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DE DOCTEUR EN MÉDECINE

La relation entre l'exposition résidentielle à la pollution atmosphérique et les micro-ARN circulants chez les adultes vivant en zone urbaine du nord de la France

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Avertissement

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Avant-propos

Cette thèse, réalisée sous la direction de Luc Dauchet, a donné lieu article publié en 2023 dans la revue Environment International : Audrey Hubert, Djamal Achour, Céline Grare, Gianni Zarcone, Manon Muntaner, Aghiles Hamroun, Victoria Gauthier, Philippe Amouyel, Régis Matran, Farid Zerimech, Jean-Marc Lo-Guidice, Luc Dauchet. *The relationship between residential exposure to atmospheric pollution and circulating miRNA in adults living in an urban area in northern France*. Environment International, Volume 174, 2023, 107913, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2023.107913 .

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Résumé

Introduction : Les micro-ARN sont des facteurs de régulation épigénétique capables de réprimer l'expression des gènes cibles et pourraient jouer un rôle dans les effets de la pollution atmosphérique sur la santé. L'objectif de la présente étude en population générale était d'examiner l'association entre l'expression des micro-ARN et l'exposition résidentielle à long terme aux PM_{10} et au NO_2.

Méthode : Nous avons inclus 998 participants adultes non-fumeurs issus de l'enquête transversale ELISABET (2010-2014) dans la région urbaine de Lille, en France. Les niveaux moyens annuels de pollution résidentielle ont été estimés à l'aide d'un système de modélisation de dispersion atmosphérique. Dix micro-ARN ont été sélectionnés sur la base des données disponibles dans la littérature, ainsi que deux micro-ARN de référence (miR-93-5p et miR-191-5p), et ont été quantifiés par RT-qPCR. Des modèles de régression linéaire multivariée ont été utilisés pour étudier l'association entre les micro-ARN et la pollution atmosphérique. Le seuil de signification statistique (après correction pour le taux de fausse découverte) a été fixé à $p < 0,1$.

Résultats : L'exposition annuelle moyenne entre 2011 et l'année d'inclusion était de 26,4 ± 2,0 µg/m³ pour les PM_{10} et de 24,7 ± 5,1 µg/m³ pour le NO_2. Chaque augmentation de 2 µg/m³ d'exposition aux PM_{10} était associée à une augmentation de 8,6 % (IC 95 % [3,1 ; 14,3]; $p_{FDR} = 0,019$) de l'expression de miR-451a. Une augmentation de 5 µg/m³ de l'exposition au NO_2 était associée à une augmentation de 5,3 % (IC 95 % [0,7 ; 10]; $p_{FDR} = 0,056$) de l'expression de miR-451a, une diminution de 3,6 % (IC 95 % [-6,1 ; -1,1]; $p_{FDR} = 0,052$) de l'expression de miR-223-

3p, une diminution de 3,8 % (IC 95 % [-6,8 ; -0,7]; p_{FDR} = 0,079) de l'expression de miR-28-3p, une diminution de 4,3 % (IC 95 % [-7,7 ; -0,8]; p_{FDR} = 0,055) de l'expression de miR-146a-5p et une diminution de 4,0 % (IC 95 % [-7,4 ; -0,4]; p_{FDR} = 0,059) de l'expression de miR-23a-5p. La différence entre les deux micro-ARN de référence miR-93-5p et miR-191-5p était également associée à l'exposition aux PM_{10} et au NO_2.

Conclusion : Nos résultats suggèrent que les micro-ARN circulants pourraient être des biomarqueurs précieux pour évaluer les effets de la pollution atmosphérique.

Abstract

Introduction: MicroRNAs are epigenetic regulatory factors capable of silencing the expression of target genes and might mediate the effects of air pollution on health. The objective of the present population-based study was to investigate the association between microRNA expression and long-term, residential exposure to atmospheric PM_{10} and NO_2.

Method: We included 998 non-smoking adult participants from the cross-sectional ELISABET survey (2010-2014) in the Lille urban area of France. The mean residential annual pollution levels were estimated with an atmospheric dispersion modelling system. Ten microRNAs were selected on the basis of the literature data, together with two housekeeping microRNAs (miR-93-5p and miR-191-5p) and were quantified with RT-qPCRs. Multivariate linear regression models were used to study the association between microRNAs and air pollution. The threshold for statistical significance (after correction for the FDR) was set to $p<0.1$.

Results:

The mean annual exposure between 2011 and the year of inclusion was 26.4 ± 2.0 $\mu g/m^3$ for PM_{10} and 24.7 ± 5.1 $\mu g/m^3$ for NO_2. Each 2 $\mu g/m^3$ increment in PM_{10} exposure was associated with an 8.6% increment (95%CI [3.1; 14.3]; p_{FDR} = 0.019) in miR-451a expression. A 5 $\mu g/m^3$ increment in NO_2 exposure was associated with a 5.3% increment ([0.7; 10]; p_{FDR}= 0.056) in miR451a expression, a 3.6% decrement (95%CI [-6.1; -1.1]; p_{FDR} = 0.052) in miR-223-3p expression, a 3.8% decrement (95%CI[-6.8; -0.7]; p_{FDR} = 0.079) in miR-28-3p expression, a 4.3% decrement (95%CI [-7.7; -0.8];

p_{FDR} = 0.055) in miR-146a-5p expression, and a 4.0% decrement (95% CI[-7.4; -0.4]; p_{FDR} = 0.059) in miR-23a-5p expression. The difference between the two housekeeping microRNAs miR-93-5p and miR-191-5p was also associated with PM_{10} and NO_2 exposure.

Conclusion: Our results suggest that circulating miRNAs are potentially valuable biomarkers of the effects of air pollution.

Liste des abréviations

miRNA (miR)	Micro-ARN
PM_{10}	Particular matter with diameter < 10 µm (Particule en suspension de diamètre inférieur à 10 µm)
NO_2	Dioxyde d'azote
FDR	False discovery rate (Taux de fausse découverte)
SD	Standard deviation (écart-type)
IQR	Interquartile range (écart interquartile)
BMI	Body mass index (Indice de masse corporelle)
HbA1c	Glycosylated hemoglobin (Hémoglobine glyquée)
HDL	High-density lipoprotein (Lipoprotéines à haute densité)
LDL	Low-density lipoprotein (Lipoprotéine à faible densité)
Ct	Cycle threshold (Seuil de cycle)
hs-CRP	High-sensitivity C-reactive protein (Protéine C-réactive à haute sensibilité)

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Contexte

I. La pollution atmosphérique

La pollution atmosphérique a un impact considérable sur la santé humaine. En 2019, l'OMS estimait que la pollution atmosphérique était responsable de 4,2 millions de décès prématurés chaque année (1).

Les particules fines, les oxydes d'azote et d'autres polluants présents dans l'air sont associés à une augmentation de la mortalité et de la morbidité à travers le monde, allant des maladies pulmonaires chroniques et des maladies cardiovasculaires à des troubles métaboliques et divers cancers (2–4).

Parmi les nombreux polluants atmosphériques les particules fines constituent un problème majeur. Ces particules, comme les PM_{10}, d'un diamètre inférieur à 10 micron, peuvent pénétrer profondément dans les voies respiratoires et entrer dans la circulation sanguine, déclenchant des réponses inflammatoires qui perturbent le fonctionnement normal des organes (5,6).

Les recherches continuent d'explorer les voies biologiques spécifiques par lesquelles la pollution atmosphérique influence la santé, notamment à travers l'analyse de biomarqueurs d'inflammation et de modifications épigénétiques, afin de mieux comprendre et atténuer ces impacts sanitaires.

II. L'épigénétique

L'épigénétique est l'étude des mécanismes qui modifient de manière réversible, transmissible et adaptative l'expression des gènes sans en changer la séquence d'ADN. Contrairement à la génétique, où les mutations affectent directement le code ADN et sont généralement irréversibles, les changements

épigénétiques sont réversibles et peuvent être influencés par divers facteurs environnementaux (7). Les principaux mécanismes épigénétiques comprennent la méthylation de l’ADN, les modifications des histones et les ARN non codants, notamment les micro-ARN (miARN).

Les micro-ARN sont de petits ARN non codants, simple brin, qui jouent un rôle crucial dans la régulation de l'expression des gènes en inhibant leur traduction en protéines (8). En se liant aux ARN messagers (ARNm), les micro-ARN inhibent leur traduction en protéines, ce qui influence divers processus biologiques clés tels que la croissance cellulaire, la différenciation, l'apoptose et le métabolisme (8). Cette capacité à moduler l'expression de nombreux gènes rend les micro-ARN cruciaux dans la régulation de fonctions cellulaires normales et pathologiques (9).

Des dérégulations des micro-ARN sont associées à une gamme étendue de maladies, y compris les cancers, les maladies cardiovasculaires et les troubles auto-immuns (9–11). En outre, les micro-ARN jouent un rôle clé dans la régulation de la structure de la chromatine et de l'expression génique, influençant des processus tels que la tumorigenèse (12).

Leur potentiel en tant que biomarqueurs épigénétiques et cibles thérapeutiques représente un domaine de recherche prometteur (13–15). En affectant l'expression de gènes critiques, les micro-ARN offrent des perspectives significatives pour le diagnostic et le traitement de diverses maladies.

En résumé, l'épigénétique aide à comprendre comment des facteurs externes comme la pollution atmosphérique peuvent avoir des impacts à long terme sur la santé humaine en modifiant l'expression des gènes. Les micro-ARN, qui jouent un rôle crucial dans la régulation épigénétique, sont particulièrement importants dans ce contexte.

III. Objectifs

L'objectif principal de notre étude était d'étudier la relation entre l'exposition résidentielle à long terme, de deux polluant atmosphériques ; les PM_{10} et le NO_2, et les niveaux circulants de dix micro-ARN chez des habitants de la région lilloise. L'objectif secondaire était d'étudier la relation entre a présence de biomarqueur de l'inflammation et les micro-ARN circulants.

Article

I. Introduction

Air pollution has a major impact on health in general and on lung, cardiovascular and metabolic diseases in particular (12,16). The association between air pollution and health is probably mediated by a number of biological pathways, which can be investigated by monitoring biomarkers of epigenetic modification or inflammation (17).

Epigenetic mechanisms have attracted increasing research interest in recent years because they can explain the interactions between environmental exposures and health-related events. Epigenetics can control gene expression through various mechanisms, ranging from structural changes in chromatin to post-transcriptional regulation. MicroRNAs (miRNAs) constitute a large family of small, non-coding post-transcriptional regulators that silence the expression of target genes by pairing with the cognate mRNAs, which leads to mRNA degradation or the abrogation of translation. Given that miRNAs modulate the expression of more than 60% of the genome, they regulate a wide variety of biological processes and are believed to be involved in the pathogenesis of many diseases, including cancer (9).

The expression of miRNAs can be tissue- and organ-specific (18). However, highly stable protein-bound miRNAs have also been detected in the majority of biological fluids, and particularly in the bloodstream (19–22). These circulating miRNAs might be either actively secreted by cells as mediators for intercellular and interorgan communication or passively released from dead cells after apoptosis, necrosis, tumor growth or tissue damage (19,23).

Several studies have reported that environmental exposure can induce alterations in the miRNA profile (24–28). Given that the level of miRNA expression

varies from one tissue to another, the profile of circulating miRNAs might reflect the specific responses of tissues exposed to a harmful environment (29). Circulating miRNAs (whether actively secreted or passively released) are therefore promising new non-invasive biomarkers of tissue damage (29).

The association between air pollution and miRNA has been only investigated in studies of small numbers of participants. The number of adults studied ranged from 14 (30) to 153 (31), and one study included 273 children (32). Furthermore, there are few published data on the association between miRNAs and long-term exposure to air pollution. Hence, the objective of the present study was to evaluate the association between mean long-term (annual) residential exposure to PM_{10} and NO_2 and levels of a number of miRNAs thought to be modified by air pollution and to mediate the impact of air pollution on health.

II. Materials and methods

1- Study population

We included male and female non-smoking adults (aged from 40 to 64) having resided in the Lille urban area of northern France for the previous 5 years. These adults were participating in the population-based, cross-sectional Enquête Littoral Souffle Air Biologie Environnement (ELISABET) epidemiological population survey, conducted between 2010 and 2013 in the Dunkirk and Lille areas. The study's methodology has been described in detail elsewhere (16,17,33). Briefly, the participants were selected from electoral rolls by random sampling, with stratification for sex, age and city area (Lille or Dunkirk), and were contacted in random order. Data were collected at home or (occasionally) during a consultation in a healthcare establishment. A blood sample was collected during the same visit. We excluded

pregnant women, incarcerated individuals, people under legal guardianship, people unable to give their informed consent, and people lacking French social security coverage. In compliance with the French legislation on biomedical research, the study protocol was approved by the local investigational review board (*CPP Nord Ouest IV, Lille, France; reference: 2010-A00065-34; ClinicalT rials.gov identifier: NCT02490553*). All the participants provided their written, informed consent to participation in the study.

With a view to increasing the study's statistical power for a small number of subjects (thus limiting the cost of analysis), we included participants from the Lille urban area only because the standard deviation of the residential air PM_{10} level was higher in Lille than in Dunkirk (1.936 µg/m^3 versus 0.999 µg/m^3, respectively). To limited missing data and enable subsequent genetic studies, we included participants of Caucasian origin with data on genetic variables. Lastly, we excluded individuals without acceptable spirometry data and those lacking a fasting blood sample for the biomarker assay.

2- Air pollution measurements

The estimation of residential air pollution exposure has been described previously (16,34,35). In brief, the annual mean concentrations of PM_{10} and NO_2 over the period from 2010 to 2013 were taken from estimates produced by ATMO–Nord Pas de Calais, using an atmospheric dispersion modelling system. The latter incorporated meteorological, topographic and land-use data, pollutant emissions from natural sources and those related to human activity, and ambient air pollution data from monitoring stations. Concentration maps for PM_{10} and NO_2 in Lille are shown on the ATMO website (36). We applied a spatial resolution of 25 × 25 m. Each

participant’s place of residence was located within a 25 m grid. We assessed the annual exposure levels at the place of residence as the mean value of the four closest points in the grid, weighted by the inverse square distance to each point (16,35). The residential exposure was defined as the mean annual exposure at the residential address from 2010 to the year of inclusion.

3- miRNAs of interest

In the present study, we assayed eight circulating miRNAs in plasma prepared from an EDTA blood sample from each study participant: miR21-5p, miR-28-3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, and miR-223-3p. These miRNAs were selected on the basis of the literature data because they are reportedly deregulated after exposure to various environmental air pollutants and/or in patients with lung disease possibly related to environmental exposure. Indeed, previous studies reported changes in the expression of miR-21-5p, miR-28- 3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, and miR-223-3p following exposure to particulate matter of various aerodynamic diameter (coarse, fine or ultrafine particles), and/or to other gaseous pollutants related to traffic or industrial/biomass combustion(26,31,37–43). On the other hand, the link between the deregulation of miR-21- 5p, miR-30b-5p, miR-126-3p, miR-146a-5p, miR-222-3p or miR-223-3p and the pathogenesis chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, cystic fibrosis or lung cancer has also been described (43–48). Four additional miRNAs were assayed: miR-23a-3p and miR-451a as controls for hemolysis and blood cell contamination (49,50), and miR-93-5p and miR-191-5p as endogenous reference genes for data normalization, as described previously (51).

The stability of these endogenous miRNAs was confirmed using NormFinder software (52).

4- miRNA assays

For miRNA extraction, 200 µL of plasma samples were incubated for 5 min at room temperature with five volumes of Qiazol Lysis Reagent (Qiagen, Courtaboeuf, France) containing 1 µg of the extraction enhancer MS2 bacteriophage RNA (Sigma-Aldrich, Saint Quentin Fallavier, France). After mixing with 200 µL of chloroform and incubation for 2 to 3 min at room temperature, the samples were centrifuged at 12,000 g for 15 min at 4°C. The RNAs were then extracted from the aqueous phase using the miRNeasy Serum/Plasma kit and the QIAcube instrument, according to the supplier's instructions (Qiagen). The purity and quantity of RNAs were assessed by spectrophotometric analysis (the Spark multimode microplate reader equipped with the NanoQuant Plate™; Tecan, M¨ annedorf, Switzerland).

Circulating miRNAs were reverse-transcribed using 2 µL of extracted RNAs and the TaqMan® Advanced miRNA cDNA Synthesis Kit, according to manufacturer's instructions (ThermoFisher Scientific, Courtaboeuf, France). Briefly, the synthesis of cDNAs started by 3′ poly(A) tailing and 5′ ligation of an adaptor sequence to extend the miRNAs at the 5´ and 3´ ends. The miRNAs were then reverse-transcribed and preamplified (using universal primers) to uniformly increase the amount of cDNA for each target while maintaining the relative differential levels. The universal primers recognize the universal sequences added to every miRNA and help to ensure the absence of amplification bias. All the target miRNAs were quantified using the TaqMan™ Fast Advanced Master Mix and the following TaqMan Advanced miRNA Assays: hsamiR-21-5p_477975; hsa-miR-23a-3p_478532; hsa-

miR-28-3p_477999; hsa-miR-30b-5p_478007; hsa-miR-93-5p_478210; hsa-miR-126- 3p_477887; hsa-miR-132-3p_477900; hsa-miR-146a-5p_478399; hsamiR-191-5p_477952; hsa-miR-222-3p_477982; hsa-miR-223- 3p_477983; hsa-miR-451a_478107 (ThermoFisher Scientific). The samples were amplified using the QuantStudio™ 12 K Flex Real-Time PCR System (Applied Biosystems, ThermoFisher Scientific), and the results were calculated using the comparative cycle threshold (Ct) method and normalized against the signals detected for miR-93-5p and miR-191-5p.

5- miRNA analysis

Using the raw extraction values and the quartiles of the distribution of each miRNA, we determined an interval [min; max] outside of which values were considered to be outliers: min = quartile 1 - (1.5 * [interquartile range (IQR)] and max = quartile 3 + (1.5 * [IQR]).

The lowest raw miRNA extraction values (expressed as -ΔCt) corresponded to a very high number of RT-PCR cycles and thus an almost undetectable amount of miRNA. We replaced the low outlier values by reassigning them with the corresponding min value.

The presence of hemolysis or red blood cell contamination in the sample was evaluated in two ways. Firstly, four medical biologists independently determined the presence or absence of hemolysis by eye. Secondly, we calculated the difference between the levels of the two hemolysis control miRNAs (miR-23a-3p and miR-45a) (50). If the difference was greater than five, the sample was potentially contaminated by red blood cells. If the difference was greater than seven, the samples were considered to be hemolyzed.

We calculated the extraction values (normalized using the ΔCt method) by subtracting the mean value of the two housekeeping miRNAs [miRNA – mean (miR-93-5p and miR-191-5p)] from the value for each miRNA. The relative expression of the miRNAs (i.e. the variation between the different samples) was expressed as $2^{-\Delta Ct}$.

6- Inflammatory biomarker assays.

The inflammatory biomarker assays have been described previously (17). Briefly, the serum concentration of highsensitivity C-reactive protein (hs-CRP) was measured in a nephelometric assay (BN ProSpec System, Siemens) with a detection range of 0.17 to 10 mg/L. Values below the limit of detection (LOD) were computed as 0.12 (LOD/√2) mg/L. For cytokine measurements, we used MesoScale Discovery® electrochemiluminescent immunoassays (Meso Scale Diagnostics LLC, Rockville, MA, USA): multiplex assays for interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17A, and tumor necrosis factor alpha (TNFα), and an individual assay for IL-22. Values below the lower limit of quantification (the lowest concentration on the standard curve which gave a percentage coefficient of variation of <20%) were counted as real concentrations.

7- Statistical analysis

We used multivariate linear regression models to estimate the effect of PM_{10} and NO_2 exposure on the expression levels of selected miRNAs (ΔCt). We adjusted our models for age, sex, body mass index, and year of inclusion. We adjusted for BMI because obesity is strongly related to many metabolism pathways including inflammation (53). We have adjusted for the year of inclusion because the

construction of the exposure variable was strongly dependent of the inclusion year which may be associated to temporal confusion bias.

Effect estimates and their 95% confidence intervals were expressed as a percentage of the change in miRNA expression level for an increment in a defined unit of pollutant or biomarker, using the equation $(2^{(-\text{estimate coefficient} \times \text{range of increment})} - 1) \times 100$. The increments of 2 $\mu g/m^3$ and 5 $\mu g/m^3$ were used because they were close to the IQR of exposure (17). We studied the associations between miRNAs (ΔCt) and biomarkers of inflammation: cytokines (IL1β, IL-6, IL-8, IL-10, IL-17A, IL-22, TNFα, and hs-CRP).

Due to the large number of comparisons, we applied Benjamini-Hochberg false discovery rate (FDR) method to correct p-values for multiple comparisons. The threshold for statistical significance (after correction for the FDR) was set to $p < 0.1$.

We performed a stratified analysis on gender and test interaction for air pollution/gender interaction.

For the sensitivity analyses, we carried out the same analyses but excluded the hemolyzed samples determined by eye or by calculation. Lastly, we conducted sensitivity analyses using other miRNA normalization techniques: either by subtracting the mean of the three most stable miRNAs (miR-93-5p and miR-191-5p and miR-23a-3p) or the mean of all the other miRNAs from the level of each individual miRNA. The normalization method based on the mean of all the other miRNAs usually requires the measurement of dozens of miRNA and so could not be applied to our main analyses; however, we felt that its use could be justified in the sensitivity analysis (with 12 miRNAs measured (54).

All statistical analyses were performed using R software (version 4.2.0).

III.Results

1- Characteristics of the study population

The ELISABET study included 1668 participants in the Lille urban area, of whom 1335 were nonsmokers (either never-smokers or people having stopped smoking at least 12 months previously). We selected the 1125 participants estimated to be Caucasian on the basis of the available genetic data. We then excluded 72 participants without acceptable spirometry data and 26 participants who had not fasted before the blood sample collection. Ultimately, biomarkers could be assayed for 1004 of the remaining participants. Measurements of the normalization housekeeping miRNAs (miR-93-5p or miR-191-5p) were missing for 6 participants, leaving 998 in the main analysis (454 (45.5%) men; median age: 54) (Table 1). In this sample, four values were missing for miR-28- 3p, 6 for miR-132-3p and 5 miR-30b-5p. There were no missing data for the other miRNAs.

Between 2011 and the year of inclusion, the mean PM_{10} exposure was 26.4 ± 2.0 µg/m^3 and the mean NO_2 exposure was 24.7 ± 5.1 µg/ m3 . The correlation between PM_{10} and NO_2 exposure levels was strong ($r_{pearson}$ = 0.79; 95%CI [0.77; 0.81]; p = < 2.2e-16). The mean and Sd of fold log2 fold change of the levels of miRNA are reported in supplemental table 1.

Table 1: Characteristics of the study participants (n = 998)

Variable	value
Age (year)	53.8 (7.2)
Male gender, n (%)	454 (45.5)
Height (cm)	169.6 (8.9)
BMI (kg/m2)	26.8 (5.0)
Mean annual levels of PM_{10} pollution between 2011 and the year inclusion ($\mu g/m^3$)	26.4 (2.0)
Mean annual levels of NO_2 pollution between 2011 and the inclusion year ($\mu g/m^3$)	24.7 (5.1)
hs-CRP (mg/L)	0.9 (0.5 ; 1.9)
IL1b (pg/mL)	0.0 (0.O ; 0.1)
IL6 (pg/mL)	0.4 (0.3 ; 0.7)
IL8 (pg/mL)	2.7 (2.1 ; 3.8)
IL10 (pg/mL)	0.2 (0.1 ; 0.3)
IL17a (pg/mL)	0.8 (0.5 ; 1.3)
IL22 (pg/mL)	0.2 (0.1 ; 0.4)
TNFα (pg/mL)	2.4 (1.9 ; 2.9)
DBP (mmHG)	126 (115 ; 139.4)
HbA1c (%)	5.5 (5.2 ; 5.9)
Glycemia (g/L)	0.9 (0.9 ; 1)
Total cholesterol (g/L)	2.2 (1.9 ; 2.5)
Triglycerides (g/L)	0.9 (0.7 ; 1.3)
HDL (g/L) median (IQR)	0.6 (0.5 ; 0.7)
LDL (g/L) median (IQR)	1.4 (1.2 ; 1.6)

Data are expressed as the mean (SD), the median [IQR] or n (%)
BMI: body mass index, PM_{10}: particulate matter < 10 µm, NO_2: nitrogen dioxide, HbA1c: glycosylated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

2- Main analysis: the association between air pollution exposure and miRNA expression

After correction for the FDR ($p_{FDR} < 0.1$), we found that one miRNA (miR-451a) was positively associated with both PM_{10} and NO_2 levels and that four miRNAs levels (miR-223-3p, miR-28-3p, miR-146a-5p, and miR-23a-5p) were negatively associated with the NO_2 level (Table 2). A 2 $\mu g/m^3$ increment in PM_{10} exposure was associated with an 8.6% increment (95% confidence interval [3.1; 14.3]; $p_{FDR} = 0.019$) in miR451a expression (Table 2). A 5 $\mu g/m^3$ increment in NO_2 exposure was associated with a 5.3% increment ([0.7; 10]; $p_{FDR} = 0.056$) in miR-451a and a 3.6% decrement ([-

6.1; − 1.1]; p_{FDR} = 0.052) in miR-223-3p, a 3.8% decrement ([-6.8; − 0.7]; p_{FDR} = 0.079) in miR-28-3p, a 4.3% decrement ([-7.7; − 0.8]; p_{FDR} = 0.055) in miR-146a-5p, and a 4.0% decrement ([-7.4; − 0.4]; p_{FDR} = 0.059) in miR-23a-5p (Table 2). We also observed that the difference between the two housekeeping miRNAs (miR-93-5p normalized against miR-191-5p or vice versa) were significantly associated with PM_{10} and NO_2.

Table 2: Association between residential PM_{10} and NO_2 and miRNA, using the level of the miRNA minus the average of the two housekeeping miRNAs

micro-RNA	PM_{10} (per 2 µg/m³ increment)			NO_2 (per 5 µg/m³ increment)		
	% difference [95CI%]	p	p FDR*	% difference [95CI%]	p	p FDR*
miR.451a	8.6 [3.1 ; 14.3]	**0.002**	**0.019**	-3.6 [-6.1 ; -1.1]	**0.005**	**0.052**
miR.28.3p	-4.3 [-7.8 ; -0.6]	**0.022**	0.112	-3.8 [-6.8 ; -0.7]	**0.016**	**0.079**
miR.223.3p	-3.1 [-6 ; -0.1]	**0.042**	0.140	-4.3 [-7.7 ; -0.8]	**0.016**	**0.055**
miR.132.3p	3.1 [-0.8 ; 7.2]	0.117	0.292	5.3 [0.7 ; 10]	**0.022**	**0.056**
miR.146a.5p	-3.0 [-7 ; 1.2]	0.164	0.328	-4.0 [-7.4 ; -0.4]	**0.029**	**0.059**
miR.23a.5p	-3.0 [-7.1 ; 1.3]	0.166	0.277	-2.2 [-4.5 ; 0.2]	0.073	0.122
miR.126.3p	-2.0 [-4.7 ; 0.9]	0.174	0.248	-2.3 [-5.6 ; 1.1]	0.175	0.249
miR.222.3p	-1.6 [-4.9 ; 1.9]	0.362	0.452	-1.9 [-4.7 ; 1]	0.205	0.256
miR.30b.5p	-1.7 [-5.6 ; 2.3]	0.395	0.438	1.5 [-1.7 ; 4.9]	0.359	0.399
miR.21.5p	0.5 [-2.7 ; 3.7]	0.781	0.781	-0.8 [-3.4 ; 2]	0.577	0.577
miR.93.5p	3.8 [1.2 ; 6.4]	**0.004**		3.5 [1.3 ; 5.7]	**0.002**	
miR.191.5p	-3.6 [-6 ; -1.2]	**0.004**		-3.4 [-5.4 ; -1.3]	**0.002**	

* p value corrected for the false discovery rate
Adjusted for age, sex, body mass index, and year of inclusion
PM_{10}: particulate matter < 10 µm, NO_2: nitrogen dioxide

3- Sensitivity analyses

Stratified analysis on gender are presented in supplemental table 2 and 3 none of the interaction test between air pollution and gender were Significant after FDR correction. miR-23a-5p, miR-223-3p and miR451a were significantly associated with NO_2 and PM_{10} were significantly associated with miR-451a and miR-132-3p after

FDR correction in women. no association with NO_2 or PM_{10} were significant in men.

A total of 130 (12.0%) samples with hemolysis were excluded: 26 by eye and 104 using the calculation method (Supplemental Table 4). Exclusion of the samples with hemolysis did not greatly modify the results, except that the association between PM_{10} and miR-28-3p became statistically significant. We also observed fewer significant associations with NO_2 exposure after correction for the FDR.

When subtracting the mean level of the three most stable miRNAs (miR-93-5p, miR-191-5p and miR-23a-3p) from each miRNA, we found that two of the other miRNAs (miR-451a and miR-132-3p) were positively associated with PM_{10} and one (miR-28-3p) was negatively associated with PM_{10} (Supplemental table 5) and NO_2. However, only the association with miR-451a remained significant after correction for the FDR (Supplemental Table 6).

When subtracting the mean of all the other miRNAs from each miRNA, we found that three miRNAs were positively associated with PM_{10} (miR-451a, miR-93-5p and miR-132-3p), three (miR-191-5p, miR28-3p,miR-223-3p) were negatively associated with PM_{10} (Supplemental Table 3), three (miR-451a, miR-93-5p and miR-132-3p) were positively associated with NO_2, and five (miR-146a-5p, miR-23a-5p, miR-223-3p, miR-28-3p and miR-191-5p) were negatively associated with NO_2.

4- Additional analyses

Association between inflammatory biomarkers and miRNA. By considering the difference with the mean of the two-housekeeping miRNA, we found positive associations between inflammatory biomarkers and miRNAs. MiR-223-3p and miR-21-5p were associated with hs-CRP, IL-6 and IL-10; miR-30b-5p was associated with hs-CRP; miR126-3p was associated with IL-6 and IL-10; and miR-23a-5p and

miR132-3p were associated with IL-10. No significant associations were observed for IL-1β, IL-8, IL-17a, TNFα, and IL-22.

Table 3: Association between inflammatory biomarkers and miRNA, using the miRNA level minus the average of the two housekeeping miRNAs.

	microRNA	% difference [95CI%]	p	p FDR*
hs-CRP	miR.223.3p	9.303 [3.1 ; 15.9]	**0.003**	**0.028**
	miR.21.5p	9.282 [2.8 ; 16.2]	**0.004**	**0.022**
	miR.30b.5p	10.545 [2.3 ; 19.5]	**0.012**	**0.040**
	miR.146a.5p	8.326 [-0.3 ; 17.7]	0.058	0.145
	miR.126.3p	5.334 [-0.3 ; 11.3]	0.063	0.126
	miR.28.3p	6.915 [-0.5 ; 14.9]	0.070	0.117
	miR.23a.5p	7.063 [-1.4 ; 16.3]	0.106	0.151
	miR.222.3p	4.344 [-2.4 ; 11.6]	0.213	0.267
	miR.451a	-5.755 [-14.8 ; 4.2]	0.250	0.277
	miR.132.3p	3.864 [-3.7 ; 12]	0.324	0.324
	miR.93.5p	-6,4 [-10,8 ; -1,7]	**0.008**	
	miR.191.5p	6,8 [1,8 ; 12,1]	**0.008**	
IL6	miR.223.3p	7.067 [2.1 ; 12.3]	**0.005**	**0.051**
	miR.21.5p	6.572 [1.4 ; 12]	**0.013**	**0.064**
	miR.126.3p	5.690 [1.1 ; 10.5]	**0.015**	**0.049**
	miR.30b.5p	4.958 [-1.5 ; 11.8]	0.133	0.332
	miR.146a.5p	4.668 [-2.1 ; 11.9]	0.181	0.361
	miR.23a.5p	3.916 [-2.8 ; 11.1]	0.263	0.438
	miR.222.3p	1.607 [-3.8 ; 7.3]	0.566	0.809
	miR.132.3p	0.329 [-5.5 ; 6.6]	0.915	1.144
	miR.28.3p	0.216 [-5.5 ; 6.2]	0.942	1.047
	miR.451a	0.091 [-7.8 ; 8.6]	0.983	0.983
	miR.93.5p	-1,9 [-5,7 ; 2]	0.331	
	miR.191.5p	2 [-1,9 ; 6]	0.331	
IL10	miR.23a.5p	26.498 [10.5 ; 44.8]	**0.001**	**0.007**
	miR.21.5p	14.571 [3.6 ; 26.7]	**0.008**	**0.042**
	miR.223.3p	13.134 [2.7 ; 24.6]	**0.012**	**0.041**
	miR.126.3p	10.429 [0.9 ; 20.8]	**0.031**	**0.077**
	miR.132.3p	13.045 [0.1 ; 27.7]	**0.049**	**0.098**
	miR.146a.5p	13.831 [-0.5 ; 30.3]	0.060	0.100
	miR.30b.5p	11.754 [-1.6 ; 26.9]	0.087	0.125
	miR.28.3p	10.364 [-1.9 ; 24.1]	0.101	0.126
	miR.451a	-8.640 [-22.6 ; 7.8]	0.284	0.316
	miR.222.3p	5.333 [-5.6 ; 17.6]	0.355	0.355
	miR.93.5p	-7,5 [-14,5 ; 0,1]	0.053	
	miR.191.5p	8,1 [-0,1 ; 17]	0.053	

* p value corrected for the false discovery rate.
hs-CRP: high-sensitivity C-reactive protein.

IV.Discussion

The results of our population-based study showed that long-term exposure to residential air pollution was associated with plasma miRNA levels and thus suggested that air pollution impacts gene regulation processes. Plasma levels of miR-223-3p, miR-28-3p, miR-146a-5p and miR-23a-5p were negatively associated with NO_2 exposure, and whereas the level of miR-451a was positively associated with NO_2 exposure. No significant interaction between gender and air pollution were observed. We didn't highlight any difference or air pollution effect between gender. When studying PM_{10}, only one association (with miR-451a) achieved statistical significance after correction for the FDR. Nevertheless, PM_{10} and NO_2 were strongly correlated, and so it is hard to identify specific effects of one or the other. The standard deviations of NO_2 were higher than those of PM_{10}, which might have resulted in greater statistical power in the analysis of the association with NO_2.

Previous studies of the association between air pollution and these miRNAs had smaller samples and gave disparate results. These studies are described in supplemental table 7. Most of previous studies focus on short term exposure: five studies had cross sectional design (25,37,38,54,55) including one with experimental exposure to diesel exhaust (54), six were small cohort with repeated measurement of exposure and miRNA (26,39,56–59) two were cross-sectional studies (32,60). Long term exposure was less studied, Only Rodosthenous et al (26) studied short- and long-term exposure (6 month and 1 year) with repeated measurement. The association with benzo[a] pyrene-r-7,t-8,t-9,c-10-tetrahydotetrol and serum albumin(BPDE-Alb), a biomarker of PM exposure was studied in children (32) and a cohort of pregnant women studied exposure in pregnancy associated to miRNA in placenta at birth.

The negative association we observed between NO_2 and miR-23a-5p was consistent with negative association observed at short term with traffic air pollution (TRAP) in chines students (55) (supplemental table 8). But conversely to our find a positive association for long term exposure were observed in the study of Rodosthenous et al (26). The negative association we observed between NO_2 and miR-28-3p has not been found in previous study. One positive association were observed at short term in a cross-sectional study (38). The negative association between NO_2 and miR-146a-5p were consistent with previous association observed with short term exposure (31,37,59) but conversely positive association at short term (26,38) and positive association with BPDE-Alb (32) were also observed. The negative association with miR-223-3p were inconsistent with positive association at short (26,54) and long term (26) observed previously. The negative association at long term we observed with miR-451a were inconstant with the positive short-term association observed by Rodosthenous et al (26). Although miR-191-5p and mir-93-5p were used as housekeeping miRNAs the results suggest that at least one of the may be associated to air pollution, indeed Rodosthenous et al have previous found significant association between air pollution these miRNAs. Finally, Other association have been observed for the miRNAs not associated to air pollution in our study and are listed in supplemental table 8 with biological effect or evaluated miRNAs. The inconsistency of result may be explained by difference population in population, exposure and methodology. More population base study with large sample are needed to confirm these results.

1- Physiological pathways

Inflammasomes are cytosolic protein complexes responsible for the activation

of inflammatory pathways in response to a wide range of pathogens and cell damage signals (55). Transcription of the most-studied inflammasome (NLR family pyrin domain containing 3 (NLRP3)) can be induced by Toll-like receptor (TLR) agonists and some inflammatory cytokines in an NF-κB-dependent manner (56). Through activation of caspase 1, activation of the NLRP3 inflammasome allows the conversion of the proinflammatory cytokines IL-1β and IL-18 into their mature forms, together with the induction of gasdermin-D-mediated pyroptotic cell death.

In order to avoid inappropriate activation, basal levels of inflammasome components are rather low in most cells. It is now well established that inflammasome functionalization can be modulated by a subset of miRNAs called inflammamiRs (57). Three of the miRNAs negatively correlated with pollution exposure in the present study are classified as inflammamiRs; miR-223-3p, miR-146a-5p, miR23a-3p.

MiR-223-3p was the first human miRNA found to directly target NLRP3 (58,59) and thus exhibits significant anti-inflammatory and antipyroptotic effects. In a number of studies, miR-223-3p expression is associated with exposure to multiple airborne contaminants. Nevertheless, the results of these studies are not always consistent and appear to vary as a function of the nature of the pollutant or the biological matrix analyzed. In a pilot study with 22 participants, Rodosthenous et al. (26) found a significant association between long-term ambient $PM_{2.5}$ exposure and circulating levels of extracellular vesicle-encapsulated miR-223-3p. In accordance with these results, several studies have described increases in expression levels of this miRNA in response to other environmental challenges (42,61). In contrast, a significant downregulation of miR-223 was observed in human and rat lungs after tobacco smoke exposure (62,63). Lastly, in line with our present results, the plasma miR-223-

3p level was low in female CD-1 mice exposed to smoke condensate samples collected from different biomass burn scenarios (64).

As with miR-223, miR-146a has an anti-inflammatory role because it can downregulate the NF-kB-mediated priming of the NLRP3 inflammasome. Indeed, miR-146a targets TLR4, myeloid differentiation primary response gene 88 (MyD88), interleukin-1 receptor-associated kinase 1 (IRAK1), and TNF-receptor-associated factor (TRAF6) – all key proteins in the canonical NF-κB pathway (57,65). Moreover, miR-146a downregulates RelB, a pivotal factor in the non-canonical NF-κB pathway (66,67). The anti-inflammatory role of miR-146a was also evidenced by the fact that miR-146a knock-out mice develop NF-κBdriven low-grade inflammation (68,69). In agreement with our findings, several researchers have observed a negative correlation between PM exposure and miR-146a-5p levels (31,37,70,71).

In contrast, a 24-participant cross-over study of personal air pollution exposure assessment gave discordant results: the circulating level of miR-146a-5p was positively correlated with exposure to airborne ultrafine particles (38).

Lastly, miR-23a-3p can also help to downregulate the inflammasome by targeting the NLRP3-activating factors NIMA-related kinase 7 (NEK7) (72) or the CXCR4 chemokine receptor involved in stabilization of thioredoxin interacting protein (TXNIP) (73). Initially, miR-23a-3p was selected (along with miR-451a) to evaluate the level of hemolysis in biological samples. Very few studies have linked the expression of this miRNA with exposure to air pollution. In their pilot study of 22 participants, Rodosthenous et al. (26) observed a significant association between long-term ambient $PM_{2.5}$ exposures and circulating miR-23a-3p levels. However, as with the two previously mentioned anti-inflammatory miRNAs (i.e. miR-223-3p and miR-146a-5p), we observed a negative correlation between the plasma miR-23a-3p

level and pollution exposure. Taken as a whole, these data suggest that organisms adapt to and control the inflammatory response induced by exposure to air pollutants. The association between short-term exposure to atmospheric air pollution and low-grade systemic inflammation previously observed in our study population might reflect this phenomenon (17).

Although not described as inflammamiRs, the two other miRNAs correlated with pollution exposure in our study (i.e. miR-28-3p and miR451a) regulate inflammatory signaling pathways. Yang et al. showed that miR-28 directly targets NRF2 (73), a major regulator of antioxidant and anti-inflammatory responses (74,75). Hence, miR-28-3p could be considered as a proinflammatory miRNA. In the present study, we observed a negative correlation between miR-28-3p levels and exposure to PM_{10} and NO_2. Krauskopf et al.'s recent preliminary study of early biomarkers in only 30 participants showed that circulating miR-28-3p was positively correlated with a mixture of compounds found in traffic-related air pollution, including black carbon, CO_2, nitrogen oxides, and ultrafine particles (38). However, Krauskopf et al. did not find an association with $PM_{2.5}$.

Based on the literature data, miR-451a is a potential anti-inflammatory miRNA. Indeed, several studies have described how miR-451a inhibits the NF-kB pathway by reducing the expression of CAB39 (76), IKKB (77) and HMGB1 (78,79). Our present study evidenced a positive correlation between the plasma level of miR-451a and long-term pollution exposure. Motta et al. (79) did not find a significant association with PM_{10} levels after 24 or 48 h of exposure. However, Motta et al.'s study included 90 overweight or obese adults, and obesity has already been shown to induce variability in the effects of PM (80,81). Similarly, Rodosthenous et al. found no association between short- and long-term $PM_{2.5}$ exposure and the miR-451a level.

(26). In contrast, Deng et al. observed low miR-451a plasma levels in coke oven workers exposed to both metals and polycyclic aromatic hydrocarbons (82).

The tight control over inflammasome assembly and signaling is crucial for enabling the immune system to mount sufficiently strong antimicrobial and inflammatory responses to environmental challenges while avoiding the excessive tissue damage that could result from an uncontrolled reaction. Thus, deregulated inflammasome activation has been linked to the development of various diseases, from inflammatory diseases to cancers. In this context, any variation in the expression of inflammation-related miRNAs might reflect or cause pathological processes. It is therefore not surprising that the deregulation of the five miRNAs correlated with pollution exposure in our study has been linked to the pathogenesis of many diseases. In particular, the inflammasome modulating miRNAs miR-23a-3p, miR-146a-5p and miR-223-3p are reportedly dysregulated in a wide range of immune inflammatory diseases (such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, type 1 diabetes, and asthma (83,84), various non-immune inflammatory diseases (such as COPD and atopic, metabolic, neuroinflammatory and cardiovascular diseases (7,84–90), and several types of cancer (91–93). The expression of the remaining miRNAs (miR-28a-3p and miR-451a) is reportedly altered in tumoral diseases; these miRNAs have been suggested as promising cancer biomarkers with therapeutic potential (14,15,94). Lastly, abnormal levels of miR-451a have been observed in patients with cardiac fibrosis (94), cardiovascular diseases (95,96) and rheumatoid arthritis (97), and serum concentrations of miR-28a-3p are potential biomarkers in severe asthma (98) and COPD (99).

2- Strengths and weaknesses

The present study had several strengths. Firstly, to the best of our knowledge, this is the first population-based present study to have measured the association between air pollution and miRNAs. Secondly, our study included a large sample (n = 998) of non-smokers, which is more than in previous studies. Our study has greater sample size than previous ones it had enough power to detect association with similar effect size than those previously observed. For example, Fossati et al (31) observed a − 19.4% decrease of miR-126 for 3.02 µg/m^3 increase of 28 days exposure to $PM_{2.5}$. In our study the standard deviation of PM_{10} exposure were 2 µg/m^3. to take in account that standard deviation(SD) of PM_{10} which include $PM_{2.5}$ are by definition higher than SD of $PM_{2.5}$ we multiply the SD of PM_{10} by 0.7 (16) and considering a SD of exposure at 1.4 µg/m^3 for PM exposure. The SD of difference of Ct between miRNA and average of the two housekeeping miRNAs were 0.604. according to these data with an alpha risk at 0.005 (to take in account FDR correction). the power our study was estimate at 98%. Thirdly, most previous studies looked at short-term exposure; we provided new data on long-term exposure with a fine-scale model (25x25m).

Our study also had some limitations. Firstly, we chose housekeeping miRNAs because of their known stability, which was confirmed here. Nevertheless, the observed association between housekeeping miRNAs and exposure might have influence the interpretation of our data. The association between housekeeping miRNAs and pollution can be explore indirectly only if several housekeeping miRNAs have been studied. This validity check is not generally described in the literature on house-keeping miRNA (28,51,100). Here, we identified a significant association

between air pollution and the difference between the two main housekeeping miRNAs; this prevented us from drawing any definite conclusions about the effect size of the observed associations. Nevertheless, our results are consistent because the associations observed in the main analysis were also seen in the sensitivity analyses.

V. Conclusion

We observed associations between residential long-term air pollution exposure and a number of miRNAs in large population-based sample of urban inhabitants. The miRNAs significantly associated with air pollution are mostly involved in inflammation suggesting that inflammation is a major pathway. Our results suggest that circulating miRNAs are potentially valuable biomarkers of the environmental risk.

Discussion

I. Conclusion sur les principaux résultats

Cette étude apporte des preuves supplémentaires quant à l'impact de la pollution de l'air à long terme sur la régulation génétique via les micro-ARN circulants. Les résultats montrent des associations significatives entre l'exposition résidentielle prolongée à des polluants atmosphériques, comme le NO_2 et les PM_{10}, et des variations spécifiques dans l'expression de certains micro-ARN plasmatiques. Ces micro-ARN, principalement impliqués dans les voies inflammatoires, révèlent des effets potentiels sur les mécanismes de régulation génétique et inflammatoire (26,32).

Le miR-223-3p est largement étudié pour son rôle dans la modulation de l'inflammation. Son association négative avec le NO2 suggère que l'exposition à long terme à ce polluant pourrait altérer ses niveaux et, par conséquent, influencer les réponses inflammatoires. Cette observation est en accord avec certaines études qui ont montré une variation de l'expression de miR-223-3p en réponse à divers stimuli inflammatoires (58,59). Toutefois, des résultats contradictoires existent dans la littérature, ce qui reflète la complexité des interactions entre micro-ARN et environnement.

De même, le miR-146a-5p, connu pour sa régulation des voies inflammatoires via l'inhibiteur de NF-κB, présente des résultats variés selon les études. Nos résultats montrent une association négative avec le NO2, suggérant un potentiel effet modulatoire de la pollution sur les réponses immunitaires (31,37,70,71). Cependant, des études antérieures ont rapporté des associations positives entre miR-146a-5p et pollution, soulignant la complexité des interactions entre micro-ARN et environnement (38).

Le miR-28-3p n'a pas été largement étudié dans le contexte de la pollution atmosphérique, mais nos résultats suggèrent une association négative. Cela pourrait refléter un effet direct ou indirect du NO2 sur les processus de régulation génétique (74,101).

Le miR-23a-5p, malgré son rôle significatif dans la régulation des processus inflammatoires et fibrogéniques, a montré une association négative dans notre étude (72). Cette découverte est intéressante car elle pourrait indiquer des mécanismes de réponse cellulaire complexes face à l'exposition prolongée aux polluants.

L'association positive entre miR-451a et le NO2 pourrait suggérer un mécanisme compensatoire ou adaptatif en réponse au stress oxydatif induit par la pollution (76–78). Le miR-451a est impliqué dans le transport de l'oxygène et la régulation du métabolisme cellulaire (75), et son élévation pourrait refléter des ajustements physiologiques face à une exposition accrue aux polluants. Cependant, des études antérieures, telles que celles de Motta et al. (79) et Deng et al. (81), ont montré des résultats variables sur l'association entre miR-451a et les niveaux de PM, ce qui souligne la nécessité de recherches supplémentaires.

II.Perspectives

Les micro-ARN jouent un rôle central dans la régulation épigénétique, influençant l'expression de nombreux gènes et divers processus biologiques et pathologiques (102,103). Leur identification comme biomarqueurs potentiels pour évaluer les effets des expositions environnementales sur la santé humaine s'inscrit dans une tendance observée dans la littérature actuelle, où ils sont de plus en plus reconnus comme des médiateurs des effets nocifs des polluants atmosphériques (25,70). Des études antérieures, bien que souvent réalisées sur des échantillons plus

réduits et avec des résultats parfois contradictoires, ont déjà mis en évidence des associations similaires (71,78). Ces variations peuvent s'expliquer par des différences dans les méthodes d'exposition, les populations étudiées, ou les types de polluants examinés.

La régulation des voies inflammatoires par les micro-ARN, notamment ceux identifiés dans notre étude, renforce l'idée que l'inflammation est un mécanisme clé par lequel la pollution atmosphérique exerce ses effets délétères sur la santé (72,104). Cette inflammation, lorsqu'elle est chronique ou mal régulée, est liée à une multitude de maladies, allant des troubles respiratoires comme la BPCO et l'asthme, aux maladies cardiovasculaires et aux cancers (37,58). Cependant, la corrélation observée entre certains micro-ARN de ménage, tels que miR-93-5p et miR-191-5p, et l'exposition à la pollution suggère des interactions complexes qui mériteraient d'être explorées plus en profondeur (74,79). Bien que les données sur l'exposition aient été modélisées avec une précision spatiale fine, d'autres facteurs environnementaux ou de style de vie non mesurés pourraient également influencer l'expression des micro-ARN (32,81).

Conclusion

En conclusion, cette étude suggère l'utilité des micro-ARN pour clarifier les relations complexes entre pollution atmosphérique et mécanismes physiopathologiques , en particulier les voies de l'inflammation. Cette voie de recherche ouvre des perspectives prometteuses pour le développement de biomarqueurs de risque environnemental, qui pourraient à terme contribuer à une meilleure prévention et gestion des maladies liées à la pollution.

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Annexes

Supplemental table 1 : Levels of miRNA

micro-RNA	Mean(SD)*
miR-21-5p	0.22 (0.648)
miR-23a-5p	0.573 (0.887)
miR-28-3p	-4.468 (0.779)
miR-30b-5p	-1.848 (0.874)
miR-126-3p	1.152 (0.604)
miR-132-3p	-5.434 (0.795)
miR-146a-5p	-0.952 (0.865)
miR-222-3p	-2.717 (0.703)
miR-223-3p	1.943 (0.644)
miR-451a	3.47 (1.158)
miR-93-5p	0.84 (0.58)
miR-191-5p	-0.84 (0.58)

* Expressed in difference of Ct between miRNA and average of the two housekeeping micro-ARN(miR-93-5p and miR-191-5p)

Supplemental table 2 : Association between residential PM_{10} and miRNA using miRNA minus- average of the two housekeeping micro-ARN.

	men			women		
	PM_{10} (per 2µg/m³ increase)			**PM_{10} (per 2µg/m³ increase)**		
micro-RNA	**% of variation [IC95%]**	**p**	**p FDR**	**% of variation [IC95%]**	**p**	**p FDR***
miR-21-5p	1.4 [-2.8 ; 5.8]	0.520	0.743	-0.3 [-4.9 ; 4.4]	0.884	0.982
miR-23a-5p	-2.8 [-8.4 ; 3.2]	0.360	0.721	-3.2 [-9 ; 3.0]	0.309	0.515
miR-28-3p	-5.9 [-10.7 ; -0.8]	0.024	0.237	-2.7 [-7.7 ; 2.6]	0.315	0.450
miR-30b-5p	1.4 [-4.1 ; 7.2]	0.619	0.773	-4.9 [-10.2 ; 0.8]	0.089	0.179
miR-126-3p	0.4 [-3.6 ; 4.5]	0.845	0.939	-4.0 [-7.8 ; -0.1]	0.046	0.116
miR-132-3p	-0.5 [-5.9 ; 5.2]	0.864	0.864	7.0 [1.5 ; 12.8]	0.013	0.064
miR-146a-5p	-2.9 [-8.6 ; 3.1]	0.337	0.842	-2.8 [-8.5 ; 3.3]	0.359	0.449
miR-222-3p	-2.6 [-7.4 ; 2.5]	0.310	0.999	-0.2 [-4.8 ; 4.7]	0.948	0.948
miR-223-3p	-1.4 [-5.5 ; 2.8]	0.505	0.842	-4.7 [-8.7 ; -0.4]	0.031	0.103
miR-451a	6.0 [-1.7 ; 14.2]	0.132	0.659	11.3 [3.7 ; 19.6]	0.003	0.033
miR-93-5p	2.2 [-1.4 ; 6]	0.227		5.2 [1.6 ; 8.9]	0.004	
miR-191-5p	-2.2 [-5.7 ; 1.4]	0.227		-4.9 [-8.2 ; -1.6]	0.004	

* False Discovery Rate corrected p value
Ajusted for age, sex, Body mass index (BMI) and year of inclusion

Supplemental table 3 : Association between residential NO_2 and miRNA using miRNA minus- average of the two housekeeping micro-ARN

	Men			Women				
	NO_2 (per 5µg/m^3 increase)			NO_2 (per 5µg/m^3 increase)				
micro-RNA	**% of variation [IC95%]**	**p**	**p FDR**	**% of variation [IC95%]**	**p**	**p FDR***	**p interaction**	**P interaction FDR**
miR-21-5p	0.1 [-3.4 ; 3.7]	0,976	0,976	-1.4 [-5.4 ; 2.6]	0,483	0,536	0,577	0,962
miR-23a-5p	-3.0 [-7.7 ; 2.0]	0,236	0,589	-4.9 [-9.8 ; 0.3]	0,065	0,093	0,653	0,725
miR-28-3p	-5.6 [-9.6 ; -1.3]	0,011	0,105	-2.0 [-6.4 ; 2.6]	0,383	0,479	0,253	0,506
miR-30b-5p	0.2 [-4.3 ; 5.0]	0,926	0,999	-5.0 [-9.7 ; -0.2]	0,043	0,086	0,101	0,507
miR-126-3p	-0.3 [-3.6 ; 3.1]	0,867	0,999	-3.9 [-7.2 ; -0.5]	0,024	0,121	0,128	0,428
miR-132-3p	-1.4 [-5.9 ; 3.3]	0,551	0,787	4.9 [0.2 ; 9.8]	0,041	0,103	0,046	0,461
miR-146a-5p	-3.2 [-7.9 ; 1.9]	0,214	0,714	-5.3 [-10.1 ; -0.2]	0,041	0,135	0,636	0,795
miR-222-3p	-2.1 [-6.2 ; 2.1]	0,313	0,522	-1.1 [-5.1 ; 3.0]	0,581	0,581	0,630	0,900
miR-223-3p	-1.9 [-5.3 ; 1.6]	0,284	0,568	-5.3 [-8.8 ; -1.7]	0,005	0,048	0,158	0,394
miR-451a	4.4 [-2.0 ; 11.1]	0,183	0,915	6.6 [0.2 ; 13.4]	0,045	0,075	0,677	0,677
miR-93-5p	1.9 [-1.1 ; 5.0]	0,222		5.0 [1.9 ; 8.2]	0,001		0,189	
miR-191-5p	-1.9 [-4.8 ; 1.1]	0,222		-4.8 [-7.6 ; -1.9]	0,001		0,189	

* False Discovery Rate corrected p value
Ajusted for age, sex, Body mass index (BMI) and year of inclusion

Supplemental table 4 : Association between residential PM_{10} and NO_2 and miRNA, using the level of the miRNA minus the average of the two housekeeping micro-ARN and after the exclusion of samples with hemolysis

PM_{10} (per 2 µg/m^3 increment)				**NO_2 (per 5 µg/m^3 increment)**			
micro-RNA	**% difference [95CI%]**	**p**	**p FDR**	**micro-RNA**	**% difference [95CI%]**	**p**	**p FDR***
miR.451a	8.8 [3.6 ; 14.3]	0,001	0,009	miR.28-3p	-3.8 [-6.6 ; -0.9]	0.010	0,104
miR.28-3p	-5.0 [-8.3 ; -1.7]	0,004	0,018	miR.223-3p	-3.1 [-5.4 ; -0.7]	0,013	0,065
miR.223-3p	-2.8 [-5.6 ; 0.0]	0,051	0,17	miR.146a-5p	-4.1 [-7.4 ; -0.8]	0,017	0,056
miR.146a-5p	-3.5 [-7.3 ; 0.6]	0,091	0,226	miR.451a	5.1 [0.8 ; 9.6]	0,021	0,052
miR.23a-5p	-3.3 [-7.0 ; 0.7]	0,104	0,208	miR.126-3p	-2.2 [-4.4 ; 0.1]	0,067	0,134
miR.126-3p	-2.1 [-4.8 ; 0.6]	0,124	0,206	miR.23a-5p	-3.1 [-6.3 ; 0.3]	0.070	0,117
miR.132-3p	2.7 [-1.3 ; 6.9]	0,185	0,264	miR.30b-5p	-2.1 [-5.4 ; 1.4]	0,245	0.350
miR.30b-5p	-1.7 [-5.7 ; 2.4]	0,405	0,506	miR.222-3p	-1.5 [-4.5 ; 1.6]	0.330	0,413
miR.222-3p	-1.5 [-5.0 ; 2.2]	0,421	0,468	miR.132-3p	1.7 [-1.7 ; 5.2]	0,332	0,369
miR.21-5p	0.2 [-3.0 ; 3.6]	0,889	0,889	miR.21-5p	-0.6 [-3.3 ; 2.3]	0,699	0,699
miR.93-5p	3.4 [1.1 ; 5.7]	0,004		miR.93-5p	2.8 [0.9 ; 4.8]	0,004	
miR.191-5p	-3.3 [-5.4 ; -1.1]	0,004		miR.191-5p	-2.8 [-4.6 ; -0.9]	0,004	

Supplemental table 5 : Association between residential PM_{10} and NO_2 and miRNA, using the level of the miRNA minus the average of the three most stable micro-ARN.

PM_{10} (per 2 µg/m³ increment)				NO_2 (per 5 µg/m³ increment)			
micro-RNA	**% difference [95CI%]**	**p**	**p FDR**	**micro-RNA**	**% difference [95CI%]**	**p**	**p FDR***
miR.451a	9.7 [3.8 ; 15.9]	0,001	0.010	miR.451a	6.7 [1.8 ; 11.9]	0,007	0,063
miR.132-3p	4.2 [0.6 ; 7.9]	0,022	0,098	miR.146a-5p	-3.0 [-5.8 ; -0.2]	0,038	0,169
miR.28-3p	-3.3 [-6.1 ; -0.4]	0,029	0,086	miR.223-3p	-2.3 [-4.5 ; -0.1]	0.040	0.120
miR.223-3p	-2.1 [-4.6 ; 0.5]	0,109	0,245	miR.28-3p	-2.6 [-5 ; 0.0]	0,046	0,104
miR.146a-5p	-2.0 [-5.3 ; 1.4]	0,248	0,446	miR.132-3p	2.9 [-0.1 ; 6.0]	0,059	0,106
miR.21-5p	1.5 [-1.1 ; 4.2]	0,271	0,407	miR.126-3p	-0.9 [-2.8 ; 1.1]	0,397	0,595
miR.126-3p	-1.0 [-3.3 ; 1.4]	0,419	0,538	miR.30b-5p	-1.0 [-3.9 ; 2.0]	0,526	0,677
miR.30b-5p	-0.7 [-4.1 ; 2.9]	0,705	0,793	miR.21-5p	0.6 [-1.6 ; 2.8]	0,607	0,682
miR.222-3p	-0.6 [-3.6 ; 2.5]	0,709	0,709	miR.222-3p	-0.5 [-3.1 ; 2.1]	0,686	0,686
miR.23a-5p	-2.0 [-4.8 ; 0.8]	0,166		miR.23a-5p	-2.7 [-5 ; -0.3]	0,029	
miR.93-5p	4.8 [1.3 ; 8.5]	0,007		miR.93-5p	4.9 [1.9 ; 8.0]	0,001	
miR.191-5p	-2.7 [-4.7 ; -0.5]	0,014		miR.191-5p	-2.0 [-3.8 ; -0.2]	0,028	

* p value corrected for the false discovery rate
Adjusted for age, sex, body mass index, and year of inclusion
PM_{10}: particulate matter <10 µm, NO^2: nitrogen dioxide

Supplemental table 6: Association between residential PM_{10} and NO_2 and miRNA, using the level of the miRNA minus the average of all the other micro-ARN.

PM_{10} (per 2 µg/m³ increment)				NO_2 (per 5 µg/m³ increment)			
micro-RNA	**% difference [95CI%]**	**p**	**p FDR**	**micro-RNA**	**% difference [95CI%]**	**p**	**p FDR***
miR.451a	10.2 [4.0 ; 16.8]	0,001	0,012	miR.451a	7.7 [2.5 ; 13.1]	0,003	0,041
miR.191-5p	-3.4 [-5.7 ; -0.9]	0,008	0,046	miR.93-5p	5.3 [1.7 ; 9.1]	0,004	0,024
miR.28-3p	-3.8 [-6.8 ; -0.8]	0,015	0,059	miR.146a-5p	-3.4 [-6.2 ; -0.6]	0,019	0,074
miR.93-5p	5.0 [0.8 ; 9.5]	0,021	0,062	miR.23a-5p	-3.0 [-5.6 ; -0.4]	0,027	0,081
miR.132-3p	4.0 [0.3 ; 7.8]	0,036	0,086	miR.223-3p	-2.3 [-4.5 ; -0.1]	0.040	0,097
miR.223-3p	-2.7 [-5.2 ; -0.1]	0,044	0,089	miR.28-3p	-2.7 [-5.3 ; -0.1]	0,041	0,081
miR.146a-5p	-3.0 [-6.2 ; 0.4]	0,079	0,136	miR.191-5p	-2.1 [-4.2 ; 0.0]	0,052	0,089
miR.23a-5p	-2.8 [-5.8 ; 0.3]	0,081	0,122	miR.132-3p	3.1 [0.0 ; 6.3]	0,052	0,078
miR.126-3p	-1.3 [-3.5 ; 0.9]	0,237	0,316	miR.126-3p	-0.8 [-2.7 ; 1.1]		0,534
miR.21-5p	1.1 [-1.2 ; 3.5]	0.350	0.420	miR.21-5p	0.8 [-1.2 ; 2.8]	0,448	0,537
miR.222-3p	-1.3 [-4.3 ; 1.7]	0,391	0,427	miR.222-3p	-0.9 [-3.5 ; 1.6]	0,471	0,514
miR.30b-5p	-1.1 [-4.4 ; 2.4]	0,539	0,539	miR.30b-5p	-0.8 [-3.7 ; 2.1]	0.570	0.570

* p value corrected for the false discovery rate
Adjusted for age, sex, body mass index, and year of inclusion
PM_{10}: particulate matter <10 µm, NO_2: nitrogen dioxide

Supplemental table 7 : description of previous study on association between air pollution and miR-21-5p, miR-23a-5p, miR-28-3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, miR-223-3p, miR-451a, miR-93-5p or miR-191-5p.

Author	year	Country	Population	Number of subjects	studied exposure	methodology	length of exposure	miRNA studied in common with our study
Tsamou (1)	2018	Belgium	pregnant women	210	$PM_{2.5}$	Cohort	exposure during pregnancy	miR-21,miR-146a,miR-222,in placenta at birth
Rider (2)	2016	Canada	Non-smoker	15	experimental exposure to diesel exhaust	Cross-over	short term	800 miRNA(bronchial brushings)
DU (3)	2022	Shanghai (China)	healthy college student	35	road session vs park session (TRAP)	Cross-over	short term	all
Chen (4)	2018	Shanghai (China)	student	55	true vs sham air purifier : $PM_{2.5}$	Cross-over	short term (9-days)	miR-21.5p,miR-146a-5p miR-93-5p,
Krauskopf (5)	2018	London (UK)	non-smoker. mean age 65	24	PM_{10}, $PM_{2.5}$,black carbon, UFP, NO2	Cross-over	short term (2-hours)	miR-30.5p,miR-223.3p
Krauskopf (6)	2019	Barcelona (spain)	Healthy non-smokers aged from 18 to 60 years	24	PM_{10}, $PM_{2.5}$,UFP, BC ,NO_2, CO, CO_2	Cross-over	Short term (7h30)	miR-28-3p, miR-30b-5p, miR-222-3p, miR-146a-5p
Hou (7)	2016	Beijing (china)	60 truck driver and 60 office worker	120	$PM_{2.5}$, EC	repeated measurement	Short term	miR-146a
Vriens (8)	2016	Belgium	childrens	80	$PM_{2.5}$, UFP	repeated measurement	short term	miR-146a (saliva)
Mancini (9)	2020	Switzerland, United Kingdom, Italy , Netherlands	heathly non-smoking adults	143	$PM_{2.5}$	repeated measurment	short term 24-hours	none

Supplemental table 7 (continued) : description of previous study on association between air pollution and miR-21-5p, miR-23a-5p, miR-28-3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, miR-223-3p, miR-451a, miR-93-5p or miR-191-5p.

Author	year	Country	Population	Number of subjects	studied exposure	methodology	length of exposure	miRNA studied common with our study
Chen (10)	2020	North Carolina (USA)	coronary artery disease patients	14	Ozone, $PM_{2.5}$	repeated measurement	short term (1 to 5-days)	miR-21–5p,miR-126–5p, miR-146–5p,
Louwies (11)	2016	Belgium	helthy adults	50	PM_{10}	repeated measurement	short term (2-hours to 1-week)	miR-21, miR-146a, miR-222
Rodosthenous (12)	2016	Boston (USA)	men between 21 and 80 years	22	$PM_{2.5}$	repeated measurement	short term (1 day) intermediate (1-week, 1-month) long term (6-month, 1-year)	miR23a-3p, miR93-5p, miR-126-3p, miR-146a-5p, miR-191-5p, miR-223-3p, miR-451a
Fossati (13)	2013	Boston (USA)	Elderly men "Normative Aging Study"	153	$PM_{2.5}$, BC	Cross sectional	short term - intermediate (4-hours to 28-days)	miR.21, miR.126, miR.146a, miR.222
Motta (14)	2016	Italy	Obese and overweight	90	PM_{10}	Cross sectional	short term	miR-21, miR-30b, miR-222, miR-451
Li (15)	2020	Jinan China	Childrens	273	(BPDE-Alb) biomarker of PM exposure	Cross sectional	long term	miR-21-5p, miR-146a-5p

BPDE-Alb : benzo[a]pyrene-r-7,t-8,t-9,c-10-tetrahydotetrol and serum albumin ; PM : particulate matter ; $PM_{2.5}$ particulate matter <2.5 µm; PM_{10}: particulate matter <10 µm ; NO_2: nitrogen dioxide; BC : Black Carbon, EC : elemental carbon ; UFC : Ultrafine particle; CO carbon monoxide; CO_2 Carbon dioxide ; TRAP: traffic air pollution.

Supplemental table 8: Significant association observed in literature between air pollution and miR-21-5p, miR-23a-5p, miR-28-3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, miR-223-3p, miR-451a, miR-93-5p or miR-191-5p

		Long term exposure		**Short term exposure**	
MiRNA Main Biological effect	**Biological effect**	**Exposure Positively associated with miRNA**	**Exposure negatively associated with miRNA**	**Exposure Positively associated with miRNA**	**Exposure negatively associated with miRNA**
miR-21-5p Inflammation	Inhibition of tumor suppressor genes such as PTEN and PDCD4 (16) Positive regulation of the NF-κB/NLRP3 pathways (17)	BPDE-Alb ; li (15)	NO_2 and $PM_{2.5}$ exposure during trimester 2 of pregnancy ; Tsamou (1)	Controlled diesel exhaust ; Rider (2)	$PM_{2.5}$; Chen 2018 (4) $PM_{2.5}$, BC ; Fossati (2) PM_{10} ; Louwies (11) TRAP ; DU (3)
miR-23a-5p inflammation	Inhibition of NLRP3-activating factors, (18,19)	PM10 (6 month 1 year) Rodosthenous (12)	NO_2 ; Hubert		TRAP ; DU (3)
miR-28-3p inflammation	Downregulation of the NRF2 signaling pathway, (20)		NO_2 ; Hubert	TRAP; Krauskopf 2019. (6)	
miR-30b-5p inflammation	Regulation of the JAK/STAT3 pathway through inhibition of SOCS3, (21)			TRAP ; Krauskopf 2019 (6)	PM_{10} ; Motta(14) TRAP ; DU (3)
miR-126-3p carcinogenesis	Restriction of cell proliferation via inhibiting PLXNB2 expression and the subsequent RhoA/ROCK signaling pathway.(22) Regulation of the PIK3/AKT signaling cascade by inhibition of IRS-1, PIK3R2 and AKT2. (23–25)	PM2.5 (6 month ,1 year) **;** Rodosthenous (12)		PM_{10} ; Rodosthenous(12)	$PM_{2.5}$; BC ; Fossati (13)
miR-132-3p inflammation	Upregulation of inflammatory and apoptosis by targeting SIRT1, (25)				TRAP ; Krauskopf 2018(5)

Supplemental table 8 (continued) : Significant association observed in literature between air pollution and miR-21-5p, miR-23a-5p, miR-28-3p, miR-30b-5p, miR-126-3p, miR-132-3p, miR-146a-5p, miR-222-3p, miR-223-3p, miR-451a, miR-93-5p or miR-191-5p

		Long term exposure		**Short term exposure**	
MiRNA Main Biological effect	**Biological effect**	**Exposure Positively associated with miRNA**	**Exposure negatively associated with miRNA**	**Exposure Positively associated with miRNA**	**Exposure negatively associated with miRNA**
miR-146a-5p inflammation	Downregulation of the NF-□B-mediated priming of the NLRP3 inflammasome, (26,27)	BPDE-Alb; li (15)	NO2, Hubert	TRAP ; Krauskopf 2019 (6) PM_{10} ; Rodosthenous(12)	$PM_{2.5}$; Chen 2018 (4) $PM_{2.5}$, BC ; Fossati (13) NO_2 **;** Chen 2020 (10)
miR-222-3p inflammation	Modulation of the JAK/STAT pathways by targeting SOCS1 (29,30)		$PM_{2.5}$ exposure during trimester 2 of pregnancy (1)	TRAP ; Krauskopf 2019 (6) UFP ; Vriens (8)	PM2.5, BC ; Fossati (2) PM10 ; Louwies (11) TRAP ; DU (3)
miR-223-3p inflammation	Inhibition of the NLRP3 inflammasome (31,32)	$PM_{2.5}$ (6 month and 1 year) **;** Rodosthenous (12)	NO_2, Hubert	PM_{10}, Rodosthenous (12) Controlled diesel exhaust ; Rider (2)	
miR-451a inflammation	Inhibition of the NF-kB pathway (33–36)	PM_{10},NO_2 ; Hubert			Rodosthenous (12)
miR-93-5p (endogenous control) inflammation	Regulation of IL-8 and VEGF gene expression (37) Involvment in oxidative stress-induced mitophagy (38)	PM_{10}, NO_2 ;Hubert $PM_{2.5}$ (6 month and 1 year) Rodosthenous(12)			
miR-191-5p (endogenous control) inflammation	Downregulation of the NLRP3 inflammasome by repressing C/EBPß,(39); Inhibition of the MAPK signaling pathway by targeting Map3k12, (40)	$PM_{2.5}$ (6 month and 1 year) Rodosthenous (12)	PM_{10}, NO_2 ; Hubert		

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Date de soutenance : 20/09/2024
Titre de la thèse : La relation entre l'exposition résidentielle à la pollution atmosphérique et les micro-ARN circulants chez les adultes vivant en zone urbaine du nord de la France

Thèse - Médecine - Lille 2024
Cadre de classement : *Médecine*
DES: DES Santé Publique et Médecine Sociale
Mots-clés : Santé environnementale, pollution atmosphérique, particules en suspension, dioxyde d'azote, micro-ARN, biomarqueurs

Résumé :
Introduction : Les micro-ARN sont des facteurs de régulation épigénétique capables de réprimer l'expression des gènes cibles et pourraient jouer un rôle dans les effets de la pollution atmosphérique sur la santé. L'objectif de la présente étude en population générale était d'examiner l'association entre l'expression des micro-ARN et l'exposition résidentielle à long terme aux PM_{10} et au NO_2.
Méthode : Nous avons inclus 998 participants adultes non-fumeurs issus de l'enquête transversale ELISABET (2010-2014) dans la région urbaine de Lille, en France. Les niveaux moyens annuels de pollution résidentielle ont été estimés à l'aide d'un système de modélisation de dispersion atmosphérique. Dix micro-ARN ont été sélectionnés sur la base des données disponibles dans la littérature, ainsi que deux micro-ARN de référence (miR-93-5p et miR-191-5p), et ont été quantifiés par RT-qPCR. Des modèles de régression linéaire multivariée ont été utilisés pour étudier l'association entre les micro-ARN et la pollution atmosphérique. Le seuil de signification statistique (après correction pour le taux de fausse découverte) a été fixé à $p < 0,1$.
Résultats : L'exposition annuelle moyenne entre 2011 et l'année d'inclusion était de 26,4 ± 2,0 µg/m³ pour les PM_{10} et de 24,7 ± 5,1 µg/m³ pour le NO_2. Chaque augmentation de 2 µg/m³ d'exposition aux PM_{10} était associée à une augmentation de 8,6 % (IC 95 % [3,1 ; 14,3]; p_{FDR} = 0,019) de l'expression de miR-451a. Une augmentation de 5 µg/m³ de l'exposition au NO_2 était associée à une augmentation de 5,3 % (IC 95 % [0,7 ; 10]; p_{FDR} = 0,056) de l'expression de miR-451a, une diminution de 3,6 % (IC 95 % [-6,1 ; -1,1]; p_{FDR} = 0,052) de l'expression de miR-223-3p, une diminution de 3,8 % (IC 95 % [-6,8 ; -0,7]; p_{FDR} = 0,079) de l'expression de miR-28-3p, une diminution de 4,3 % (IC 95 % [-7,7 ; -0,8]; p_{FDR} = 0,055) de l'expression de miR-146a-5p et une diminution de 4,0 % (IC 95 % [-7,4 ; -0,4]; p_{FDR} = 0,059) de l'expression de miR-23a-5p. La différence entre les deux micro-ARN de référence miR-93-5p et miR-191-5p était également associée à l'exposition aux PM_{10} et au NO_2.
Conclusion : Nos résultats suggèrent que les micro-ARN circulants pourraient être des biomarqueurs précieux pour évaluer les effets de la pollution atmosphérique.

Composition du Jury :

Président :	Monsieur le Professeur Philippe AMOUYEL
Assesseurs :	Monsieur le Docteur Jean-Marc LO GUIDICE
	Madame la Docteur Victoria GAUTHIER
Directeur de thèse :	Monsieur le Docteur Luc DAUCHET