significant associations were detected for the remaining pollutant/outcome combinations. Regarding the short-term exposure scenario, the number of effect estimates were insufficient to be meta-analysed for each pollutant/outcome combination. Based on the GRADE approach, all the cumulative evidence from the meta-analysis were considered very low level evidence (Table S4, Supplemental material).

4. Discussion

Despite the few studies included in the meta-analysis, our study suggests that, there is already some epidemiologic evidence supporting the association between PM_{10} and NO_2 exposures and TG levels in the adults from the general population. In a long-term exposure scenario, we found a 3.14% (1.36%–4.95%) increase in TG

Table 5
Summary of the statistical significant associations found in the included studies, in a short-term exposure scenario.

Population	Authors	Pollutant	Continuous Outcome (Lipid levels)				Categorical Outcome (Yes/No)				
			TC	HDL-C	LDL-C	TG	High TC	Low HDL-C	High LDL-C	High TG	Dyslipidaemia[a]
Adults	Bell et al. (2017)	$PM_{2.5}$		NA							
	Chuang et al. (2010)	PM_{10}		**A**	NA	NA					
		NO_2		NA	NA	NA					
		O_3		NA	NA	NA					
		CO		NA	NA	NA					
	Eze et al. (2015)	PM_{10}						NA		NA	
		NO_2						NA		NA	
	Li et al. (2019)	$PM_{2.5}$		NA							
		PNC_{5-50}		NA							
		PNC_{50-100}		**A**							
		$PNC_{100-500}$		NA							
		NO_2		**A**							
		SO_2		**A**							
		BC		**A**							
		CO		NA							
Elderly	Bind et al. (2016)	$PM_{2.5}$		**A**	**A**	**A**					
		BC		**A**	**A**	**A**					
	Wu et al. (2019)	$PM_{2.5}$	NA	NA	NA	NA					
	Wallwork et al. (2017)	$PM_{2.5}$						NA		NA	
Midlife women in menopausal transition	Wu et al. (2019)	$PM_{2.5}$	NA	NA	NA	NA					
Patients	Sade et al. (2016)	$PM_{2.5}$	NA	NA	**A**	NA					
		PM_{10}	NA	NA	**A**	NA					
	Chen et al. (2016)	$PM_{2.5}$	**A**	NA	**A**	NA					
		NO_2	NA	NA	NA	NA					
		O_3	NA	NA	NA	NA					
	Wang et al. (2018)	PM_{10}	**A**	**A**	**A**	NA					
		NO_2	NA	**A**	**A**	**A**					
		SO_2	**A**	NA	**A**	**A**					
	Yeatts et al. (2007)	$PM_{2.5}$	NA			NA					

Abbreviations: PM - particulate matter; PNC – ultrafine particulate number concentration; NO_2–nitrogen dioxide; NO_x–nitrogen oxides; SO_2–sulphur dioxide; O_3–ozone; CO – carbon monoxide; BC-Black Carbon; TC – Total cholesterol; HDL-C - High Density Lipoprotein; Cholesterol, LDL-C - Low Density Lipoprotein Cholesterol; TG – Triglycerides; A - Statistical significant association; NA - Not statistical significant association

[a] Dyslipidaemia condition was defined through autorrepored information, considering dyslipidaemia diagnosed by a physician.

levels per 10 $\mu g/m^3$ PM_{10} increment and a 4.24% (1.37%–7.19%) increase in TG levels per 10 $\mu g/m^3$ NO_2 increment.

The biological mechanisms explaining the effect of AAP on lipid profile parameters are still not very clear but one hypothesis is that the oxidative stress and the systemic inflammation caused by AAP exposure could induce a dysfunction of the lipid metabolism (Li et al., 2013). Another plausible mechanism is the DNA methylation of genes related to lipid metabolism caused by exposure to AAP (Li et al., 2018). Nevertheless, to the best of our knowledge, there is no plausible biological mechanism that could explain a different deleterious effect of the AAP on TG levels compared to the other lipid profile parameters, as our results suggest. Consequently, we hypothesize that our meta-analysis in not correctly detecting the deleterious effect of ambient air pollutants on the other lipid profile parameters and this may be due to the bias introduced by the inclusion of lipid-lowering medicated participants in the included studies. In fact, lipid-lowering medication was not considered in the 3 studies quantitatively analysed, resulting in lower than the real values analysed in this study. Taking into account that statins are still used as the first line medication to lower lipid profile parameters levels and achieve substantial cholesterol reduction, evidence shows that reduction in TG levels are more modest when using statins (Miller et al., 2008; Watts and Karpe, 2011). Thus we hypothesize that medicated participants who will have the values of the other lipid parameters controlled, will most likely continue to show uncontrolled TG values. This can explain the stronger associations between ambient air pollutants exposure and TG levels in the few included studies because the confounding effect of medication is lower or absent for this parameter. However, this hypothesis cannot be guaranteed because use of other drugs targeted at TG has become increasingly frequent to deal with high TG in addition to statins, especially in the most recent years (Ahn and Choi, 2015) or the use of non-pharmacological therapeutics such as diet behaviour modifications and physical exercise practice that also will have impact on TG levels. Consequently, to validate this hypothesis, more information about the medicated participants of the various included studies would be needed.

Through our systematic review, we also verify that the most studied ambient air pollutant, among the 22 considered studies, was particulate matter (PM). This could be a consequence of a publication bias, that was not possibly to evaluate conveniently due to the small number of included studies, but it remains unclear if some pollutants were considered and not reported in the articles. It is also plausible to assume that the deleterious effect of the gaseous pollutants, namely NO_2, SO_2, O_3 or CO, on lipid profile parameters are less explored and must be considered in future studies. In fact, there is more available evidence supporting the deleterious effect of the particulate matter on cardiovascular health (Fiordelisi et al., 2017; Hamanaka and Mutely, 2018). However, available evidence supports the importance of the gaseous pollutants on cardiovascular health (Basu et al., 2017), advising to explore its effects also on the lipid profile. Another plausible reason is that PMs data could be the most used due its greater spatial and temporal availability.

Additionally, we found a huge diversity of methods to assess the air pollutants exposure which make it difficult to compare published results. The traditional method of air pollution exposure assessment is through direct measurements obtained from fixed air quality network sites (Chuang et al., 2010; Chuang et al., 2010; Poursafa et al., 2017). This method is still a commonly used method but some studies reported in this systematic review already used

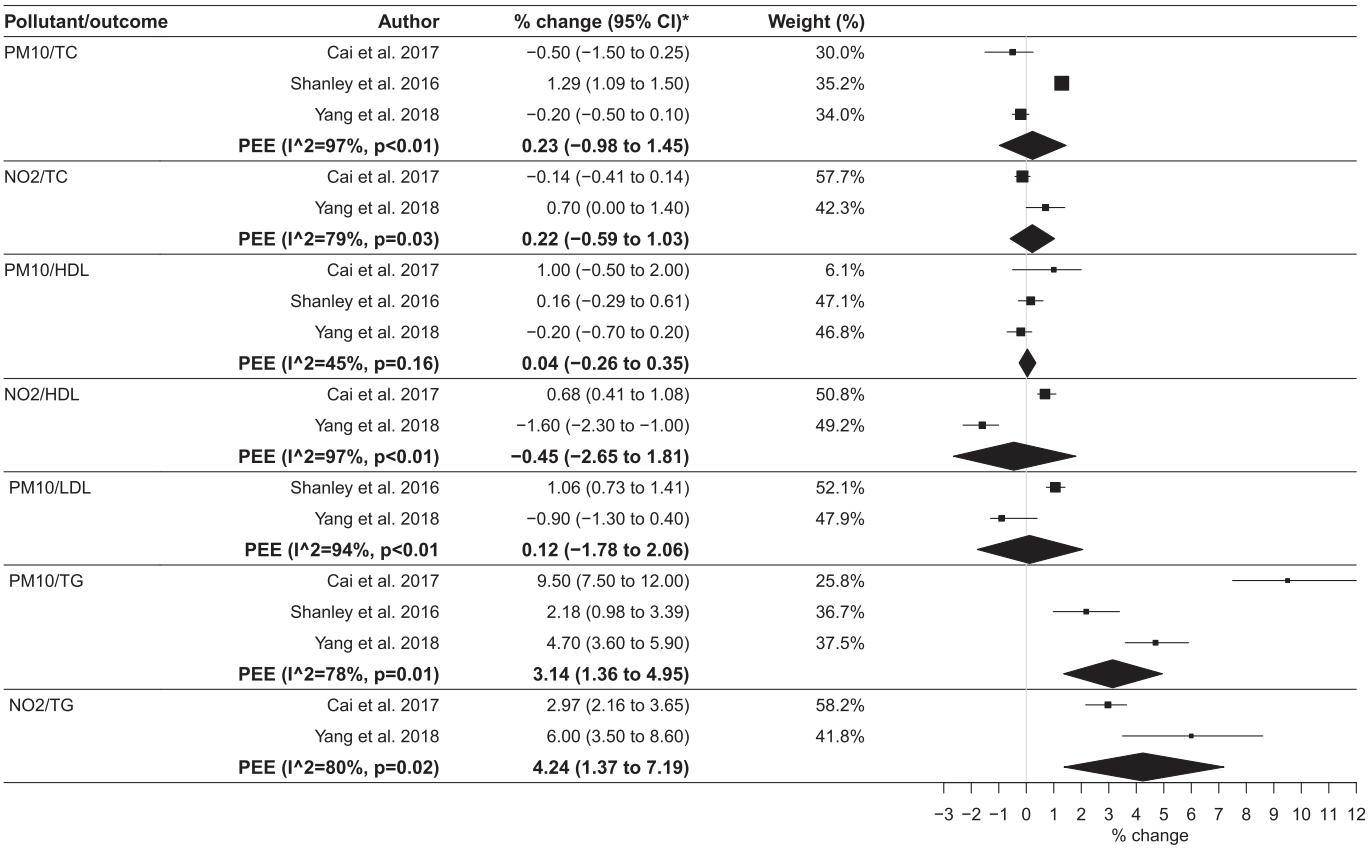

Fig. 3. Forestplots of the seven meta-analyses performed regarding each pollutant/outcome combination in a long-term exposure scenario (*percentage change in the outcome per 10 μg/m^3 pollutant increase. Abbreviations: PEE = Pooled effect estimate; I^2 = measure of between-study heterogeneity; p = Cochran's Q test *p-value*)

more complex approaches namely spatiotemporal hybrid modelling (Sade et al., 2016; Bell et al., 2017; Wallwork et al., 2017). Although it is expected that there is a higher percentage of misclassification associated with traditional methods compared to more advanced methods (Steinle et al., 2013), it was not possible to detect a clear pattern of influence of exposure misclassification on estimated values in our study. Regarding this issue, it is still important to mention that even these more sophisticated methods are problematic regarding their capacity to assess the real individual exposure and the use of new technology, namely GPS, smartphones or smaller pollution sensors are promising new methods to assess more real individualized exposures (Hoek, 2017) and reduce exposure misclassification. So, more adequate approaches to quantify the individual air pollution exposure is warranted in order to standardize effect measures obtained from different epidemiological studies.

Another important consideration about our systematic review and meta-analysis is related to residual confounding. Although all studies reported effect estimates values based on models adjusted for multiple confounding variables, there is not consistency in the chosen confounding variables among the selected studies and important covariates were not considered in some studies. This could led to a considerable residual confounding related to the number and type of variables not included in the models. When we look at the 3 studies that we meta-analysed, all of them include age, sex, smoking status, individual socioeconomic factors as confounding variables, but important variables related to area-level socioeconomic status, for example, were only considered by two of them (Shanley et al., 2016; Yang et al., 2018a). To clarify the influence of each confounding variable in the effect estimates values, more information would be necessary and, consequently, it is recommended to provide supplemental data regarding available data and the modelling process in futures studies.

The present meta-analysis includes a small number of studies found in the literature review, which does not allow sensitivity analyses to be performed and it would be important for validation of the meta-analysis results. Moreover, the between-study heterogeneity is very high for nearly all meta-analyses, which might have reduced the confidence of the cumulative evidence.

Effect estimates included in the present meta-analysis were based on a single-pollutant model and interactions between the ambient air pollutants were not evaluated. Despite multipollutant models being difficult to implement and validate, it is known that there are important interactions between the pollutants, namely the potential additive effects of multiple pollutants and they should be considered in future studies (Oakes et al., 2014; Davalos et al., 2017). Finally, the outcome assessment in the different studies was not uniform. The definitions of dyslipidaemia conditions varied in each study which compromises the comparison of the effect estimates of the different studies (Eze et al., 2015; Wallwork et al., 2017; Yang et al., 2018a; Lee et al., 2019; Shin et al., 2019). Additionally, while some studies performed lipid profile parameters determination in a fasting condition, other considered the non-fasting state, which could be considered a source of bias. It is well known that while cholesterol levels only display modest postprandial variations, TG show significant postprandial elevations according to the diet content (Cohen et al., 1988; Ginsberg et al., 1994). However, in the study in which participants were all in a fasting state (Yang et al., 2018a), the effect of PM_{10} and NO_2 exposures on TG levels remains statistically significant.

5. Conclusions and recommendations

To our knowledge, this is the first study approaching the systematic review and meta-analysis of epidemiologic evidence on the association between AAP exposure and lipid profile parameters or dyslipidaemia conditions. Despite the very inclusive research strategy used, including no restrictions in the study design or population groups, we found only a few number of recently published studies on the association between air pollution and lipid profile. Nevertheless, we report results that could help to guide future research in these area. Moreover, given the high prevalence of dyslipidaemia (Farzadfar et al., 2011) and the increasing AAP levels (Cohen et al., 2017), we consider that our findings are of considerable and growing global public health importance. We suggest that if air pollution were continuously reduced, it could potentially reduce the incidence of dyslipidaemias and therefore the incidence of cardiovascular events.

As recommendations in the future studies about the association between exposure to ambient air pollutants and lipid profile parameters or dyslipidaemia conditions, we suggest further investigation of the gaseous pollutants exposure, that were less frequently included. We also recommend to explore the potential additive effects of multiple pollutants, as well as developing more robust spatiotemporal models to assess air pollution exposure more precisely.

Competing financial interests

The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.113036.

References

Ahn, C.H., Choi, S.H., 2015. New drugs for treating dyslipidemia: beyond statins. DMJ 39 (2), 87–94.
Araujo, J.A., 2010. Particulate air pollution, systemic oxidative stress, inflammation, and atherosclerosis. Air Qual. Atmos. Health 4, 79–93.
Atkinson, R.W., Cohen, A., Mehta, S., et al., 2012. Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. Air Qual. Atmos. Health 5 (4), 383–391.
Balshem, H., Helfand, M., Schünemann, H.J., et al., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64 (4), 401–406.
Basu, R., Malig, B., Broadwin, R., et al., 2017. Association between gaseous air pollutants and inflammatory, hemostatic and lipid markers in a cohort of midlife women. Environ. Int. 107, 131–139.
Bell, G., Mora, S., Greenland, P., et al., 2017. Association of air pollution exposures with high-density lipoprotein cholesterol and particle number: the multiethnic study of atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 37, 976–982.
Bind, M.A., Peters, A., Koutrakis, P., et al., 2016. Quantile regression analysis of the distributional effects of air pollution on blood pressure, heart rate variability, blood lipids, and biomarkers of inflammation in elderly American men: the Normative Aging Study. EHP 124 (8), 1189.
Brook, R.D., 2008. Cardiovascular effects of air pollution. Clin. Sci. 115 (6), 175–187.
Brook, R.D., Rajagopalan, S., Pope, C.A., et al., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121 (21), 2331–2378.
Cai, Y., Hansell, A.L., Blangiardo, M., et al., 2017. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. EHJ 38 (29), 2290–2296.
Chen, Z., Salam, M.T., Toledo-Corral, C., et al., 2016. Ambient air pollutants have adverse effects on insulin and glucose homeostasis in Mexican Americans. Diabetes Care dc151795.
Chuang, K.J., Yan, Y.H., Cheng, T.J., 2010. Effect of air pollution on blood pressure, blood lipids, and blood sugar: a population-based approach. JOEM 52 (3), 258–262.
Chuang, K.J., Yan, Y.H., Chiu, S.Y., et al., 2011. Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. Occup. Environ. Med. 68 (1), 64–68.
Cohen, A.J., Brauer, M., Burnett, R., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. The Lancet 389 (10082), 1907–1918.
Cohen, J.C., Noakes, T.D., Benade, A.J., et al., 1988. Serum triglyceride responses to fatty meals: effects of meal fat content. Am. J. Clin. Nutr. 47, 825–827.
Davalos, A.D., Luben, T.J., Herring, A.H., et al., 2017. Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures. Ann. Epidemiol. 27 (2), 145–153.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
EPA (United States Environmental Protection Agency), 2011. Vocabulary catalog list detail—integrated risk information system (IRIS) glossary. Available: https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary. (Accessed 25 October 2018).
Eze, I.C., Schaffner, E., Foraster, M., et al., 2015. Long-term exposure to ambient air pollution and metabolic syndrome in adults. PLoS One 10 (6), e0130337.
Farzadfar, F., Finucane, M.M., Danaei, G., et al., 2011. National, regional and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 377, 578–586.
Fioravanti, S., Cesaroni, G., Badaloni, C., et al., 2018. Traffic-related air pollution and childhood obesity in an Italian birth cohort. Environ. Res. 160, 479–486.
Fiordelisi, A., Piscitelli, P., Trimarco, B., et al., 2017. The mechanisms of air pollution and particulate matter in cardiovascular diseases. Heart Fail. Rev. 22 (3), 337–347.
Ghosh, R., Gauderman, W.J., Minor, H., et al., 2018. Air pollution, weight loss and metabolic benefits of bariatric surgery: a potential model for study of metabolic effects of environmental exposures. Pediatr. Obes. 13 (5), 312–320.
Ginsberg, H.N., Karmally, W., Siddiqui, M., et al., 1994. A dose-response study of the effects of dietary cholesterol on fasting and postprandial lipid and lipoprotein metabolism in healthy young men. Arterioscler. Thromb. Vasc. Biol. 14, 576–586.
Gordon, M., Lumley, T., 2017. Forestplot: Advanced Forest Plot Using 'grid' Graphics.
Hamanaka, R.B., Mutely, G.M., 2018. Particulate matter air pollution: effects on the cardiovascular system. Front. Endocrinol. 9.
Harrop, O., 2002. Air Quality Assessment and Management—A Practical Guide. Clay's Library of Health and the Environment.
Higgins, J.P., Thompson, S.G., Deeks, J.J., et al., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.
Higgins, J.P., White, I.R., Anzures-Cabrera, J., 2008. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. Stat. Med. 27 (29), 6072–6092.
Higgins, J.P.T., Green, S. (Eds.), 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from. http://handbook.cochrane.org.
Hoek, G., 2017. Methods for assessing long-term exposures to outdoor air pollutants. Curr. Environ. Health Rep. 4 (4), 450–462.
JCDCG (Joint Committee for Developing Chinese Guidelines), 2007. Chinese guidelines on prevention and treatment of dyslipidemia in adults. Chin. J. Epidemiol. 35, 390–419.
Lee, S., Park, H., Kim, S., et al., 2019. Fine particulate matter and incidence of metabolic syndrome in non-CVD patients: a nationwide population-based cohort study. Int. J. Hyg Environ. Health 222 (3), 533–540.
Li, H., Chen, R., Cai, J., et al., 2018. Short-term exposure to fine particulate air pollution and genome-wide DNA methylation: a randomized, double-blind, crossover trial. Environ. Int. 120, 130–136.
Li, J., Zhou, C., Xu, H., et al., 2019. Ambient air pollution is associated with HDL (high-density lipoprotein) dysfunction in healthy adults. Arterioscler. Thromb. Vasc. Biol. 39 (3), 513–522.
Li, R., Navab, M., Pakbin, P., et al., 2013. Ambient ultrafine particles alter lipid metabolism and HDL antioxidant capacity in LDLR-null mice. J. Lipid Res. 54, 1608–1615.
McGuinn, L.A., Schneider, A., McGarrah, R.W., et al., 2019. Association of long-term PM2. 5 exposure with traditional and novel lipid measures related to cardiovascular disease risk. Environ. Int. 122, 193–200.
Meo, S.A., Suraya, F., 2015. Effect of environmental air pollution on cardiovascular

diseases. Eur. Rev. Med. Pharmacol. Sci. 19 (24), 4890–4897.
Miller, M., Cannon, C.P., Murphy, S.A., et al., 2008. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. JACC (J. Am. Coll. Cardiol.) 51, 724–730.
Moher, D., Liberati, A., Tetzlaff, J., et al., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Am. Coll. Physicians 151 (4), 264–269.
Moola, S., Munn, Z., Tufanaru, C., et al., 2017. Chapter 7: systematic reviews of etiology and risk. In: Aromataris, E., Munn, Z. (Eds.), Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. Available from: https://reviewersmanual.joannabriggs.org/.
NCEP-ATP III, 2002. Third report of the national cholesterol education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III). Final report. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation 106 (25), 3143–3421.
Oakes, M., Baxter, L., Long, T.C., 2014. Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environ. Int. 69, 90–99.
Poursafa, P., Amin, M.M., Mansourian, M., et al., 2017. Association of exposure to fine particulate matter and risk factors of non-communicable diseases in children and adolescents. Int. J. Pediatr. 5 (10), 5871–5880.
R Core Team, 2017. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Reiner, Z., Catapano, A.L., De Backer, G., et al., 2011. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the european society of cardiology (ESC) and the european atherosclerosis society (EAS). Eur. Heart J. 32 (14), 1769–1818.
Sade, Y., Kloog, M., Liberty, I., et al., 2016. The association between air pollution exposure and glucose and lipids levels. J. Clin. Endocrinol. Metab. 101 (6), 2460–2467.
Schwarzer, G., 2007. meta: an R package for meta-analysis. R. News 7 (3), 40–45.
Shanley, R.P., Hayes, R.B., Cromar, K.R., et al., 2016. Particulate air pollution and clinical cardiovascular disease risk factors. Epidemiology 27 (2), 291.
Shin, J., Choi, J., Kim, K.J., 2019. Association between long-term exposure of ambient air pollutants and cardiometabolic diseases: a 2012 Korean Community Health Survey. Nutr. Metab. Cardiovasc. Dis. 29 (2), 144–151.
Simkhovich, B.Z., Kleinman, M.T., Kloner, R.A., 2008. Air pollution and cardiovascular injury: epidemiology, toxicology, and mechanisms. J. Am. Coll. Cardiol. 52 (9), 719–726.
Sørensen, M., Hjortebjerg, D., Eriksen, K.T., et al., 2015. Exposure to long-term air pollution and road traffic noise in relation to cholesterol: a cross-sectional study. Environ. Int. 85, 238–243.
Stroup, D.F., Berlin, J.A., Morton, S.C., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama 283 (15), 2008–2012.
Steinle, S., Reis, S., Sabel, C.E., 2013. Quantifying human exposure to air pollution—moving from static monitoring to spatio-temporally resolved personal exposure assessment. Sci. Total Environ. 443, 184–193.
Wallwork, R.S., Colicino, E., Zhong, J., et al., 2017. Ambient fine particulate matter, outdoor temperature, and risk of metabolic syndrome. Am. J. Epidemiol. 185 (1), 30–39.
Wang, M., Zheng, S., Nie, Y., et al., 2018. Association between short-term exposure to air pollution and dyslipidemias among type 2 diabetic patients in Northwest China: a population-based study. Int. J. Environ. Res. Public Health 15 (4), 631.
Watts, G.F., Karpe, F., 2011. Triglycerides and atherogenic dyslipidaemia: extending treatment beyond statins in the high-risk cardiovascular patient. Heart 97 (5), 350–356.
WHO (World Health Organization), 2016. Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease. Available: https://www.who.int/phe/publications/air-pollution-global-assessment/en/. (Accessed 25 October 2018).
WHO (World Health Organization), 2018. Ambient (Outdoor) Air Quality and Health. Available: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health. (Accessed 20 May 2019).
Wu, W., Broadwin, R., Basu, R., et al., 2019. Associations between fine particulate matter and changes in lipids/lipoproteins among midlife women. Sci. Total Environ. 654, 1179–1186.
Yang, B.Y., Bloom, M.S., Markevych, I., et al., 2018a. Exposure to ambient air pollution and blood lipids in adults: the 33 Communities Chinese Health Study. Environ. Int. 119, 485–492.
Yang, B.Y., Qian, Z., Howard, S.W., et al., 2018b. Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. Environ. Pollut. 235, 576–588.
Yang, B.Y., Guo, Y., Markevych, I., et al., 2019. Association of long-term exposure to ambient air pollutants with risk factors for cardiovascular disease in China. JAMA Network Open 2 (3) e190318-e190318.
Yeatts, K., Svendsen, E., Creason, J., et al., 2007. Coarse particulate matter (PM2.5–10) affects heart rate variability, blood lipids, and circulating eosinophils in adults with asthma. Environ. Health Perspect. 115 (5), 709.