Exposition des femmes enceintes aux polluants atmosphériques :

Détermination des indicateurs d'exposition pertinents et conséquences de l'exposition sur la santé cardiovasculaire, les échanges materno-fœtaux, et la croissance fœtale

Acronyme : ***EDEN-AIR PLUS***

Rapport scientifique final

A l'attention de l'ANSES

Projet soutenu dans le cadre de l'APR Environnement-Santé-Travail 2007

Projet n°EST-09-97

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Abréviations

AASQA : Associations agrées de Surveillance de la Qualité de l'Air

IC, CI : Intervalle de Confiance

LUR : Land Use Regression

NO2 : Dioxyde d’azote

PM10 : Particules en suspension avec un diamètre aérodynamique inférieur à 10 μm

Résumé

Contexte : Différentes études épidémiologiques ont suggéré que l'exposition maternelle aux polluants atmosphériques durant la grossesse pourrait influencer la croissance fœtale. Sur le plan de l'estimation des expositions, la plupart de ces travaux se sont appuyés sur le réseau des stations permanentes de surveillance de la qualité de l'air, dont la résolution spatiale est limitée. Sur le plan des mécanismes d'action sous-jacents, si certaines hypothèses ont été formulées, aucune n'a été réellement étudiée alors que ce point est central pour discuter la plausibilité biologique des associations observées.

Objectifs : Nos objectifs étaient *1) sur le plan de l'expologie*, de développer différents modèles d'exposition aux polluants atmosphériques (et notamment un modèle Land Use Regression, ou *LUR*) et de les comparer aux modèles utilisés par le passé, à la fois en termes de niveau d'exposition et d'association avec le poids de naissance ; *2) sur le plan étiologique*, de caractériser l'impact de la pollution atmosphérique sur *la pression artérielle* de la femme enceinte, sur *les échanges materno-fœtaux, la croissance placentaire* et sur *la croissance fœtale*.

Méthodes : Nous nous sommes appuyés sur la cohorte mère-enfants EDEN (Nancy, Poitiers) dans laquelle environ 1900 femmes enceintes ont été recrutées et suivies jusqu'à la naissance et au-delà. Leur pression artérielle a été mesurée de façon répétée en cours de grossesse. Un modèle de type land-use regression (LUR) a été développé à partir de campagnes de mesures du NO_2 réalisées à différentes saisons d'une année. Les différents modèles déjà disponibles (modèle géostatistique, modèle de dispersion implémenté sous ADMS-Urban et approche reposant sur la station de surveillance la plus proche) ont été comparés. L'impact à court terme des polluants atmosphériques sur la pression artérielle a été estimé à partir d'un modèle longitudinal ajusté sur les conditions météorologiques. Les échanges materno-placentaires ont été caractérisés à partir de mesures Doppler à 20-24 et 30-34 semaines de gestation. La croissance du fœtus a été suivie à l'aide des mesures échographiques réalisés simultanément aux examens Doppler, et les poids du placenta et du fœtus mesurés à la naissance. Les données de la cohorte ont été incluses dans le projet européen ESCAPE pour étudier l'effet des polluants atmosphériques sur le poids de naissance à terme.

Résultats : Le modèle LUR a été développé et implémenté dans les deux agglomérations. La corrélation entre les modèles en terme de niveau de NO_2 prédit était élevée entre les modèles LUR et de dispersion, et modérée pour les autres comparaisons ; malgré cela, il y avait une certaine concordance entre modèles en termes d'associations entre polluants et poids de naissance. Les niveaux de pollution avaient un effet à court terme sur la pression artérielle de la femme enceinte, tout comme la température extérieure. Un effet possible des niveaux de particules (PM_{10}) sur le poids du placenta a été observé à Nancy (où les niveaux de pollution étaient plus importants) mais pas à Poitiers. Les niveaux de pollution (moyenne dans les 30 jours avant l'examen) étaient associés à une diminution de l'indice de résistance de l'artère ombilicale et à une augmentation de l'indice de résistance de l'artère fœtale cérébrale ainsi que de l'indice cérébro-placentaire. Au sein du projet ESCAPE, les niveaux de particules fines étaient associés à une augmentation du risque de petit poids de naissance (<2500 g) à terme, et à une diminution du périmètre crânien à la naissance.

Conclusion : Le projet Eden-Air+ et les projets connexes ont permis de développer un ensemble très complet de modèles d'exposition aux polluants atmosphériques de façon standardisée dans les agglomérations de Nancy et Poitiers (approche stations, modèle de dispersion, modèle géostatistique *saisonnalisé*, modèle LUR *saisonnalisé*). Ces travaux ont mis en évidence un effet à court terme des polluants atmosphériques sur la pression artérielle de la femme enceinte et les échanges sanguins materno-placentaires. Ils ont aussi contribué à confirmer que les polluants atmosphériques peuvent augmenter le risque de petit poids de naissance à terme et altérer la croissance du périmètre crânien.

Mots-clés : grossesse, modélisation, modèle de dispersion, pollution atmosphérique, pression artérielle.

Résumé anglais

Background: Several epidemiological studies suggested that maternal pregnancy exposure to atmospheric pollutants could impact on fetal growth. In terms of exposure assessment, most previous studies relied on the network of permanent air quality monitoring stations, which provide a limited spatial resolution. In terms of underlying mechanism, although several hypotheses have been formulated, none has been deeply investigated, which is important to discuss the plausibility of the epidemiological associations observed.

Aims: Our aims were 1) in terms of exposure assessment, to develop several models of exposure to atmospheric pollutants, including a Land Use Regression (LUR) model, and to compare this LUR model to those used in the past, in terms of predicted exposure levels and of association with birth weight; 2) from an etiological point of view, to characterize the impact of atmospheric pollutants on the blood pressure of pregnant women, on maternal-fetal exchanges assessed by Doppler measures, on placental growth and fetal growth.

Methods: We relied on EDEN mother-child cohort, conducted in Nancy and Poitiers areas, in which 1900 pregnant women were recruited and followed-up until pregnancy and beyond. Blood pressure has been characterized by repeated measures during pregnancy. A LUR model has been developed from repeated measurement campaigns of nitrogen dioxide (NO_2), and compared to the models that we had previously developed in the area (geostatistical model, dispersion model developed using ADMS-Urban software, and approach relying on the permanent network of monitoring stations). Maternal-placental exchanges were characterized from Doppler measures of uterine, umbilical and fetal brain arteries at 20-24 and 30-34 gestational weeks. Ultrasound measures performed simultaneously allowed to characterize fetal growth. Finally, Eden cohort was pooled within ESCAPE European cohort to study the impact of atmospheric pollutants on the risk of low birth weight (<2500 g) among term births.

Results: The correlation between predicted NO_2 levels was high for LUR and dispersion models, and moderate for the other exposure models. Nonetheless, models were in relative agreement in terms of association with birth weight. Atmospheric pollutants were associated with maternal blood pressure, as well as outside temperature. A possible effect of particulate matter (PM_{10}) on placental weight was observed in Nancy area (where exposure levels were higher), but not in Poitiers area. Atmospheric pollutants in the 30 days before the Doppler examination were associated with a decrease in the resistance index of umbilical artery and an increase in the resistance index of the fetal brain artery as well as in the brain-placental index. Within ESCAPE project (60,000 births among 14 cohorts), fine particulate matter ($PM_{2.5}$) pregnancy levels were associated with an increased risk of low birth weight at term and a decrease in head circumference at birth.

Conclusion: Eden-Air+ and the related projects have allowed developing a very large array of exposure models in two areas. These allowed highlighting a possible short-term effect of atmospheric pollutants on maternal blood pressure during pregnancy, and possible effects on maternal-placental and placental-fetal blood flow. This work also contributed confirming that atmospheric pollutants can increase the risk of term low birth weight and alter head circumference.

Key-words: air pollution modeling, blood pressure, cardiovascular function, dispersion modeling, pregnancy.

Résumé grand public

Projet Eden-Air plus

Exposition des femmes enceintes aux polluants atmosphériques : *Détermination des indicateurs d'exposition pertinents et conséquences de l'exposition sur la santé cardiovasculaire, les échanges materno-fœtaux, et la croissance fœtale*

Depuis une dizaine d'années, des études épidémiologiques ont suggéré que l'exposition maternelle à la pollution de l'air pourrait influencer le déroulement de la grossesse, et notamment réduire la durée de gestation et le poids de naissance. Les premiers travaux se sont surtout appuyés sur des registres de naissance, qui recueillent peu de données sur les facteurs de confusion potentiels, et ont caractérisé l'exposition à partir des concentrations mesurées par les réseaux fixes de surveillance de la qualité de l'air. Nous présentons ici les résultats obtenus à partir de la cohorte mère-enfant EDEN (Étude des Déterminants pré- et post-natals de la santé de l'ENfant), dans laquelle nous avons 1) développé différents modèles d'exposition à la pollution atmosphérique afin d'en discuter la pertinence, et 2) étudié ses effets sur le déroulement de la grossesse.

EDEN est une cohorte mère-enfant dans laquelle 2002 femmes enceintes ont été recrutées avant la 22e semaine de grossesse dans les maternités des hôpitaux de Nancy et Poitiers entre 2002 et 2006. Les données sur les antécédents médicaux et la santé des femmes et de leurs enfants ont été recueillies au cours de la grossesse puis après la naissance, par questionnaires et examens médicaux ad-hoc. En particulier, la croissance fœtale a été suivie pendant la grossesse à l'aide de mesures échographiques, puis par des mesures anthropométriques du nourrisson et de l'enfant. Concomitamment, des mesures Doppler ont permis de caractériser les flux sanguins dans l'artère ombilicale et l'artère cérébrale du fœtus, qui renseignent sur la qualité des échanges entre la mère, le placenta et le fœtus. Le placenta a également été pesé et un échantillon prélevé à la naissance. Les adresses des domiciles des femmes au cours de la grossesse ont été géocodées. Des modèles de pollution ayant une résolution spatiale très fine, et prenant en compte les sources de pollution locales (trafic, habitat, industrie) ainsi que les fluctuations saisonnières ont été

développés.

Les niveaux de pollution avaient un effet à court terme sur la pression artérielle de la femme enceinte, tout comme la température extérieure. Un effet possible des niveaux de particules en suspension (PM_{10}) sur le poids du placenta a été observé à Nancy (où les niveaux de pollution étaient plus importants) mais pas à Poitiers. Les niveaux de pollution (moyenne dans les 30 jours avant l'examen) étaient associés à une diminution de l'indice de résistance de l'artère ombilicale et à une augmentation de l'indice de résistance de l'artère fœtale cérébrale ainsi que de l'indice cérébro-placentaire. Le sens de ces effets était contraire à celui attendu, et leur implication n'est pas claire en l'état actuel des connaissances.

Les données de la cohorte Eden ont été incluses dans le projet européen ESCAPE pour étudier l'effet des polluants atmosphériques sur le poids de naissance à terme à partir d'un effectif de naissance considérable (environ 60 000 naissances). Les niveaux de particules fines étaient associés à une augmentation du risque de petit poids de naissance (<2500 g) à terme, et à une diminution du périmètre crânien à la naissance. A l'échelle des centres urbains européens considérés, la fraction de cas de petits poids de naissance à terme attribuables à la pollution atmosphérique était du même ordre de grandeur que celle attribuable au tabagisme actif maternel. Ceci s'expliquait par le fait que l'effet de la pollution atmosphérique sur le poids de naissance, plus faible au niveau individuel que l'effet du tabagisme actif, est compensé par la grande fréquence d'exposition aux polluants atmosphériques en population générale.

Ce travail a permis de confirmer un effet des polluants atmosphériques urbains (dont les niveaux de particules en suspension constituent un marqueur) sont susceptibles d'augmenter le risque de petit poids de naissance. Il a aussi permis de montrer que ces polluants peuvent probablement perturber la fonction cardiovasculaire de la femme enceinte, et peut-être altérer la fonction placentaire, qui est essentielle pour permettre le développement du fœtus.

Ce projet a été rendu possible par la collaboration entre plusieurs équipes de recherche de l'Inserm, deux réseaux agréés de surveillance de la qualité de l'air, deux centres hospitaliers universitaires, ainsi qu'une équipe de recherche du Helmholtz Center for Environmental Health de Munich.

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A. Introduction et objectifs

I. Introduction

De nombreux travaux, publiés essentiellement dans les dix dernières années, ont indiqué une association possible entre l'exposition maternelle aux polluants atmosphériques pendant la grossesse et la croissance fœtale de l'enfant, en général estimée par le poids de naissance (Glinianaia, et al., 2004, Slama, et al., 2008, Sram, et al., 2005).

En 2007, un workshop (soutenu par l'ANSES) qui s'est tenu au Helmholtz Center Munich, a fait le point sur les forces et faiblesses de cette littérature (Slama, et al., 2008). *Du point de vue de l'estimation des expositions*, un constat était que la plupart des études publiées ont reposé sur un modèle d'exposition construit uniquement à partir des données des stations de mesure de la qualité de l'air les plus proches du domicile de chaque femme, approche susceptible d'entraîner d'importants biais de classement de l'exposition. Les modèles d'exposition avec une résolution spatiale et temporelle fine, comme les modèles de dispersion ou les modèles *Land-Use Regression* (LUR) (Brauer, et al., 2008, Slama, et al., 2007) ont été proposés comme des alternatives qu'il est important d'explorer. *Du point de vue des événements étudiés,* le poids de naissance est un indicateur a posteriori de la croissance fœtale alors que les mesures réalisées au cours de la grossesse par échographie permettent de caractériser l'impact de l'exposition maternelle à la pollution atmosphérique tout au long de la grossesse et de détecter des éventuels effets précoces et phénomènes de rattrapage de croissance. A ce jour, une étude australienne, dans laquelle l'exposition était estimée sur la base des mesures de la station de surveillance de la qualité de l'air, a reposé sur des données échographiques (Hansen, et al., 2008), ainsi que nos travaux réalisés dans le cadre du projet Eden-Air (Slama, et al., 2009). *Du point de vue des mécanismes biologiques* potentiellement responsables de ces effets, plusieurs hypothèses existent mais elles restent peu étayées à ce jour, ce qui limite la possibilité de juger de la plausibilité de l'effet observé sur la croissance fœtale.

La plupart de ces travaux ont été conduits hors d'Europe de l'ouest, à l'exception d'une étude réalisée auprès de la population de Munich (Slama, et al., 2007) et d'une étude française (Slama, et al., 2009). Cette dernière étude, financée dans le cadre du projet Eden-Air par l'ANSES, s'était appuyée sur une estimation de l'exposition personnelle à l'aide d'échantillonneurs passifs auprès de 280 femmes de la cohorte Eden, approche pertinente mais difficile à appliquer à des effectifs importants.

II. Objectifs

Les objectifs du projet sont répartis entre un volet d'expologie et un volet étiologique :

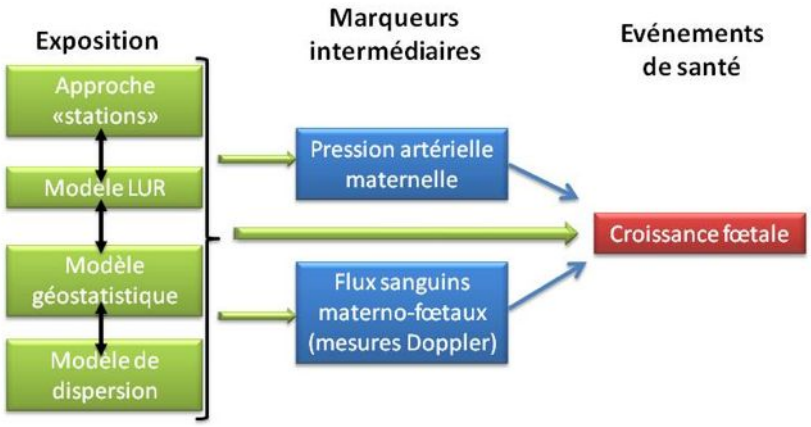
Volet d'expologie :

1) Comparer différents modèles d'expositions aux polluants atmosphériques et déterminer l'indicateur pertinent pour estimer l'exposition des femmes enceintes.

Volet étiologique :

2) Caractériser l'influence de la pollution atmosphérique sur la croissance fœtale, en estimant l'exposition à partir de différents modèles avec des résolutions spatiale et temporelle fines ;
3) Caractériser l'influence de l'exposition de la femme enceinte aux polluants atmosphériques sur sa fonction cardio-vasculaire, sur les échanges sanguins materno-fœtaux et sur le poids du placenta[1], marqueurs intermédiaires pouvant expliquer un effet de la pollution atmosphérique sur la croissance fœtale.

Figure 1 : Aperçu des principaux objectifs du projet Eden-Air Plus.



[1] L'étude du poids placentaire ne figurait pas dans les objectifs initiaux et a été ajouté en cours de projet. Elle est détaillée dans l'article de Rahmalia et coll. (2012) joint en annexe.

B. Volet expologie

I. Développement d'un modèle Land Use Regression (LUR) à Nancy et Poitiers

1. Généralités

Les modèles de type « Land Use Regression » (Hoek, et al., 2008) visent à modéliser les variations spatiales dans les niveaux de pollution atmosphérique (dioxyde d'azote dans le cas de notre projet). Il consiste à réaliser des modèles d'exposition de la population à partir d'un nombre conséquent de variables géolocalisées, et des niveaux de pollution mesurés sur la zone d'étude lors de campagnes répétées.

Le modèle créé est obtenu par la réalisation d'une régression linéaire entre d'une part les niveaux de pollutions mesurés, et d'autre part l'ensemble des variables géolocalisées disponibles.

2. Méthodologie

Le développement du modèle s'est fait selon les procédures décrites dans le cadre du projet européen ESCAPE (European Studies of Cohorts of Air Pollution Effects)(Beelen, et al., 2013), dont certaines études de notre consortium sont partenaires ; cette approche a été conduite en parallèle dans une trentaine de villes européennes (financement UE, FP7), avec lesquelles nous pourrons donc comparer nos résultats à Nancy et Poitiers. Deux types de modèles sont recherchés : des modèles de globaux, utilisant l'intégralité des données disponibles ; et des modèles de fond, ne s'appuyant que sur les données hors influence des sources d'émissions.

Le modèle de régression est progressivement construit selon une procédure itérative visant, à chaque itération, à améliorer les résultats du modèle (adéquation aux données) tout en conservant les acquis des précédentes itérations.

Ces procédures ont été appliquées à différentes zones d'études à travers l'Europe. Dans le cadre d'EDEN Air, des modèles *LUR* ont été développés pour les années 2005 et 2009 sur Poitiers et 2002 pour Nancy.

L'ensemble de la démarche destinée à obtenir *in fine* les modèles LUR se répartit selon les étapes suivantes :

- mesures de la pollution en plusieurs points de la zone d'étude et à plusieurs reprises sur une année ;
- estimation de la pollution annuelle moyenne en ces différents points ;
- collecte de données géolocalisées (Corine Land Cover, Eurostreet, BD Topo, etc.) ;
- transformations et combinaisons des données géolocalisées disponibles afin d'obtenir un maximum de variables candidates pour les modèles ;
- construction des modèles selon la procédure spécifique à ESCAPE, telle que définit dans le protocole de l'étude ESCAPE (Beelen, et al., 2013).

La procédure spécifique à ESCAPE pour la réalisation d'un modèle consiste en premier lieu à calculer la régression linéaire des concentrations de polluants en fonction de chaque variable explicative candidate individuellement. La variable expliquant le mieux la variabilité des concentrations est retenue (le R^2 ajusté est utilisé).

Suite à cette première étape, une nouvelle régression linéaire est déterminée pour chaque variable restante. Le modèle inclut la variable précédemment retenue. À nouveau, et sous réserve de respect de certains critères, la variable améliorant au mieux le modèle sera retenue.

L'étape précédente est répétée de manière itérative jusqu'à ce le gain sur le R^2 ajusté soit inférieur à un seuil fixé au préalable.

Le modèle obtenu est validé selon certains critères statistiques au moyen des tests appropriés : influence de valeurs extrêmes, hétéroscédasticité, autocorrélation spatiale, normalité des résidus.

En dernier lieu, une validation croisée est réalisée afin de valider le modèle obtenu.

La procédure étant quelque peu lourde à mettre en place, un programme interfacé a été développé afin de rendre son application plus aisée et de réduire le risque d'erreur.

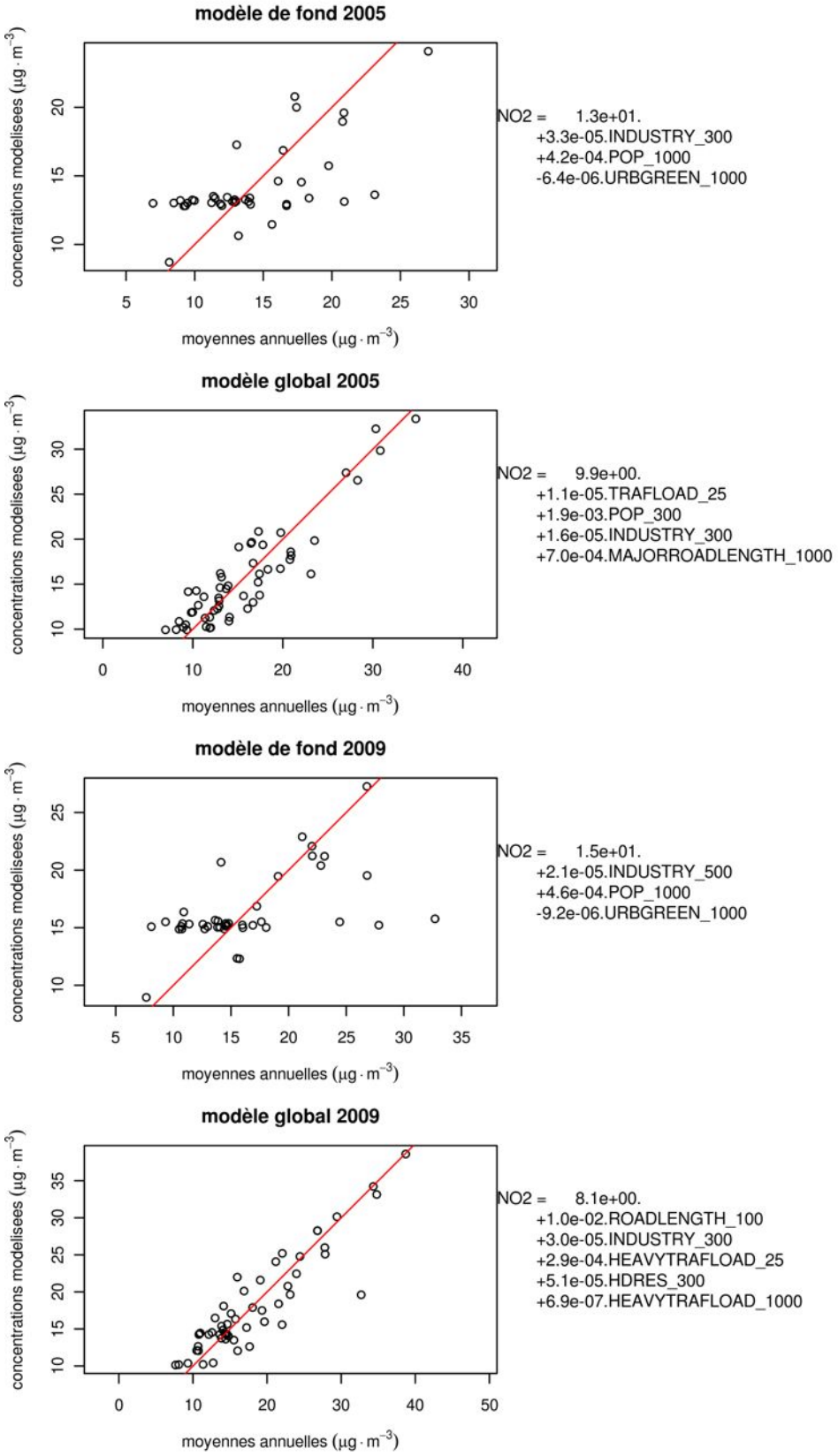
3. Résultats : modèles obtenus

Les variables retenues pour chaque modèle sont indiquées Figure 2.

Les noms des différentes variables explicatives sont composés de 2 éléments : la donnée ayant servie au calcul et la taille en mètres du buffer dans lequel la donnée est agrégée.

Les modèles de fond (excluant les sites trafic) reproduisent assez mal la variabilité des données mesurées. Ce résultat est fréquemment observé dans les autres zones du projet ESCAPE, lorsque les variations des concentrations mesurées sont faibles.

Figure 2 : Modèles LUR définis dans l'agglomération de Poitiers : accord avec les mesures des campagnes (cercles) et liste des variables retenues.

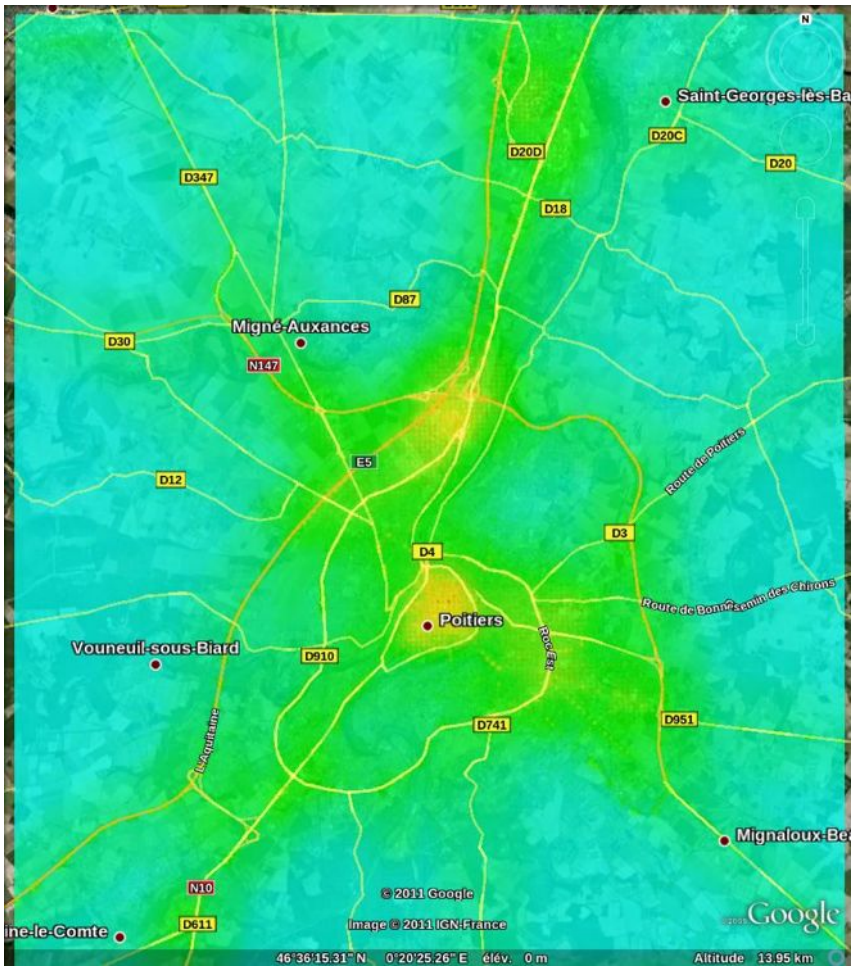


Les modèles globaux s'appuient sur l'ensemble des mesures réalisées. Du fait qu'ils ne sont pas limités au 'fond', des variables liées à la proximité des sources d'émissions de dioxyde d'azote (routières notamment) sont prises en compte dans le développement des modèles. Ces deux éléments sont plus représentatifs à la fois des variations réelles observées sur les

niveaux de concentrations en dioxyde d'azote et des émissions responsables des variations observées. Les modèles globaux sont par conséquent de meilleure qualité que les modèles 'de fond', et sont à même de restituer la variabilité des concentrations observées dans l'air ambiant.

La cartographie Figure 3 représente le résultat du modèle global de 2005 appliqué sur une grille de cent mètres sur la zone de Poitiers.

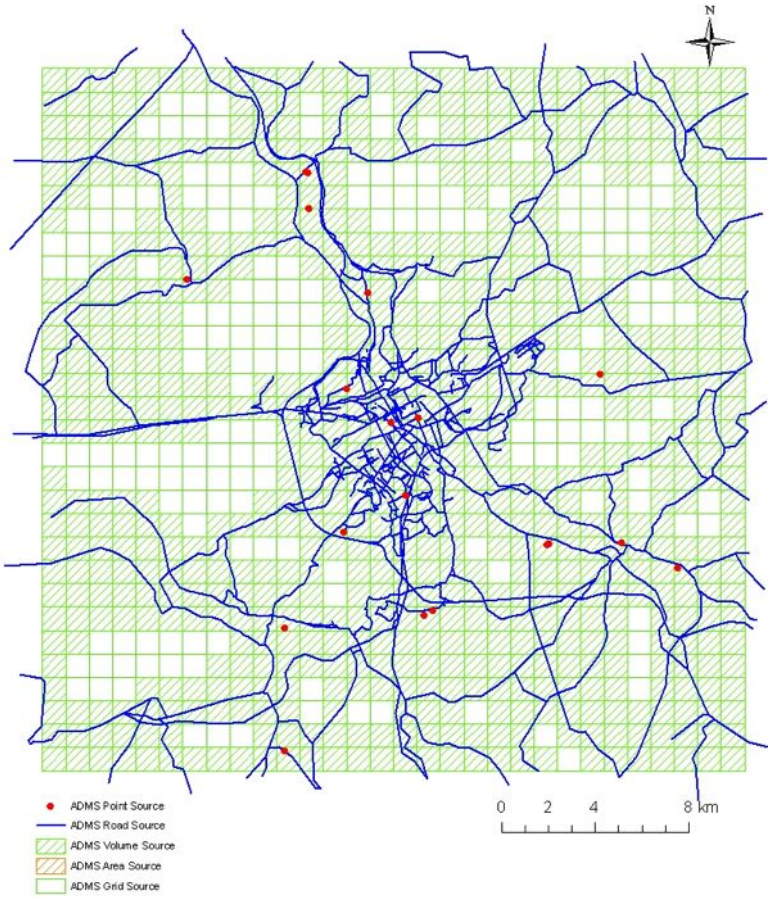
Figure 3 : Niveaux moyens de NO_2 dans l'agglomération de Poitiers estimés par le modèle LUR (année 2005). La couleur jaune indique les niveaux les plus élevés, le bleu les niveaux les plus faibles.



II. Développement d'un modèle de dispersion atmosphérique à Nancy et Poitiers

Ce modèle a été développé à l'aide de financements antérieurs de l'ANSES et de l'ADEME et sa construction ne sera pas détaillée. Elle s'est appuyée sur des données sur l'intensité du trafic sur l'ensemble des axes des agglomérations considérées, sur les principales sources industrielles des zones, sur les cadastres d'émissions liées notamment au chauffage urbain (Figure 4), sur les données de certaines stations permanentes de fond (pollution de fond non locale) ainsi que sur les paramètres météorologiques.

Figure 4 : Représentation des données sur les émissions de NO_2 prises en compte dans l'implémentation du modèle de dispersion ADMS (agglomération de Nancy).



L'étape de validation du modèle a permis de montrer une bonne corrélation entre les mesures horaires des stations de surveillance de la qualité de l'air et les prédictions du modèle sur le site correspondant (Figure 5).

Dans les deux villes, l'erreur relative était inférieure au site de 30% défini dans les règles de l'UE. Les valeurs prédites pour le NO_2 par le modèle sont présentées Figure 6. Un modèle pour les PM_{10} a été défini de façon similaire. Les valeurs moyennes annuelles prédites étaient de 30 µg/m^3 pour NO_2 et de 22 µg/m^3 pour les PM_{10} à Nancy, contre 20 µg/m^3 (NO_2) et 18 µg/m^3 (PM10) à Poitiers.

Figure 5 : Comparaison des mesures des stations permanentes et des prédictions du modèle de dispersion au même site (exemple des stations de l'agglomération de Poitiers.

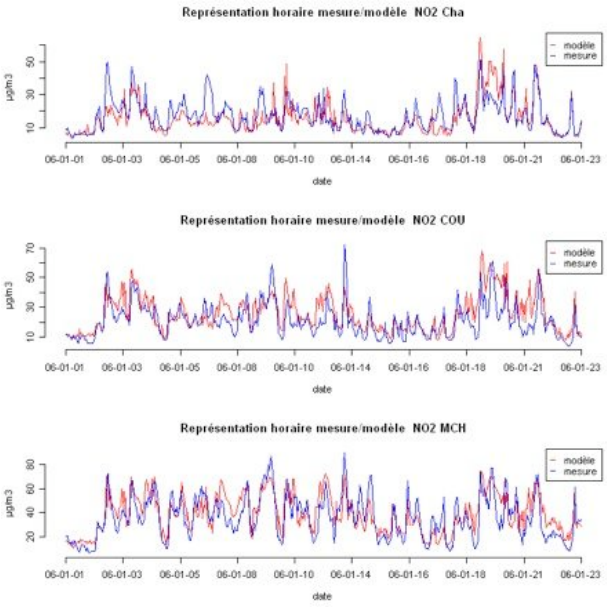
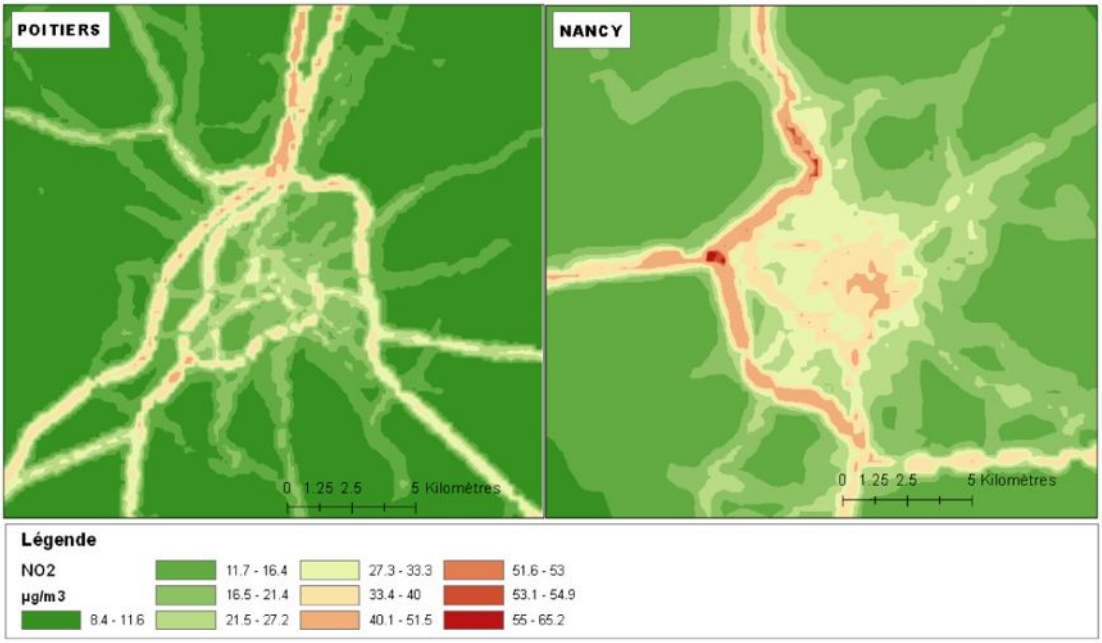


Figure 6 : Estimations des niveaux de NO_2 dans les agglomérations de Poitiers et Nancy obtenues par le modèle de dispersion ADMS-Urban.



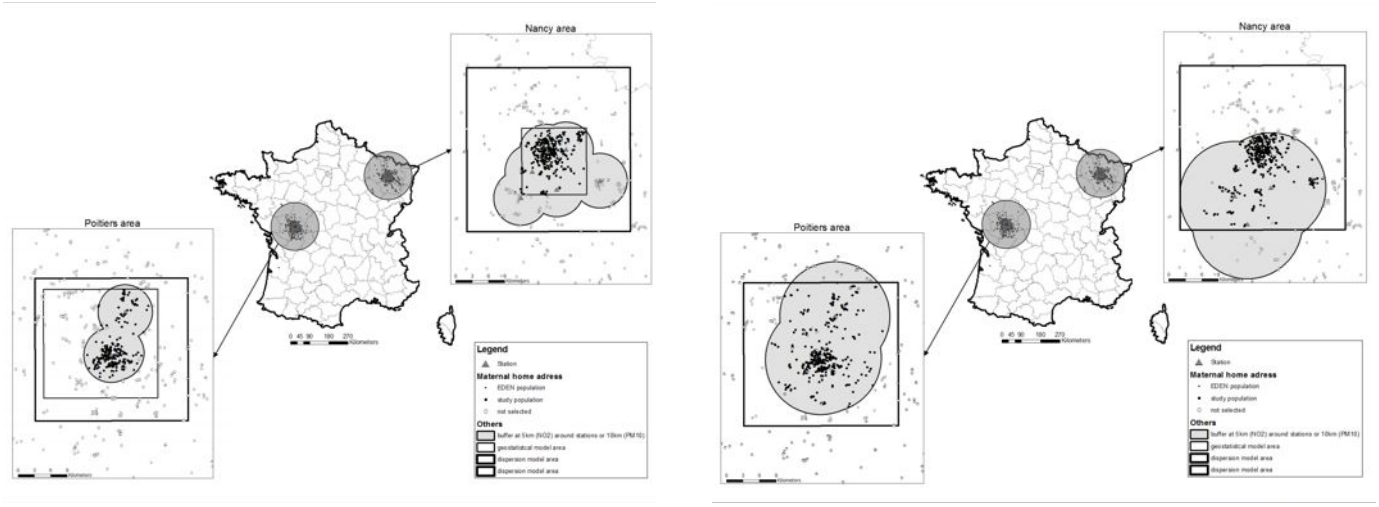
III. Quel modèle est le plus adapté pour caractériser l'impact de la pollution atmosphérique durant la grossesse ?

1. Population et méthodes

1.1. Zone d'étude

L'agglomération de Poitiers compte 120 000 habitants et celle de Nancy plus de 300 000. Deux polluants ont été étudiés, le dioxyde d'azote (NO_2) et les particules de diamètre aérodynamique inferieur à 10 µm (PM_{10}). La comparaison des modèles a été réalisée sur la zone géographique commune aux trois modèles. Les zones d'étude s'étendaient sur 155km^2 autour du centre ville de Poitiers et sur 143 km^2 autour du centre ville de Nancy pour le NO_2 (Figure 7a), et sur 443 km^2 et 394 km^2 pour les PM_{10}, respectivement (Figure 7b).

Figure 7 : Zone d'étude a) du NO_2 et b) des PM_{10} à Poitiers et Nancy (cohorte EDEN).



Les adresses des femmes participant à l'étude ont été géocodées afin d'être intégrées à un système d'information géographique. L'exposition des femmes à la pollution atmosphérique a été estimée à leur domicile à partir des 3 modèles d'exposition. Les déménagements ont été pris en compte. Lorsqu'un déménagement survenait au cours d'une période d'exposition donnée, l'exposition estimée de la femme correspondait à une moyenne pondérée par le temps passé à chaque adresse. Ceci est valable pour les 3 modèles.

1.2. Fenêtre d'exposition

Pour chaque femme, l'exposition à la pollution atmosphérique a été calculée (moyenne) pour 4 fenêtres d'exposition : chacun des 3 trimestres de la grossesse ainsi que l'ensemble de la grossesse. Pour pouvoir calculer un niveau d'exposition moyen, au moins 75% des données devaient être disponibles (seuil réglementaire utilisé par les AASQA).

1.3 Population d'étude

Parmi les 2002 femmes de la cohorte, nous avons sélectionné celles qui étaient dans la zone géographique recoupant les trois modèles d'exposition, et qui avaient des données sur le poids de naissances de leur enfant, et des expositions estimées par les trois modèles pour au moins un trimestre de grossesse.

1.4. Modèles d'exposition

Le modèle LUR étant en cours de finalisation, trois modèles ont pour l'heure été comparés : le modèle dit *station*, le modèle *géostatistique saisonnalisé* et le modèle *de dispersion*.

1.4.1. Modèle *stations*

Il est basé sur les données des stations de surveillance de la qualité de l'air situées dans les zones urbaine et périurbaine de Poitiers et Nancy qui comptent respectivement 3 stations de fond mesurant le NO_2 et les PM_{10} à Poitiers (Figure 8a) et 6 mesurant le NO_2 et 4 mesurant les PM_{10} à Nancy.

Le calcul de l'exposition des femmes selon le modèle *stations* consistait à moyenner les concentrations mesurées par la station la plus proche du domicile de la femme sur la fenêtre d'exposition souhaitée. Différents buffers de 1 à 10 km de diamètre autour de chaque station ont été pris en compte. Le NO_2 étant un polluant dont la concentration varie rapidement dans l'espace, la taille maximale des buffers a été limitée à 5 km. Pour les PM_{10}, la taille maximale des buffers était de 10 km car il s'agit d'un polluant plus homogène spatialement. Les stations mesuraient en continu (mesure horaire) les polluants atmosphériques.

1.4.2. Modèle géostatistique

Ce modèle repose sur des campagnes de mesures du NO_2 par tubes passifs. Dans les deux villes, les campagnes étaient réparties sur les 4 saisons. A Poitiers, 9 campagnes ont été réalisées, pour une durée de 14 jours à chaque campagne, avec 61 échantillonneurs passifs distribués dans les zones dites « de fond ». A Nancy, 10 campagnes de mesures ont été réalisées sur des durées de 10-15 jours à chaque campagne avec 98 échantillonneurs passifs implantés en zone « de fond ». Lors de ces campagnes, seul le NO_2 a été mesuré.
Les mesures de NO_2 réalisées lors des campagnes précédemment décrites ont été lissées à l'aide de méthodes de krigeage (Figure 8b) puis une composante temporelle basée sur les mesures des stations de surveillance de la qualité de l'air a été ajoutée pour saisonnaliser les estimations et ainsi permettre d'évaluer les niveaux d'exposition de chaque femme au cours de la grossesse, selon une approche que nous avons précédemment proposée (Slama, et al., 2007).

1.4.3. Modèle de dispersion

Le modèle intègre des données sur les émissions de polluants, les conditions météorologiques, l'occupation des sols, le relief, et la configuration des bâtis à proximité des routes ; il intègre les réactions chimiques et modélise la dispersion des polluants (voir II. ci-dessus). Ce modèle a été implémenté sous le logiciel ADMS-Urban (Figure 8c). Il fournit des estimations horaires sur un maillage de 40 m. Le calage du modèle a été fait à partir de l'ensemble des mesures des polluants considérés réalisées par les AASQA dans les zones d'étude.

Figure 8 : Niveaux moyens de NO_2 autour de Poitiers estimés par les modèles (a) *station* (année 2005 ; les triangles indiquent la localisation des volontaires Eden), (b) *géostatistique* (année 2005), et (c) de *dispersion* (moyenne sur 24h).

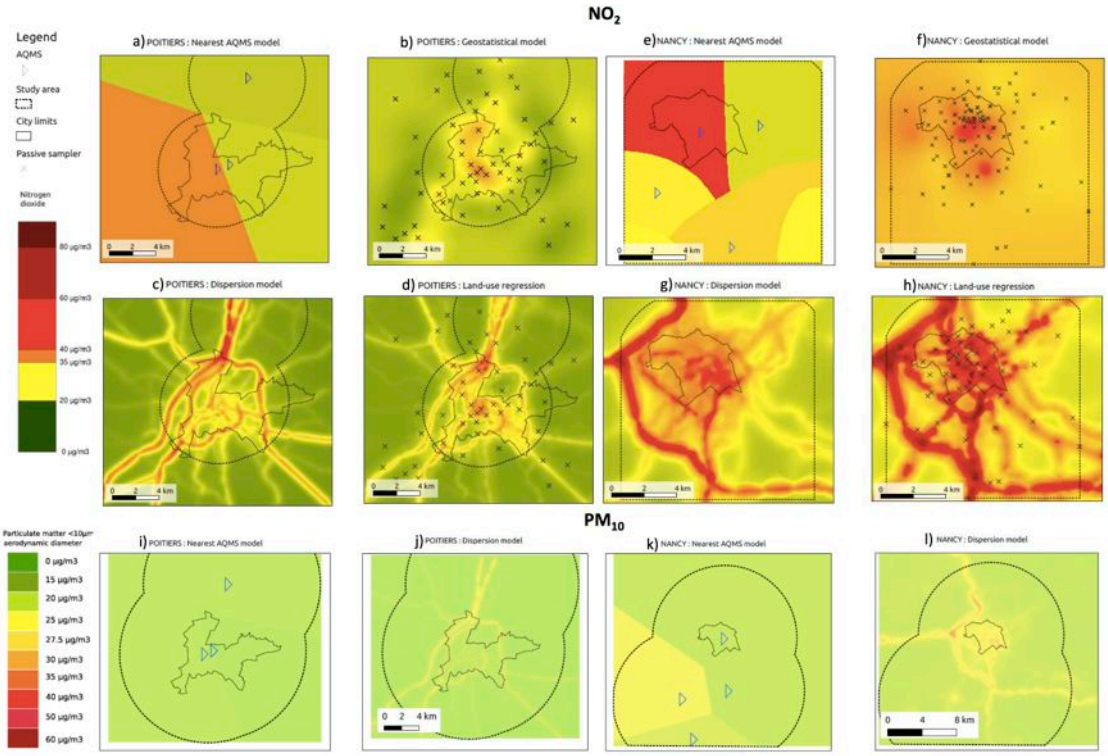


Tableau 1 : Résumé des caractéristiques générales des modèles utilisés pour estimer l'exposition aux polluants atmosphériques dans la cohorte Eden.

modèles	Prise en compte de la pollution de fond	Prise en compte de la proximité trafic	Résolution temporelle	Résolution spatiale	Prise en compte de toutes les situations d'exposition	Facilité d'implémentation
Station de mesures permanentes	+	+/-	++	-	+/-	+++
géostatistique	+	+/-	+/-	+	-	++
dispersion	+	++	+	++	-	- -

L'exposition au NO_2 était donc disponible pour les trois modèles. Pour les PM_{10}, seuls les modèles stations et dispersion étaient disponibles. Un résumé des caractéristiques de ces 3 modèles est fourni dans le Tableau 1.

1.5. Analyse statistique

La comparaison a porté sur les concentrations de NO_2 estimées par le modèle station, jusqu'ici le plus couramment utilisé dans la littérature épidémiologique, et les 2 alternatives récemment proposées : modèles géostatistique et de dispersion. Pour les PM_{10}, la comparaison a été effectuée entre les modèles station et de dispersion.

Pour le modèle *stations*, différents buffers (10, 5, 2, 1 km) ont été étudiés. Le choix du buffer représente la composante spatiale du modèle station mais il détermine également les effectifs étudiés, en fonction du nombre de femmes vivants à 1, 2, 5 ou 10 km d'une station.

1.5.2. Concentrations au domicile des femmes

La comparaison des expositions a été réalisée sur la base de la distribution des expositions en continu et des coefficients de corrélation. Des coefficients de concordance inter-modèles (Kappa) basés cette fois sur des expositions en tertiles ont également été calculés.

1.5.3. Comparaison des effets estimes sur le poids de naissance

L'association entre polluants atmosphériques, estimés à l'aide des trois modèles d'exposition, et le poids de naissance a été estimée à l'aide de régressions linéaires ajustées sur les facteurs connus pour influencer le poids fœtal : le sexe de l'enfant, l'âge gestationnel à la naissance, la taille, le poids et l'âge maternels, la parité de la mère, la consommation de tabac, le niveau socio-économique, et la saison de la conception.

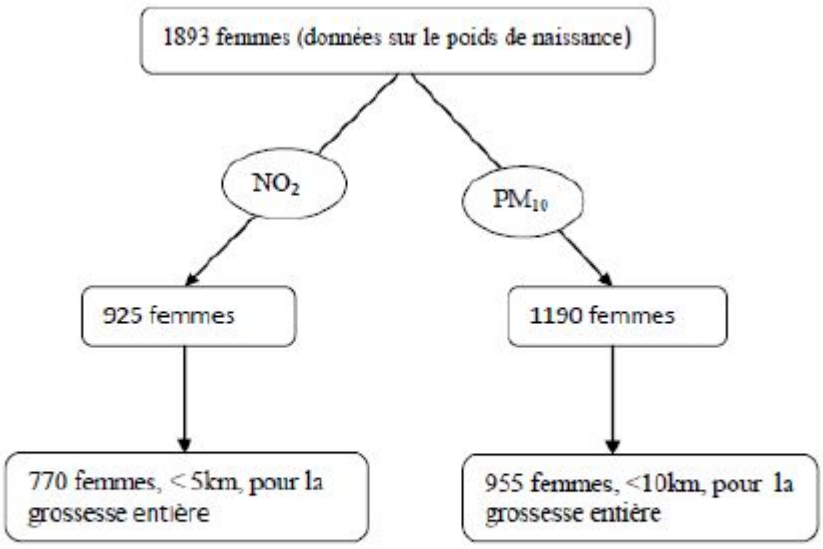
Les résultats sont exprimés en variation du poids de naissance pour une augmentation de 10 $\mu g/m^3$ du NO_2 et des PM_{10}. Ces régressions ont été effectuées séparément pour chaque polluant et chaque fenêtre d'exposition.

2. Résultats

2.1 Description de la population d'étude

L'échantillon d'étude concernant le NO_2 incluait 770 femmes et celui concernant les PM_{10}, 955 femmes (Figure 9).

Figure 9 : Sélection de la population d'étude.



Les caractéristiques des populations étudiées sont présentées dans le

Tableau 2. Le poids moyen (± écart type) des enfants à la naissance était de 3349 g (± 432 g) pour l'échantillon d'étude portant sur le NO_2 (n=770) et de 3362 g (± 440) pour l'échantillon d'étude restreint à 5 km et portant sur les PM_{10} (n=452).

Tableau 2 : Caractéristiques de la population étudiée vivant à moins de 5 km d'une station fixe mesurant le NO_2 (n=770 femmes) ou les PM_{10} (n=452 femmes).

	échantillon NO_2			échantillon PM_{10}		
	Poitiers et Nancy	Ville		Poitiers et Nancy	Ville	
Caractéristique	n (%)	Poitiers	Nancy	n (%)	Poitiers	Nancy
Sexe						
Garçon	393 (51.0)	176 (55.7)	217 (47.8)	247 (54.7)	176 (55.7)	71 (52.2)
Fille	377 (49.0)	140 (44.3)	237 (52.2)	205 (45.4)	140 (44.3)	65 (47.8)
Durée de gestation (SA)						
30-36	46 (6.0)	17 (5.4)	29 (6.4)	26 (5.8)	17 (5.4)	9 (6.6)
37-38	126 (16.4)	49 (15.5)	77 (17.0)	72 (15.9)	49 (15.5)	23 (16.9)
39-40	436 (56.6)	181 (57.3)	255 (56.1)	257 (56.9)	181 (57.3)	76 (55.9)
≥ 41	161 (20.9)	68 (21.5)	93 (20.5)	95 (21.0)	68 (21.5)	27 (19.9)
Valeurs manquantes	1 (0.1)	1 (0.3)	0	2 (0.4)	1 (0.3)	1 (0.7
Parité						
primipare	362 (47.1)	155 (49.2)	207 (45.6)	204 (45.2)	155 (49.2)	49 (36.0)
2ème pare	262 (34.1)	97 (30.8)	165 (36.3)	156 (34.6)	97 (30.8)	59 (43.4)
multipare	145 (18.9)	63(20.0)	82 (18.1)	91 (20.2)	63 (20.0)	28 (20.6)
Valeurs manquantes	1 (0.1)	1 (0.3)	0	1 (0.2)	1 (0.3)	0 (0)
Trimestre de conception						
Janvier-mars	165 (21.4)	79 (25.0)	86 (18.9)	111 (24.6)	79 (25.0)	32 (23.5)
Avril-juin	183 (23.8)	64(20.3)	119 (26.2)	90 (19.9)	64 (20.3)	26 (19.1)
Juillet-septembre	224 (29.1)	75(23.7)	149 (32.8)	121 (26.8)	75 (23.7)	46 (33.8)
Octobre-décembre	198 (25.7)	98(31.0)	100 (22.0)	130 (28.8)	58 (31.0)	32 (23.5)
Age Maternel à la conception (années)						
<25	183 (23.8)	90 (28.5)	93 (20.5)	118 (26.1)	90 (28.5)	28 (20.6)
25-29	289 (37.5)	112 (35.4)	177 (39.0)	156 (34.5)	112 (35.4)	44 (32.4)
30-34	201 (26.1)	70 (22.2)	131 (28.9)	122 (27.0)	70 (22.2)	52 (38.2)
≥ 35	97 (12.6)	44 (13.9)	53 (11.7)	56 (12.4	44 (13.9)	12 (8.8)
Taille maternelle (cm)						
<160	187 (24.5)	81 (26.1)	106 (23.5)	115 (25.7)	81 (26.1)	34 (25.0)
160-169	456 (59.8)	182 (58.5)	274 (60.6)	262 (58.6)	182 (58.5)	80 (58.8)
≥ 170	120 (15.7)	48 (15.4)	72 (15.9)	70 (15.7)	48 (15.4)	22 (16.2)
Valeurs manquantes	7 (0.9)	5 (1.6)	2 (0.4)	5 (1.1)	5 (1.6)	0 (0)
Poids maternel préconceptionel (kg)						
<50	82 (10.7)	35 (11.2)	47 (10.4)	51 (11.4)	35 (11.2)	16 (11.9)
50-59	330 (43.0)	132 (42.0)	198 (43.6)	190 (42.3)	132 (42.0)	58 (43.0)
60-69	209 (27.2)	81 (25.8)	128 (28.2)	109 (24.3)	81 (25.8)	28 (20.37)
70-79	87 (11.3)	36 (11.5)	51 (11.2)	54 (12.0)	36 (11.5)	18 (13.3)
≥ 80	60 (7.8)	30 (9.6)	30 (6.6)	45 (10.0)	30 (9.6)	15 (11.1)
Valeurs manquantes	2(0.3)	2 (0.6)	0 (0.0)	3 (0.7)	2 (0.6)	1 (0.7)
Indice de masse corporelle (kg/m^2)						
<18.5	81(10.6)	34 (11.0)	47 (10.4)	45 (10.1)	34 (11.0)	11 (8.2)
18.5 à 24.9	507 (66.6)	198 (64.1)	309 (68.4)	288 (64.9)	198 (64.1)	90 (66.7)
25 à 29.9	111(14.6)	47 (15.2)	64 (14.2)	68 (15.3)	47 (15.2)	21 (15.6)
≥30	62(8.2)	30 (9.7)	32 (7.1)	43 (9.7)	30 (9.7)	13 (9.6)
Valeurs manquantes	9(1.2)	7 (2.2)	2 (0.4)	3 (0.6)	7 (2.2)	1 (0.3)
Centre						
Poitiers	316(41.0)	316(100)	0	316 (69.9)	316 (100)	0
Nancy	454 (59.0)	0	454 (100)	136 (30.1)	0	136 (100)

Age maternel à la fin de l'enseignement						
≤16 ans	51 (6.6)	22 (7.0)	29 (6.4)	26 (5.8)	22 (7.0)	4 (2.9)
17-18 ans	103 (13.4)	55 (17.4)	48 (10.6)	71 (15.7)	55 (17.4)	16 (11.8)
19-20 ans	123 (16.0)	56 (17.7)	67 (14.8)	85 (18.8)	56 (17.7)	29 (21.3)
21-22 ans	163 (21.2)	64 (20.3)	99 (21.8)	104 (23.0)	64 (20.3)	40 (29.4)
23-24 ans	174 (22.6)	57 (18.0)	117 (25.8)	85 (18.8)	57 (18.0)	28 (20.6)
≥ 25 ans	156 (20.3)	62 (19.6)	94 (20.7)	81 (17.9)	62 (19.6)	19 (14.0)
Fumeuse passive (2^{nd} trimestre)						
Non	503 (65.8)	209 (67.0)	294 (64.9)	305 (68.2)	209 (67.0)	96 (71.1)
Oui	262 (34.3)	103 (33.0)	159 (35.1)	142 (31.8)	103 (33.0)	39 (28.9)
Valeurs manquantes	5 (0.6)	4 (1.3)	1 (0.2)	5 (1.1)	4 (1.3)	1 (0.7)
Fumeuse active (2^{nd} trimestre)						
Non	638 (83.1)	246 (78.3)	392 (86.3)	360 (80.0)	246 (78.3)	114 (83.8)
Oui	130 (16.9)	68 (21.7)	62 (13.7)	90 (20.0)	68 (21.7)	22 (16.2)
Valeurs manquantes	2 (0.3)	2 (0.6)	0 (0.0)	2 (0.4)	2 (0.6)	0 (0)

2.2. Estimation des expositions au NO_2 et PM_{10}

Quels que soient les modèles et la fenêtre d'exposition, les niveaux de NO_2 estimés à Nancy étaient plus élevés qu'à Poitiers (31,2 ± 8,7 µg/m^3, 24,9 ±10,6 µg/m^3 pour l'ensemble de la grossesse, respectivement, pour les stations fixes ; 27,8 ± 7,1 versus 18,4 ± 5,0 µg/m^3 pour le modèle de dispersion, Tableau 3). Dans une moindre mesure, les niveaux moyens de PM_{10} estimés étaient légèrement plus élevés à Nancy qu'à Poitiers, avec respectivement 21,2 ± 2,5 versus 18,1 ± 1,6 µg/m^3 avec les stations fixes pour l'ensemble de la grossesse, et respectivement 22,0 ± 1.9 versus 16,3 ± 1,1 µg/m^3 avec le modèle de dispersion (Tableau 4). Les résultats étaient similaires lorsque l'on s'intéressait aux trimestres de grossesse.

Tableau 3 : Exposition maternelle au NO_2 (µg/m^3) estimée par les différents modèles d'exposition, en fonction de la fenêtre d'exposition pendant la grossesse et de la zone géographique pour les 770 femmes vivant à moins de 5 km d'une station.

		Stations fixes	Modèle géostatistique.	Modèle de dispersion
zone geographique				
Fenêtre d'exposition	n	moyenne ± ET* (percentile 5, 50,95)	moyenne ± ET (percentile 5, 50,95)	moyenne ± ET (percentile 5, 50,90)
Deux villes				
1^{er} trimestre	764	28.8 ±10.9 (11.2, 30.1, 43.6)	23.7 ± 6.2 (13.6, 23.0, 34.5)	23,8 ± 8.6 (11.6, 22.5, 38.0)
2^{nd} trimestre	765	29.0 ±10.9 (11.4, 30.0, 43.9)	24.1 ± 6.5 (13.6, 23.6, 34.4)	24,4± 9,1 (11.7, 23.5, 39.5)
3^{rd} trimestre	764	28.1 ±11.1 (10.4, 29.4, 44.2)	23.3 ± 6.8 (12.5, 22.8, 34.8)	23,7± 9,2 (11.3, 22.7, 39.9)
Grossesse.	770	28.6 ±10.0 (13.3, 32.4, 41.8)	23.7 ± 5.0 (16.1, 23.8, 32.3)	24,0± 7,8 (13.3, 23.2, 36.9)
Poitiers				
1^{er} trimestre	310	25.6 ±11.9 (9.2, 21.6, 43.0)	20.9 ±6.3 (12.0, 20.4, 35.9)	19,0 ± 6,5 (10.4, 18.0, 31.9)
2^{nd} trimestre	311	25.2 ±11.6 (10.0, 22.2, 42.8)	20.4 ±6.1 (11.8, 19.9, 32.1)	18,5± 6,0 (10.5, 17.5, 29.6)
3^{rd} trimestre	310	23.9 ±11.3 (8.5, 21.7, 42.1)	19.4 ±6.3 (11.5, 19.0, 30.8)	17,6± 6,0 (9.8, 16.2, 29.3)
Grossesse	316	24.9 ±10.6 (12.4, 18.8, 40.5)	20.3 ±4.7 (14.7, 19.2, 30.0)	18,4± 5,0 (11.9, 17.7, 27.4)
Nancy				
1^{er}trimestre	454	31.0 ± 9.5 (13.6, 31.4, 44.2)	25.7 ±5.2 (17.9, 25.5, 34.5)	27,1± 8,3 (14.2, 26.8, 40.5)
2^{nd} trimestre	454	31.7± 9.6 (13.9, 32.0, 44.5)	26.7 ±5.5 (18.5, 26.6, 35.6)	28,6± 8,5 (14.7, 29.3, 41.1)
3^{rd} trimestre	454	31.0± 10.1 (13.3, 31.5, 45.0)	26.0 ±5.8 (17.5, 25.7, 36.2)	27,9± 8,6 (14.0, 28.2, 42.3)
Grossesse	454	31.2 ± 8.7 (16.9, 34.5, 42.5)	26.1 ±3.7 (20.8, 25.7, 32.9)	27,8± 7,1 (17.0, 27.7, 40.0)

ET : Ecart type

Quelles que soient la ville et la fenêtre d'exposition, les niveaux moyens de NO_2 estimés par les stations fixes étaient plus élevés que les niveaux estimés par les modèles géostatistique et de dispersion, qui eux avaient des niveaux moyens très proches l'un de l'autre : 28,6 ± 10,0 µg/m^3 pour l'ensemble de la grossesse estimée par le modèle station, *versus* 23,7 ± 5,0 et 24,0 ±7,8 µg/m^3 pour les modèles géostatistique et dispersion respectivement. Pour les PM_{10}, les niveaux moyens étaient similaires entre le modèle station et le modèle de dispersion.

Tableau 4 : Exposition maternelle aux PM10 et accord entre les niveaux estimés par les 3 modèles de PM_{10} entre les stations fixes et modèle de dispersion, pour chaque trimestre et chaque buffer.

Villes		Stations fixes (5km buffer)	Modèle de dispersion (5km buffer)															
Fenêtre				Distance [a] <10km				Distance [a] <5km				Distance [a] <2km				Distance [a] <1km			
D'exposition	n			n	r	c	k	n	r	c	k	n	r	c	k	n	r	c	k
2 villes																			
1er trimestre	455	19.2 ± 2.9 (14.6, 18.9, 25.1	18.1 ± 3.5 (13.5, 17.1, 24.7)	943	0.53	51.8	0.28	455	0.64	48.8	0.23	200	0.72	50.0	0.25	85	0.72	47.1	0.21
2ème trimestre	442	19.0 ±2.7 (14.8, 18.8, 23.8)	18.2 ± 3.1 (13.7, 17.5, 23,7)	899	0.46	49,1	0.24	442	0.61	57.5	0.36	196	0.67	55.1	0.33	83	0.64	47.0	0.21
3ème trimestre	442	18.8 ± 2.8 (14.7, 18.5, 24.6)	17.9 ± 3.2 (13.5, 16.9, 24.1)	903	0.54	53.1	0.30	442	0.62	55.6	0.33	199	0.71	49.3	0.24	85	0.70	49.4	0.24
Gss. entière	461	19.0 ± 2.4 (15.8, 18.6, 24.7)	18.0 ± 2.9 (14.7, 16.8, 23.7)	955	0.52	55.8	0.34	461	0.62	61.0	0.42	200	0.76	64.5	0.47	85	0.71	58.8	0.38
Poitiers																			
1er trimestre	323	18.2 ± 2.4 (14.5, 18.3, 21.8)	16.2 ± 1.9 (13.3, 16.2, 19.5)	445	0.59	55.3	0.33	323	0.58	53.5	0.30	187	0.56	50.8	0.26	75	0.55	45.3	0.18
2ème trimestre	316	18.1 ± 2.2 (14.4, 18.2, 21.9)	16.5 ± 1.9 (13.4, 16.5, 19.7)	435	0.61	57.0	0,36	316	0.62	55.3	0.33	185	0.58	55.0	0.27	75	0.58	48.0	0.22
3ème trimestre	313	17.9 ± 2.1 (14.5, 18.1, 21.8)	16.2 ± 1.7 (13.4, 16.2, 19.6)	427	0.55	53.7	0.30	313	0.53	52.6	0.29	185	0.46	45.6	0.25	75	0.48	48.0	0.22
Gss. entière	325	18.1 ± 1.6 (15.7, 18.0, 21.2)	16.3 ± 1.1 (14.5, 16.4, 18.2)	447	0.52	55.9	0.34	325	0.53	57.9	0.37	187	0.48	61.3	0.42	75	0.45	64.0	0.46
Nancy																			
1er trimestre	132	21.5 ± 3.1 (17.0, 20.5, 27.4)	22.4 ± 2.7 (18.7, 21.7, 27.6)	498	0.26	42.5	0.14	132	0.28	35.6	0.07	19	0.63	57.9	0.37	10	0.72	60	0.39
2ème trimestre	126	21.0± 2.6 (17.6, 20.5, 26.2)	21.9 ± 2.1 (18.8, 21.8, 26.7)	464	0.05	40.7	0.11	126	0.023	30.9	(-) 0.05	16	0.42	31.3	0.15	8	0.47	62,5	0.42
3ème trimestre	129	21.0 ± 3.2 (17.1, 20.1, 26.9)	21.8 ± 2.5 (17.9, 21.6, 26.6)	476	0.31	43.4	0.13	129	0.33	41.9	0.13	19	0.47	42.1	0.13	10	0.37	20.0	(-) 0.21
Gss. entière	136	21.2 ± 2.5 (18.4, 20.1, 25.8	22.0 ± 1.9 (19.8, 21.6, 26.5)	508	0.06	42.6	0.14	136	(-) 0.004	30.9	(-) 0.05	19	0.55	57.9	0.37	10	0.55	40.0	0.09

2.3. Accord entre les estimations des modèles

2.3.1. NO_2

Dans l'ensemble la corrélation entre les modèles était modérée et la concordance mesurée par les coefficients kappas étaient considérée comme modérée, voir médiocre, selon la grille de lecture de Landis et Koch (Landis and Koch, 1977)(Tableau 5-Tableau 7).

Quelle que soit la fenêtre d'exposition, l'accord entre les modèles station-géostatistique et station-dispersion estimé par le coefficient de corrélation et le K augmentait lorsque la taille du buffer diminuait de 5, à 2 puis 1 km.

Tableau 5 : Accord entre les modèles station et géostatistique concernant l'estimation des expositions au NO_2, en fonction de la fenêtre d'exposition et de la taille du buffer autour des stations.

Fenêtre d'exposition	Accord inter-modèles (station *vs.* géostatistique)								
	Distance [a] <5km			Distance [a] <2km			Distance [a] <1km		
	n	r	K	n	r	K	n	r	K
1er trimestre	767	0.67	0.41	429	0.70	0.43	158	0.83	0.63
2ème trimestre	766	0.69	0.40	426	0.72	0.37	156	0.82	0.60
3ème trimestre	767	0.74	0.44	428	0.79	0.52	155	0.87	0.68
Grossesse	770	0.65	0.44	428	0.70	0.46	157	0.85	0.59

[a] Distance maximale entre l'adresse du domicile et la station la plus proche (taille du buffer). K : coefficient d'accord Kappa (exposition catégorisée en tertiles).

Tableau 6 : Accord entre les modèles *stations* et de dispersion concernant l'estimation des niveaux de NO_2, en fonction de la fenêtre d'exposition et de la taille du buffer autour des stations.

Villes / Fenêtre d'exposition	taille des buffers autour des stations											
	Distance [a] <5km				Distance [a] <2km				Distance [a] <1km			
	n	r	c	k	n	r	c	k	n	r	c	k
Deux villes												
1er trimestre	764	0.62	55.8	0.34	428	0.64	57.9	0.37	157	0.73	63.7	0.46
2nd trimestre	765	0.66	58.4	0.38	426	0.68	59.6	0.39	156	0.75	67.3	0.51
3rd trimestre	764	0.68	60.7	0.41	426	0.71	65.5	0.48	155	0.81	70.1	0.56
Grossesse	770	0.61	58.3	0.37	428	0.64	61.9	0.43	157	0.75	70.1	0.55
Poitiers												
1er trimestre	310	0.51	55.2	0.33	181	0.55	52.5	0.29	75	0.71	70.7	0.56
2nd trimestre	311	0.53	59.2	0.39	179	0.61	56.4	0.35	74	0.66	60.8	0.41
3rd trimestre	310	0.54	57.1	0.36	179	0.62	63.7	0.46	73	0.64	58.9	0.38
Grossesse	316	0.46	50.3	0.25	181	0.55	50.8	0.26	75	0.65	56.0	0.34
Nancy												
1er trimestre	454	0.63	61.0	0.41	247	0.67	61.0	0.33	83	0.65	50.0	0.25
2nd trimestre	454	0.66	56.8	0.35	247	0.71	56.8	0.33	83	0.72	64.6	0.47
3rd trimestre	454	0.68	60.8	0.41	247	0.73	60.8	0.38	83	0.82	63.4	0.45
Grossesse	454	0.61	57.9	0.37	247	0.66	57.9	0.36	83	0.67	51.2	0.27

Abréviations: n, échantillon d'étude ; r, coefficient de corrélation Pearson; c, pourcentage de concordance (niveau de NO_2 catégorisé en terciles) ; k, coefficient kappa (niveau de NO_2 catégorisé en terciles).
[a] Distance maximale entre l'adresse du domicile et la stations la plus proche (taille du buffer)

En revanche, pour les modèles géostatistique-dispersion, l'accord ne variait que très faiblement en fonction de la taille du buffer (Tableau 7), ce qui était attendu.

Tableau 7 : Accord entre les modèles *géostatistique* et de *dispersion* concernant les niveaux de NO_2, en fonction de la fenêtre d'exposition et de la taille du buffer autour des stations.

Villes / Fenêtre d'exposition	taille des buffers autour des stations											
	Distance [a] <5km				Distance [a] <2km				Distance [a] <1km			
	n	r	c	k	n	r	c	k	n	r	c	k
Deux villes												
1er trimestre	770	0.72	64.3	0.47	428	0.71	65.5	0.48	157	0.72	65.6	0.48
2nd trimestre	769	0.74	68.0	0.52	428	0.73	68.7	0.53	157	0.74	67.5	0.51
3rd trimestre	769	0.76	71.2	0.57	428	0.79	72.5	0.59	157	0.79	67.5	0.51
Grossesse	770	0.70	68.4	0.53	428	0.68	66.6	0.50	157	0.68	67.5	0.51
Poitiers												
1er trimestre	316	0.71	68.4	0.53	181	0.74	66.9	0.50	75	0.79	80.0	0.70
2nd trimestre	315	0.70	66.3	0.50	181	0.72	61.3	0.42	75	0.77	60.0	0.40
3rd trimestre	315	0.71	66.0	0.49	181	0.74	63.0	0.44	75	0.72	56.0	0.34
Grossesse	316	0.60	68.4	0.53	181	0.61	61.9	0.43	75	0.67	66.7	0.50
Nancy												
1er trimestre	454	0.66	61.0	0.42	247	0.68	63.1	0.45	82	0.67	63.7	0.45
2nd trimestre	454	0.65	62.5	0.44	247	0.66	64.0	0.46	82	0.71	68.3	0.52
3rd trimestre	454	0.67	64.3	0.46	247	0.72	62.8	0.44	82	0.80	68.2	0.52
Gss. entière	454	0.54	56.2	0.34	247	0.55	56.3	0.34	82	0.56	59.8	0.40

Abréviations: n, échantillon d'étude ; r, coefficient de corrélation Pearson; c, pourcentage de concordance (niveau de NO_2 catégorisé en terciles) ; k, coefficient kappa (niveau de NO_2 catégorisé en terciles).[a] Distance maximale entre l'adresse du domicile et la station la plus proche (taille du buffer)

2.3.2. PM_{10}

De même que pour le NO_2, dans l'ensemble la corrélation entre les modèles station et dispersion était modérée et la concordance mesurée par les coefficients kappas était considérée comme modérée, voire médiocre (Tableau 4). L'accord dispersion-station augmentait lorsque l'on diminuait la taille des buffers de 10 à 2 km. En revanche entre 2 et 1 km, l'accord entre les modèles n'était pas amélioré.

2.4. Association entre exposition et poids de naissance

Concernant le NO_2, quelle que soit la fenêtre d'exposition, l'association avec le poids de naissance était similaire lorsque l'exposition était estimée par les modèles géostatistique et station alors que l'utilisation du modèle de dispersion indiquait des résultats proches des deux autres modèles uniquement pour le buffer 1 km (Tableau 8).

Lorsque la taille du buffer diminuait, les effets estimés du NO_2 sur le poids de naissance étaient plus importants.

Concernant les PM10, les fenêtres d'exposition pour laquelle l'association entre niveaux de pollution et poids de naissance était la plus nette étaient le 1er trimestre et l'ensemble de la grossesse pour les modèles *stations* et *dispersion*, quelques soient les buffers (Tableau 9).
Les associations avec le poids de naissance issues des modèles *stations* et *dispersion* étaient influencées par les buffers considérés, notamment au 1er trimestre et pour la grossesse entière.

Tableau 8 : Association ajustée entre les niveaux de NO_2 et le poids de naissance, pour différents modèles d'exposition, tailles de buffer et fenêtres d'exposition.

Fenêtre d'exposition	Modèles			NO_2		
		buffers	n	β (g)	p *	[IC95%]
1er trimestre	Stations[b]	<5km	703	-18	0.20	[-47;9.6]
		<2km	396	-33	0.10	[-72;6.4]
		<1km	148	-49	0.2	[-118;21]
	Dispersion[c]	<5km	703	2.8	0.90	[-40;4.6]
		<2km	396	-29	0.34	[-83;31]
		<1km	148	-107	**0.05***	[-215;1]
	Géostatistique[d]	<5km	703	-28	0.37	[-90;34]
		<2km	396	-52	0.20	[-131;28]
		<1km	148	-53	0.33	[-161;54]
2eme trimestre	Stations	<5km	703	-6.1	0.68	[-35;2.3]
		<2km	393	-17	0.43	[-58;24]
		<1km	146	-32	0.37	[-102;39]
	Dispersion	<5km	703	17	0.42	[-26;61]
		<2km	393	12	0.72	[-53;76]
		<1km	146	-28	0.63	[-144;87]
	Géostatistique	<5km	703	14	0.67	[-50;78]
		<2km	393	-0.6	0.99	[-82;83]
		<1km	146	-43	0.46	[-159;72]
3eme trimestre	Stations	<5km	705	-15	0.32	[-45;15]
		<2km	396	-24	0.26	[-66;18]
		<1km	146	-49	0.21	[-126;28]
	Dispersion	<5km	705	1.0	0.96	[-43;46]
		<2km	396	-14	0.67	[-79;50]
		<1km	146	-112	**0.05***	[-225;0.5]
	Géostatistique	<5km	702	-2.0	0.95	[-67; 63]
		<2km	394	-19	0.65	[-102; 64]
		<1km	146	-97	0.10	[-215 ; 22]
Grossesse en entière	Stations	<5km	706	-13	0.40	[-43;17]
		<2km	395	-25	0.24	[-68;17]
		<1km	147	-46	0.23	[-122;29]
	Dispersion	<5km	706	10	0.69	[-38;58]
		<2km	395	-12	0.74	[-82;58]
		<1km	147	-103	0.11	[-228;22]
	Géostatistique	<5km	706	-6.0	0.87	[-81;69]
		<2km	395	-32	0.51	[-128;64]
		<1km	147	-83	0.22	[-214;49]

*p –valeur significatif <0.05

[a] paramètre associé à une augmentation de la concentration de 10 µg/m^3 de NO_2, obtenu par régression linéaire ajustée sur la durée de gestation, le sexe, la parité, le trimestre de conception, l'âge de la femme, le poids de la femme, le niveau socio-économique et la consommation (actif et passif) de tabac au 2ème trimestre de grossesse.

[b] Stations fixes; [c]modèle de dispersion ADMS, [d]modèle géostatistique saisonnalisé

Tableau 9 : Associations ajustées entre les niveaux de PM10 et le poids de naissance, pour différents modèles d'exposition, tailles de buffer et fenêtres d'exposition.

Fenêtre d'exposition /modèles			PM_{10}			
		buffers	n	β (g)	p *	[IC95%]
1er trimestre	Stations[b]	<10km	852	-61	0.27	[-170;4.8]
		<5km	403	-136	0.06	[-278;-5.4]
		<2km	180**	-15	0.91	[-281;251]
		<1km	78**	-305	0.16	[-731;120]
	Dispersion[c]	<10km	852	-6.9	0.88	[-86;99]
		<5km	403	-142	0.11	[-137;-33]
		<2km	180**	-209	0.22	[-541;124]
		<1km	78**	-219	0.39	[-722;284]
2eme trimestre	Stations	<10km	820	34	0.58	[-87;156]
		<5km	393	12	0.88	[-147;172]
		<2km	176**	156	0.28	[-128;441]
		<1km	76**	-116	0.60	[-559;326]
	Dispersion	<10km	820	83	0.11	[-20;187]
		<5km	393	153	0.14	[-49;355]
		<2km	176**	27	0.88	[-33;38.7]
		<1km	76**	56	0.85	[-56.3;676]
3eme trimestre	Stations	<10km	821	3.3	0.96	[-110; 117]
		<5km	393	25	0.75	[-128; 179]
		<2km	179**	219	0.12	[-61; 500]
		<1km	78**	-42	0.83	[-443; 359]
	Dispersion	<10km	821	29	0.57	[-72; 130]
		<5km	393	20	**0.05***	[-2.5; 40]
		<2km	179**	328	0.07	[-28; 684]
		<1km	78**	444	0.15	[-162; 1051]
Grossesse en entière	Stations	<10km	863	-23	0.76	[-170; 124]
		<5km	407	-71	0.45	[-258; 116]
		<2km	180	173	0.32	[-172; 518]
		<1km	78	-226	0.38	[-742; 289]
	Dispersion	<10km	863	-45	0.1	[-10,5; 1,6]
		<5km	407	-78	0.2	[-20,2; 4,5]
		<2km	180**	-166	0.2	[-71.3; -2.2]
		<1km	78**	-278	0.1	[-65.3; 9.7]

**Effectif pour Nancy trop faible, résultats ininterprétables
*p –valeur significatif <0.05
[a] paramètre associé à une augmentation de la concentration de 10 µg/m^3 des PM_{10}, obtenu par régression linéaire ajustée sur la durée de gestation, le sexe, la parité, le trimestre de conception, l'âge de la femme, le poids de la femme, le niveau socio-économique et la consommation (actif et passif) de tabac au 2ème trimestre de grossesse.
[b] Stations fixes; [c]modèle de dispersion ADMS

2.5. Discussion

Malgré des niveaux estimés de NO_2 parfois très différents, et un accord modéré entre les expositions estimées par les 3 modèles, les résultats concernant l'association avec le poids de naissance étaient cohérents entre les 3 modèles d'exposition, qui avaient tendance à indiquer un effet délétère mais non statistiquement significatif du NO_2 sur le poids de naissance. Une restriction de la taille du buffer entraînait une meilleure concordance du modèle station avec les modèles géostatistiques et de dispersion. Ceci illustre l'importance de la taille du buffer utilisée avec un modèle station, ce qui constitue une limite potentielle de

ce type d'approche car il n'y a pas de méthode validée pour choisir a priori le buffer optimal. Le fait que l'effet estimé soit plus fort pour les buffers restreints à 2 ou 1 km pourrait être soit dû à une réduction de l'erreur de mesure, soit à un biais de sélection. La comparaison des caractéristiques des populations vivant dans les différents buffers n'était pas en faveur d'un tel biais de sélection (non détaillé).

Concernant les PM_{10}, les 2 modèles indiquaient là-aussi des résultats concordants, avec une association négative la plus nette au 1er trimestre et pendant l'ensemble de la grossesse avec le poids de naissance. De même que pour le NO_2, l'amplitude des effets estimés à l'aide du modèle de dispersion était plus importante que celle du modèle reposant sur les stations.

Les tendances positives mises en évidence avec le modèle de dispersion pour les PM_{10} ont déjà été observées dans une autre étude (Madsen, et al., 2010). Ces résultats inattendus soulèvent la question de l'impact de la prise en compte du budget espace temps, qui semble particulièrement pertinente dans le cas d'un modèle avec une résolution spatiale très fine comme le modèle de dispersion. Ainsi, l'erreur de mesure pourrait, pour certaines femmes être plus grande avec un modèle de dispersion qu'avec un modèle station de résolution spatiale moins fine mais qui potentiellement prendrait mieux en compte l'exposition des sujets « moyennée » sur l'ensemble de la zone de vie, et non pas simplement au domicile.

C. Volet étiologique

I. Pollution atmosphérique et croissance fœtale

1. Objectifs

Notre objectif principal était de caractériser l'impact de la pollution atmosphérique sur la croissance fœtale.

2. Population et méthodes

2.1 Population et biométrie fœtale

L'étude s'appuie sur la cohorte mère-enfant Eden. Nous avons restreint l'analyse aux femmes vivant dans les zones géographiques autour de Nancy et Poitiers pour lesquelles le modèle de dispersion atmosphérique a été développé (cf. plus haut, B). Les échographies étaient prévues autour de la 13ème semaine de gestation, de 20-24 et 30-34 semaines. Le diamètre biparietal a été estimé à chaque échographie ; pour les échographies à 20-24 et 30-34, ont en plus été mesurés les paramètres suivants : longueur fémorale (FL), diamètre abdominal transverse (TAD), périmètre abdominal (AC), périmètre crânien (HC, fortement corrélé au diamètre biparietal). Le poids fœtal a par ailleurs été estimé avec la formule de Hadlock (Hadlock, 1994), prenant compte des mesures échographiques. A la naissance, poids, périmètre crânien et longueur du nouveau-né ont été mesurés.

Les résultats des examens échographiques réalisés dans le cadre du suivi normal de la grossesse ont été enregistrés (Slama, et al., 2009). Avant le début de l'étude, les cinq premiers examens échographiques réalisés par chaque obstétricien impliqué dans l'étude ont été revus par le référent obstétrical de l'étude.

2.2 Estimation de l'exposition aux polluants atmosphériques

L'exposition aux polluants atmosphériques a été estimée à l'aide du modèle de dispersion atmosphérique ADMS (cf. plus haut, B). Les fenêtres d'exposition considérées étaient chaque trimestre de la grossesse ainsi que l'ensemble de la grossesse. Les changements d'adresse en cours de grossesse ont été pris en compte en estimant une moyenne des niveaux d'exposition à chaque adresse dans la période correspondante, pondérée par la durée de résidence à chaque domicile.

2.3 Modèles de régression

L'effet de chaque polluant à chaque fenêtre d'exposition a été estimé séparément par régression linéaire. L'ensemble des analyses ont été ajustées sur l'âge gestationnel lors de l'examen échographique (termes linéaire et quadratique), défini à partir de la date des dernières règles. Les autres facteurs d'ajustement étaient le sexe de l'enfant, le tabagisme maternel actif et passif pendant la grossesse, la taille maternelle et paternelle (variables continues), le poids maternel avant la grossesse (modèle en bâton cassé avec cassure à 60 kg), l'âge maternel à la fin des études et le centre.

3. Résultats

Un total de 3547 examens échographiques ont été réalisés parmi la population de 1228 femmes enceintes pour lesquelles les données d'exposition étaient disponibles. La grande majorité des femmes (90%) ont eu trois échographies, alors que 10 n'en ont eu qu'une. Les fœtus avaient des mensurations plus grandes à Nancy qu'à Poitiers (non détaillé).

Les niveaux de NO_2 moyens sur l'ensemble de la grossesse étaient de 21 $\mu g/m^3$ ($5^{ème}$, $50^{ème}$ et $95^{ème}$ centiles, 11, 19, 35) à Poitiers, et de 25 $\mu g/m^3$ ($5^{ème}$, $50^{ème}$ et $95^{ème}$ centiles, 14, 25, 38) à Nancy. Les coefficients de corrélation entre les niveaux de NO_2 et PM_{10} variaient selon la fenêtre d'exposition considérée entre 0,53 et 0,78.

Les associations entre les niveaux de pollution et la croissance du fœtus ainsi que la taille du nouveau-né, ajustées sur les facteurs mentionnés plus haut, sont représentées

Figure 10. Concernant le NO_2, il n'y avait pas d'éléments en faveur d'un effet délétère de l'exposition sur la biométrie fœtale et sur les caractéristiques du nouveau-né, si on excepte des tendances à la diminution du diamètre abdominal transverse (TAD) et du périmètre abdominal mesurés lors du deuxième trimestre, en lien avec l'exposition au NO_2 lors du trimestre précédant (

Figure 10a).

Concernant les PM_{10}, le diamètre abdominal transverse (TAD) mesuré lors du troisième trimestre tendait à diminuer avec les niveaux de pollution lors du premier trimestre de grossesse. La taille du nouveau-né tendait à être associée avec les niveaux de PM_{10} durant les premier et deuxième trimestres de grossesse.

4. Discussion

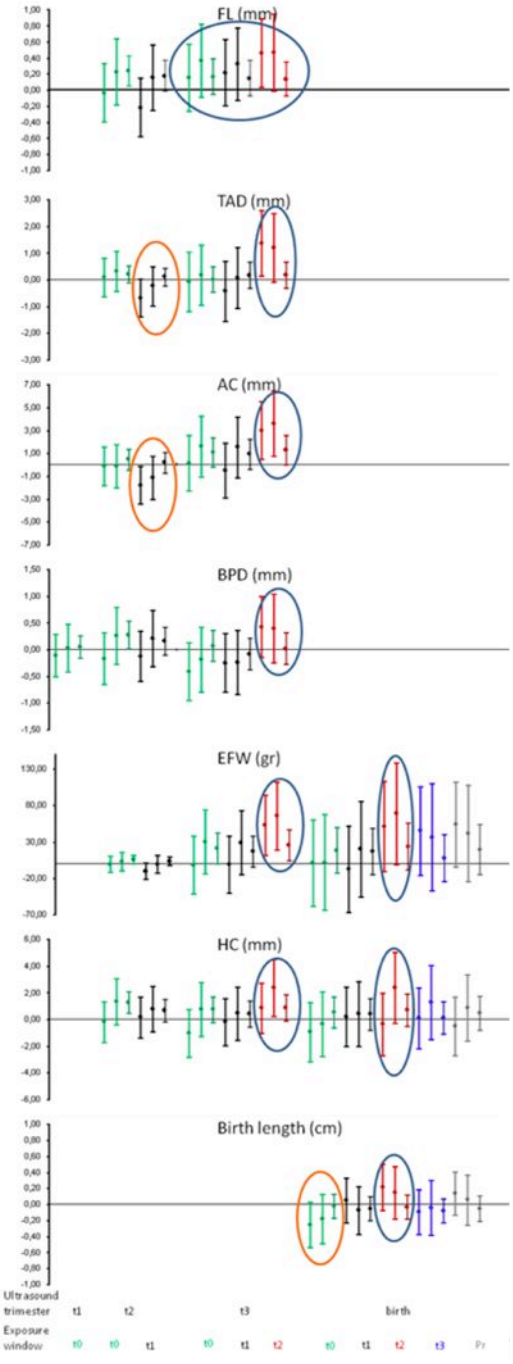
Notre étude n'a pas mis en évidence d'effet net des polluants atmosphériques estimés à l'aide d'un modèle de dispersion sur la croissance des fœtus de l'échantillon étudié d'environ 1200 grossesses de la cohorte Eden. Ces résultats doivent être interprétés en gardant à l'esprit l'effectif, et donc la puissance statistique, relativement limités. L'analyse réalisée à partir d'un nombre important de cohortes du projet ESCAPE, mais limitée à la biométrie à la naissance, permet de pallier certaines de ces limites (voir II ci-dessous).

Notre modèle d'exposition (modèle de dispersion) avait une résolution spatiale limitée, intégrait les changements d'adresse durant la grossesse, mais ne prenait pas en compte le budget espace-temps des femmes. Dans la mesure où les femmes enceintes passent probablement de l'ordre de 40 à 60% de leur temps au domicile (données non publiées, cohorte SEPAGES-faisabilité, Grenoble), cette non prise en compte est susceptible d'entraîner des erreurs de classement et potentiellement un biais dans la relation dose-réponse.

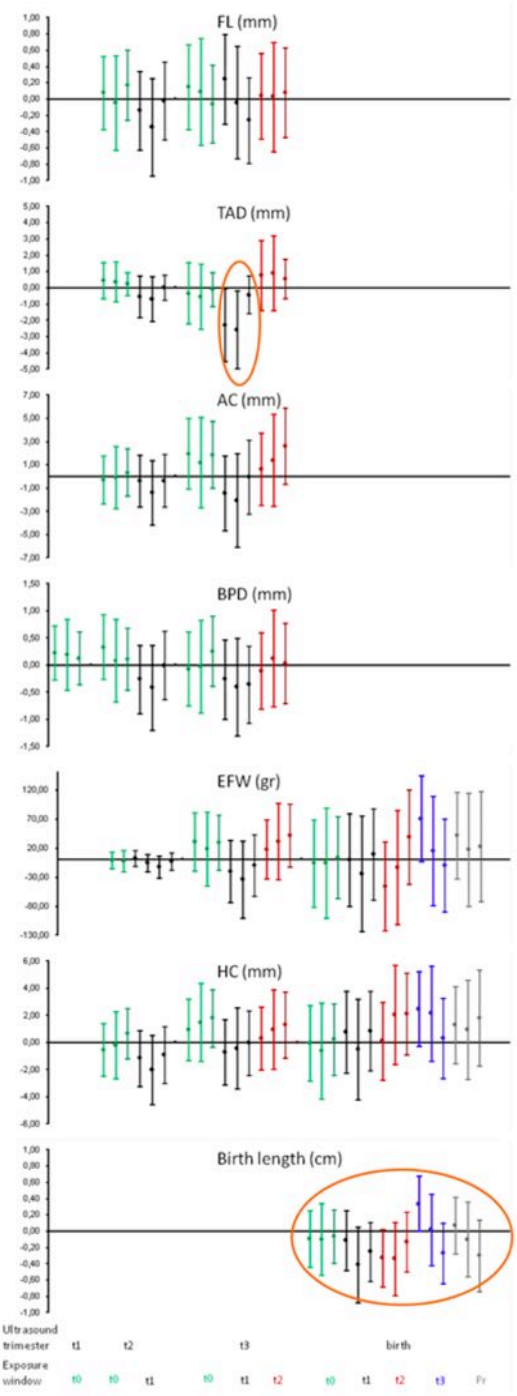
Nos précédents travaux dans la cohorte Eden s'appuyant sur une mesure personnelle de l'exposition avaient mis en évidence une association entre les niveaux de benzène et le périmètre crânien durant la grossesse et à la naissance, qui diminuait avec l'exposition (Slama, et al., 2009) ; dans le contexte de la cohorte Generation R à Rotterdam, une diminution du périmètre crânien durant la grossesse (mais pas à la naissance) avait été mis en évidence (van den Hooven, et al., 2012).

Figure 10 : Association ajustée entre la biométrie fœtale estimée par échographie durant la grossesse, les caractéristiques du nouveau-né à la naissance, et les niveaux moyens de NO_2 (a) et PM_{10} (b) durant le trimestre précédent. Les barres d'erreur indiquent les intervales de confiance à 95% (1236 grossesses, cohorte Eden).

A) NO_2 et croissance fœtale



B) PM_{10} et croissance fœtale



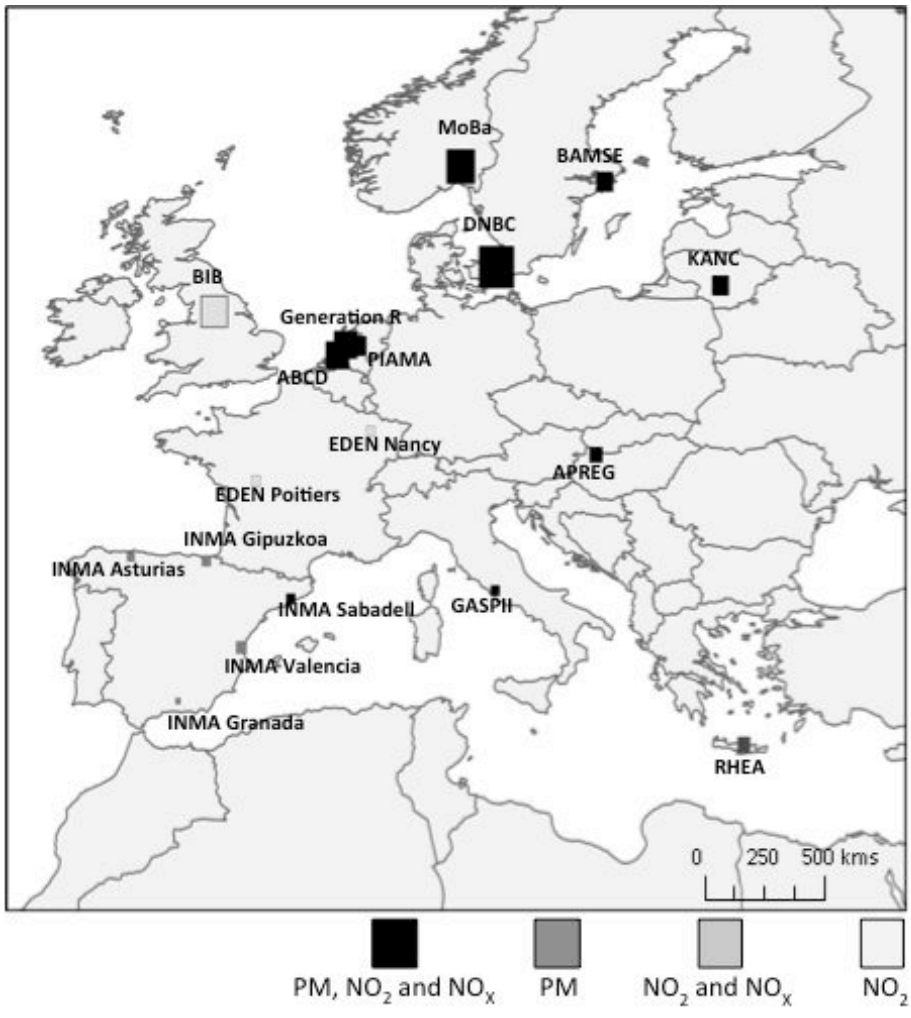
II. Pollution atmosphérique et poids de naissance dans les cohortes du projet ESCAPE

Nous présentons ici le résultat principal du projet européen ESCAPE concernant le poids de naissance. Le projet était coordonné par Bert Brunekreef (IRAS, Utrecht), et le groupe de travail sur les issues de grossesse, faisant partie du *work package* sur les cohortes de naissance, par Rémy Slama (Inserm Grenoble). Ce projet a été financé par l'Union Européenne (FP7), via un financement qui n'incluait initialement pas de partenaire français au sein du work package sur les cohortes de naissance. Le financement du projet Eden-Air Plus par l'ANSES, permettant de développer un modèle LUR similaire à celui qui a été mis en place dans l'ensemble des villes du projet ESCAPE, a permis la participation de la cohorte EDEN au sein de ce projet.

Les détails de ce travail sont présentés dans un article de Pedersen et coll. accepté pour publication dans *The Lancet Respiratory Medicine*.

Ce travail s'appuyait sur 14 cohortes européennes (dont la cohorte Eden pour la France), comprenant au total environ 62 000 naissances (Figure 11). L'exposition a été estimée à partir d'un modèle de type Land Use Regression saisonnalisé, développé de façon standardisée.

Figure 11 : Localisation des cohortes de naissance incluses dans le projet européen ESCAPE, et polluant modélisé dans chaque zone.



L'analyse poolée de ces cohortes à l'aide d'un modèle de régression logistique avec un effet aléatoire pour le centre indiquait une augmentation du risque de petit poids de naissance à terme en association avec les niveaux de $PM_{2,5}$ et de PM_{10} (Tableau 10). L'association était statistiquement plus nette pour la fraction fine (en-dessous de 2,5 μ) des poussières en suspension que pour la fraction de diamètre plus important. Une diminution du périmètre crânien à la naissance était aussi observée en association avec les concentrations de particules fines ($PM_{2,5}$) durant la grossesse (non détaillé).

Tableau 10 : Association ajustée entre les niveaux de pollution atmosphérique et la probabilité de naissance à terme avec un petit poids de naissance (<2500 g), parmi 62 000 naissances de 14 cohortes faisant partie du projet européen ESCAPE.

Models (exposure)	N	n	OR	95% CI
One-pollutant models[1]				
$PM_{2·5}$	50,151	675	1·18	1·06 to 1·33
$PM_{2·5–10}$	48,995	666	1·01	0·88 to 1·15
PM_{10}	50,151	675	1·16	1·00 to 1·35
$PM_{2·5}$ absorbance	50,835	679	1·17	0·95 to 1·39
NO_2 in areas with $PM_{2·5}$	49,285	656	1·05	0·95 to 1·16
NO_2 in all areas	61,452	1,074	1·09	1·00 to 1·19
NO_X in all areas	60,254	1,046	1·04	0·97 to 1·11
Traffic density on nearest street	59,030	1,000	1·06	1·01 to 1·11
Traffic load on major road within 100 m	60,254	1,039	1·01	0·96 to 1·07
Two-pollutant models[2]				
$PM_{2·5}$ adjusted for $PM_{2·5–10}$	48,995	666	1·20	1·07 to 1·35
$PM_{2·5}$ adjusted for $PM_{2·5}$ absorbance	49,931	670	1·18	1·03 to 1·36
$PM_{2·5}$ adjusted for NO_2	49,285	656	1·18	1·04 to 1·33
$PM_{2·5–10}$ adjusted for $PM_{2·5}$	48,995	666	0·93	0·81 to 1·06
$PM_{2·5–10}$ adjusted for NO_2	48,134	647	1·02	0·85 to 1·22
PM_{10} adjusted for $PM_{2·5}$ absorbance	49,931	670	1·12	0·93 to 1·35
PM_{10} adjusted for NO_2	49,285	656	1·19	1·00 to 1·42
$PM_{2·5}$ absorbance adjusted for $PM_{2·5}$	49,931	670	0·99	0·79 to 1·24
$PM_{2·5}$ absorbance adjusted for $PM_{2·5–10}$	48,776	661	1·20	0·97 to 1·48
$PM_{2·5}$ absorbance adjusted for NO_2	50,136	664	1·12	0·87 to 1·46
NO_2 adjusted for $PM_{2·5}$	49,285	656	1·01	0·91 to 1·11
NO_2 adjusted for $PM_{2·5–10}$	48,134	647	1·04	0·92 to 1·17
NO_2 adjusted for $PM_{2·5}$ absorbance	50,136	664	1·01	0·88 to 1·15

N, total number of subjects; n, number of term low birth weight cases; OR, odds ratio; CI, confidence interval.
[1]Effect of pregnancy mean exposure to air pollutants on term low birth weight estimated in pooled analyses using logistic regression with random effect on centre adjusted for gestational age (weeks and weeks[2]), sex, parity (0, 1, 2 or more), maternal height (cm), pre-pregnancy weight (broken stick model with a knot at 60 kg), maternal active smoking during 2nd trimester (cigarettes/day), maternal age (years), maternal education (low, middle, high) and season of conception (January-March, April-June, July-September, October-December). Traffic density on nearest street and traffic load models were further adjusted for background levels of NO_2 ($\mu g/m^3$).
[2]Further adjusted for the indicated pollutant.
All effect estimates correspond to an increment in 5 $\mu g/m^3$ for $PM_{2·5}$ and $PM_{2·5–10}$, 10 $\mu g/m^3$ for PM_{10}, 1 10^{-5}/m for $PM_{2·5}$ absorbance, 10 $\mu g/m^3$ for NO_2, 20 $\mu g/m^3$ for NO_X, 5000 vehicles/day for traffic density, and 4,000,000 vehicles/day x m for traffic load.

III. Pollution atmosphérique et pression artérielle de la femme enceinte

1. Objectifs

Notre objectif principal était de caractériser l'impact à court terme de la pollution atmosphérique sur la pression artérielle de la femme enceinte. Un objectif intermédiaire était de caractériser l'impact de la température extérieure sur la pression artérielle de la femme enceinte.

2. Population et méthodes

2.1 Population

Nous nous sommes ici restreints aux femmes de la cohorte Eden sans antécédent d'hypertension et pour lesquelles nous disposions d'au moins deux mesures de la pression artérielle en cours de grossesse. La pression artérielle a été mesurée par les sages-femmes lors des examens de surveillance anténataux de routine. Jusqu'à 12 examens ont été réalisés au total sur l'ensemble de la grossesse. Les caractéristiques générales des femmes ont été extraites des dossiers obstétricaux et des questionnaires spécifiques de l'étude Eden ; elles sont données

Tableau 11. Afin d'estimer les expositions (voir plus bas), nous nous sommes restreints aux femmes vivant à moins de 20 km d'une station fixe de surveillance de la qualité de l'air.

2.2 Estimation de l'exposition aux polluants atmosphériques

Les caractéristiques météorologiques (température, pression, humidité) ont été obtenues auprès de Météo France pour chacune des deux villes sur une base horaire. Les niveaux de pollution atmosphérique (NO_2, PM_{10}) ont été obtenues à partir des données des réseaux de stations fixes de surveillance de la qualité de l'air Atmo Poitou-Charentes et Air Lorraine. Cette approche a été privilégiée sur les autres modèles disponibles dans la mesure où nous nous intéressions aux effets à court terme de la pollution atmosphérique et où il s'agissait d'une étude longitudinale, dans laquelle les variations d'exposition intra-sujet étaient probablement plus importantes à considérer que les variations inter-sujets (c'est-à-dire spatiales) ; l'approche reposant sur les stations, avec une résolution spatiale limitée mais une très bonne résolution temporelle, répondait à ces objectifs. Dans une analyse supplémentaire (non détaillée), nous avons répété les principales analyses en utilisant le modèle de dispersion que nous avons développé pour estimer les niveaux de NO_2 et PM_{10}. Les niveaux de pollution et les variables météorologiques ont été moyennées sur différentes fenêtres court-terme précédant chaque examen médical durant lequel la pression a été mesurée ; notre choix a priori était de considérer des fenêtres temporelles de 24 heures durant chacun des 7 jours précédant l'examen ; une moyenne sur l'ensemble des 7 jours précédant chaque examen a aussi été construite. L'heure exacte de l'examen n'ayant pas été enregistrée, ces moyennes ont été construites en supposant que l'examen avait lieu à 8 heures du matin.

Tableau 11 : Caractéristiques des 1500 femmes de la cohorte Eden vivant à moins de 20 km d'une station de surveillance de la qualité de l'air.

	All	Poitiers	Nancy
Based on number of women			
	(n = 1500)	**(n = 657)**	**(n = 843)**
Age (years); mean (SD)	29.2 (4.9)	29.0 (5.0)	29.3 (4.9)
Height (cm); mean (SD)	163.6 (6.1)	162.9 (6.1)	164.2 (6.1)
Weight before pregnancy (kg); mean (SD)	61.9 (12.5)	62.1 (12.7)	61.7 (12.3)
Body mass index before pregnancy (kg/m^2)			
Distribution			
<25	1124 (75)	473 (72)	651 (77)
25–29.9	258 (17)	122 (19)	136 (16)
≥30	118 (8)	62 (9)	56 (7)
Mean (SD)	23.1 (4.5)	23.4 (4.6)	22.9 (4.4)
Gestational hypertension			
Yes	75 (5)	24 (4)	51 (6)
No	1425 (95)	633 (96)	792 (94)
Gestational diabetes			
Yes	94 (6)	40 (6)	54 (6)
No	1406 (94)	617 (94)	789 (94)
Previous pregnancies			
0	673 (45)	312 (48)	361 (43)
1	558 (37)	230 (35)	328 (39)
≥2	269 (18)	115 (17)	154 (18)
Smoking in the 1st trimester of pregnancy			
Yes	384 (26)	189 (29)	195 (23)
No	1116 (74)	468 (71)	648 (77)
Passive smoking in the 1st trimester of pregnancy			
Yes	472 (31)	189 (29)	283 (34)
No	1028 (69)	468 (71)	560 (66)
Based on number of antenatal visits			
	(n = 11220)	**(n = 4697)**	**(n = 6523)**
Trimester			
1st (0–13 weeks)	1849 (16)	436 (9)	1413 (22)
2nd (14–27 weeks)	4587 (41)	1855 (39)	2732 (42)
3rd (>27 weeks)	4784 (43)	2406 (51)	2378 (36)
Weekend visit			
Yes	322 (3)	275 (6)	47 (1)
No	10898 (97)	4422 (94)	6476 (99)
Season of visit			
Winter (Oct–Mar)	5744 (51)	2137 (45)	3607 (55)
Summer (Apr–Sep)	5476 (49)	2560 (55)	2916 (45)
Smoking in the trimester of the visit			
Yes	2008 (18)	887 (19)	1121 (17)
No	9212 (82)	3810 (81)	5402 (83)
Passive smoking in the trimester of the visit			
Yes	3256 (29)	1228 (26)	2028 (31)
No	7964 (71)	3469 (74)	4495 (69)

	All	Poitiers	Nancy
Gestational age of visit (days); mean (SD)	172.9 (66.8)	189.3 (61.8)	161.1 (67.8)
Diastolic blood pressure (mm Hg); mean (SD)	65.0 (9.3) (n = 11209)	67.1 (9.0) (n = 4693)	63.5 (9.2) (n = 6516)
Systolic blood pressure (mm Hg); mean (SD)	116.6 (12.6) (n = 11218)	114.2 (10.9) (n = 4697)	118.3 (13.4) (n = 6521)

[a]No. (%), unless otherwise indicated.

2.3 Analyse statistique

L'analyse statistique a été faite à l'aide d'un modèle de régression adapté aux données répétées. Ce modèle linéaire mixte avait une structure de covariance de type *compound symmetry* et un effet aléatoire prenant en compte la variabilité inter-individus dans le niveau

de base de la pression artérielle. Il a été implémenté avec le logiciel SAS (version 9.1, SAS Institute Inc., Cary, NC, USA). La pression artérielle systolique (SBP) et diastolique (DBP) ont été étudiées dans des modèles séparés ; toutes les analyses ont été ajustées sur les principales caractéristiques individuelles des sujets (âge, indice de masse corporelle avant la grossesse, âge gestationnel lors de la mesure de la pression, parité, tabagisme actif durant le premier trimestre de grossesse et tabagisme passif). Un effort particulier a été fait dans l'optimisation du codage des variables quantitatives, notamment par des modèles de spline (non détaillé). Les modèles incluant la pollution atmosphérique ont été ajustés sur une tendance temporelle long terme (jour de l'étude, pour prendre en compte les variations saisonnières de la pression artérielle), la température et l'humidité relative moyennées sur la même période que la pollution atmosphérique. Les effets de la température sont donnés pour une diminution de 10°C, comme dans des travaux précédant ; les effets de la pollution atmosphérique sont donnés pour une augmentation des niveaux de pollution correspondant à l'écart interquartiles. Les associations sont présentées en variations relatives (%) de la pression artérielle pour une variation donnée de la température (-10°C) ou du niveau de pollution (augmentation interquartiles) durant la fenêtre d'exposition considérée.

3. Résultats

Les 1500 femmes répondant aux critères d'inclusion avaient subi au total 11 000 examens, soit 7,5 examens en moyenne par femme durant la grossesse ($5^{ème}$ – $95^{ème}$ percentiles, 4 à 11 visites/femme) avec une mesure de la pression artérielle. Le délai moyen entre 2 examens était de 27 jours ($5^{ème}$ – $95^{ème}$ percentiles, 5-43 jours). La pression artérielle diastolique était en moyenne plus faible à Nancy qu'à Poitiers, alors que la pression systolique était plus élevée en moyenne à Nancy. La pression artérielle systolique moyenne était de 117,0 mm Hg (mercure, écart-type, 12,9 mm) en hiver, et 116,3 mm Hg (9,2) en été. La pression artérielle tendait à être plus faible dans le deuxième que dans les premier et troisième trimestres de grossesse.

3.1 Température et pression artérielle

La température moyenne était de 16,5°C en été et 5,4°C en hiver. Les variations de la pression artérielle en fonction de la température sont données Figure 12.

Une diminution de 10°C de la température était associée avec une augmentation immédiate (*lag* 0) de la pression artérielle systolique de 0,5% (intervalle de confiance (IC) à 95%, 0,1% à 1,0%) ; la température avait aussi un effet retardé (de 6 jours) correspondant à une augmentation de 0,4% (0,0% à 0,9%) de la pression systolique (Figure 12A). Ces augmentations correspondent à des variations de 0,6 mm Hg (0,1 à 1,1 mm Hg) et 0,5 mm Hg (0,0 à 1,0 mm Hg), respectivement. Après ajustement sur les niveaux de NO_2, ce qui entraînait une diminution d'environ 10% du nombre d'observations, les effets estimés de la température tendaient à augmenter pour les *lags* de 1, 2 et 5 jours, ainsi que pour l'effet de la température moyennée sur 7 jours (Figure 12A). L'ajustement sur les niveaux de PM_{10} était lui sans impact sur l'effet estimé de la température (non détaillé). Enfin, les effets de la température sur la pression artérielle étaient plus importants entre avril et septembre qu'entre octobre et mars (Figure 12B).

Figure 12 : Variations de la pression artérielle pour une diminution de 10°C de la température.

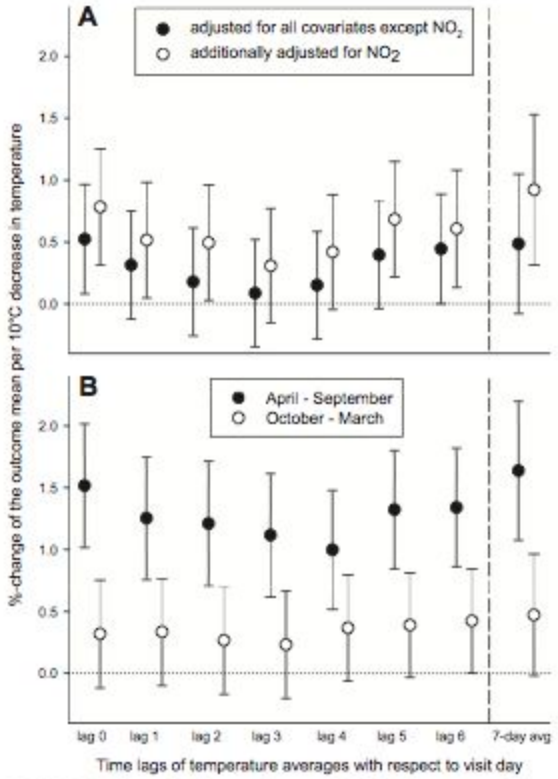


FIGURE 1. Adjusted changes in systolic blood pressure during pregnancy associated with a 10°C decrease in 24-hour and 7-day air temperature averages by (A) adjustment variables and (B) season.

3.2 Pollution atmosphérique et pression artérielle

Les valeurs médianes de l'écart interquartile des moyennes sur 24 heures et 7 jours des mesures de chaque station étaient de 14,4 et 11,4 $\mu g/m^3$, respectivement, pour NO_2, et 11,3 et 7,7 $\mu g/m^3$ pour les PM_{10}, respectivement. La Figure 13A indique les associations entre NO_2 et la pression systolique, ajustée sur les caractéristiques des femmes ainsi que les caractéristiques météorologiques avant l'examen. Une augmentation des niveaux de NO_2 correspondant à l'écart interquartile dans les 24 heures précédant l'examen durant lequel la pression artérielle a été mesurée était associée à une variation de la pression systolique de -0,3% (IC 95%, -0,5% à -0,1%), soit -0,4 mm Hg (-0.6 à 0,1 mm Hg). Des diminutions d'amplitude similaire de la pression artérielle ont été observées avec un décalage de 1, 5 et 6 jours. C'était la moyenne des polluants sur les 7 jours avant l'examen qui était le plus fortement associée à la pression artérielle, tant pour le NO_2 (-0,4%, IC 95% de -0,7% à -0,2%, soit -0,5 mm Hg, IC 95% : -0,8% à -0,2% mm Hg) que pour les PM_{10} (-0,3%, IC 95%, -0,5% à 0,0%, ou -0,3 mm Hg, de -0,6% à 0,0%).

L'effet estimé du NO_2 sur la pression systolique était plus fort (en valeur absolue) que l'effet estimé des PM_{10}, lorsque l'ensemble des examens réalisés durant la grossesse étaient considérés simultanément. Il n'y avait pas d'association nette entre les niveaux de polluants et la pression artérielle diastolique (Figure 13B).

Figure 13 : Variations de la pression artérielle en fonction des niveaux de NO_2 et PM10.

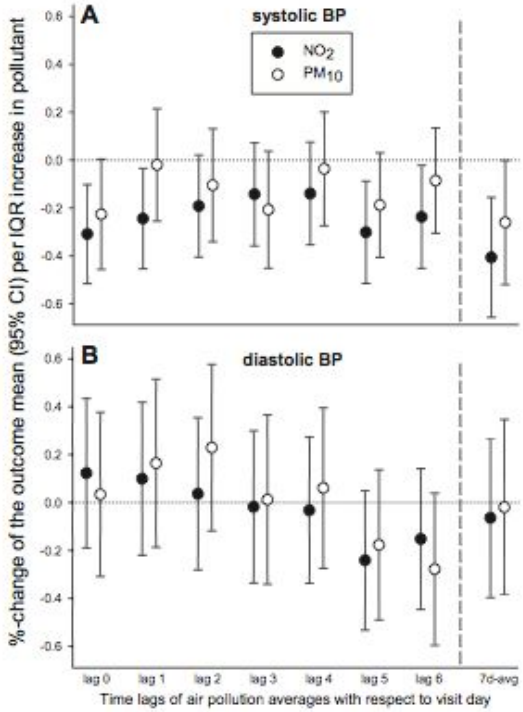


FIGURE 2. Adjusted associations between 24-hour and 7-day averages of NO_2 and PM_{10} and (A) systolic and (B) diastolic blood pressure during pregnancy. Associations are reported for an increase in air pollutants corresponding to the interquartile range.

3.3 Modification de la mesure de l'effet des polluants atmosphériques

Les effets estimés de la pollution atmosphérique étaient similaires quand les agglomérations de Nancy et Poitiers étaient considérées séparément (non détaillé). Les effets estimés étaient qualitativement similaires entre les saisons chaude et froide, avec une tendance à des effets négatifs plus faibles entre avril et septembre, comparé à la période d'octobre à mars (Figure 14A-B). Le test d'interaction comparant l'effet de la pollution entre les saisons n'était statistiquement significatif que pour les PM, dont l'effet était de -0,3% (IC 95%, -0,7% à 0,0), contre 0,1% (IC 95%, -0,2% à 0,5% entre avril et septembre, test d'interaction, p=0,04). Les effets des niveaux de NO_2 sur la pression systolique tendaient à être plus prononcés chez les femmes qui ne fumaient pas que chez celles qui fumaient (p du test d'interaction le plus net, 0,12).

Pour les PM_{10}, l'effet sur la pression artérielle variait fortement avec le trimestre de la grossesse (Figure 14C-D) ; ce n'était pas le cas pour les effets du NO_2, qui étaient similaires quelque soit le trimestre de la grossesse. L'interaction statistique la plus nette s'observait pour le décalage de 4 jours : les niveaux de PM10 étaient associés à une variation de 1,0% (0,5% à 1,5%) de la pression systolique durant le 1er trimestre de grossesse ; ils étaient associés à une variation de -0.3% (IC 95, 0,6% à 0,0%) et de -0,2% (-0.6% à 0,2%) durant les 2ème et 3ème trimestre de grossesse, respectivement (P d'interaction <0,001).

Figure 14 : Effet des polluants atmosphériques sur la pression artérielle – modèles avec interaction sur la saison de l'examen (A, B) ou le trimestre de grossesse lors de l'examen (C, D).

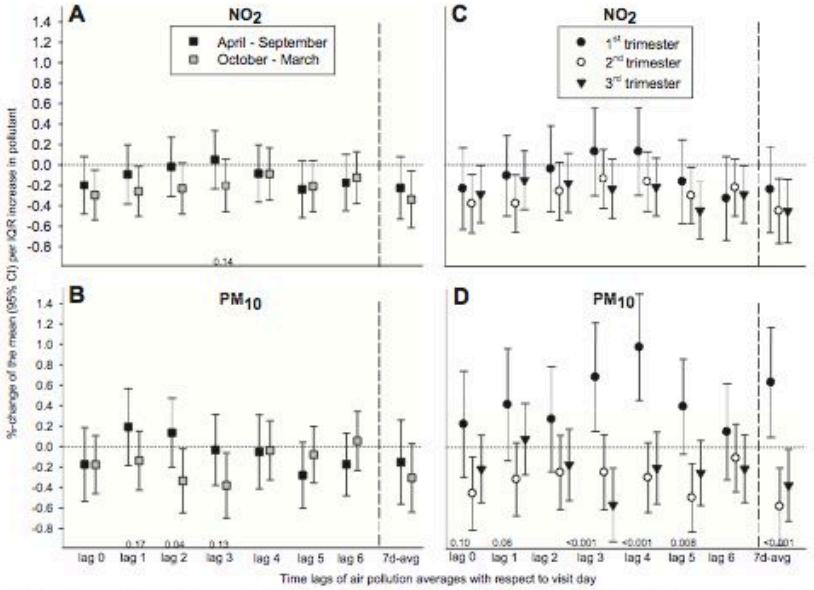


FIGURE 3. Adjusted associations between 24-hour and 7-day NO_2 (A and C) and PM_{10} (B and D) averages and systolic blood pressure (interquartile range increases), modified by season and trimester of pregnancy. Only *P* values <0.2 for interaction terms are indicated.

3.4 Analyses de sensibilité

Les résultats restaient globalement inchangés par différentes analyses de sensibilité (exclusion des examens réalisés le week-end, modification des hypothèses sur la structure de la corrélation entre la pression artérielle lors des différents examens d'une même femme…)(Hampel, et al., 2011). L'effet estimé des polluants tendait à s'accentuer quand on se restreignait aux femmes vivant à une distance plus faible des stations de surveillance de la qualité de l'air, ce qui est conforme avec ce qui était observé pour le poids de naissance (cf. B.III.2). Quand on estimait les niveaux de pollution à l'aide du modèle de dispersion implémenté dans les deux zones, les effets du NO_2 sur la pression étaient similaires qu'avec l'approche station ; les effets des PM_{10} sur la pression systolique étaient plus forts quand la grossesse était considérée dans son ensemble ; en revanche, l'interaction entre niveaux de PM10 et trimestre de grossesse ne s'observait plus nettement quand l'exposition était estimée avec le modèle de dispersion (p d'interaction, 0,37).

4. Discussion

Notre étude suggère que les niveaux de NO_2 sont associés à une diminution à court terme (dans les jours suivants) de la pression artérielle systolique chez la femme enceinte ; dans le cas des particules (PM10), une augmentation de leurs niveaux était associée à une augmentation à court terme de la pression artérielle systolique lors du premier trimestre de la

grossesse, et à une diminution à court terme de la pression en fin de grossesse ; une telle modification de l'effet de la pollution en cours de la grossesse était plausible du fait des modifications fortes de la fonction cardiovasculaire en cours de grossesse (Kaaja and Greer, 2005), mais elle ne s'observait qu'avec un seul de nos modèles d'exposition.

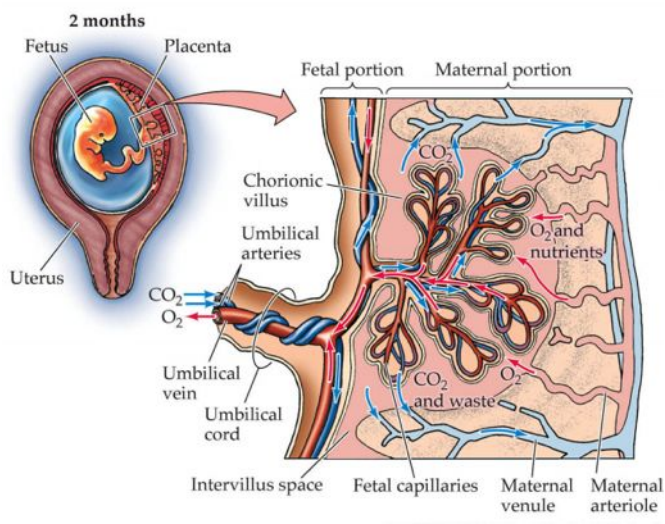
Plusieurs études se sont intéressées aux effets de la pollution atmosphérique à court terme sur la pression artérielle, surtout chez des sujets âgés ou atteints de pathologies spécifiques (Ibald-Mulli, et al., 2001, Ibald-Mulli, et al., 2004, Zanobetti, et al., 2004) ; les résultats de ces études ne sont pas tout à fait concordants. Très peu de travaux ont été réalisés spécifiquement chez la femme enceinte. Une étude hollandaise a été publiée peu avant la nôtre, à partir des femmes de la cohorte *Generation R* (van den Hooven, et al., 2011). Elle n'est pas totalement comparable à notre étude, car elle prenait en compte les variations à long terme de la pollution, et s'appuyait davantage sur une comparaison inter-individus qu'intra-individu, contrairement à notre étude. Elle suggérait aussi un effet de la pollution atmosphérique sur la pression artérielle, avec une modification de l'effet observé en fonction du trimestre de la grossesse.

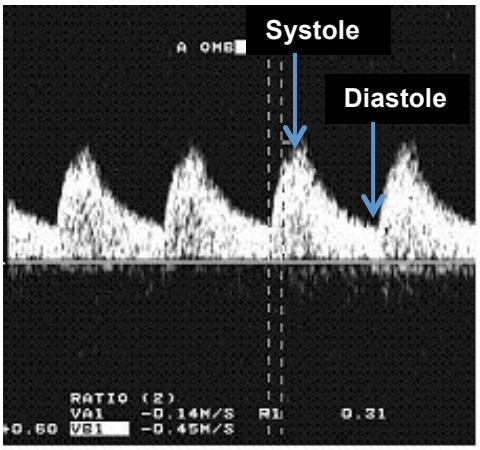
IV. Pollution atmosphérique et échanges sanguins materno-placentaires

1. Introduction et objectifs

Notre dernier objectif étiologique visait à d'étudier l'effet de l'exposition de femmes enceintes à la pollution atmosphérique sur le flux sanguin dans les artères utérines, ombilicales et l'artère fœtale cérébrale.

Figure 15 : A) Le placenta et sa vascularisation. B) Illustration d'une mesure Doppler.





2. Population et méthodes

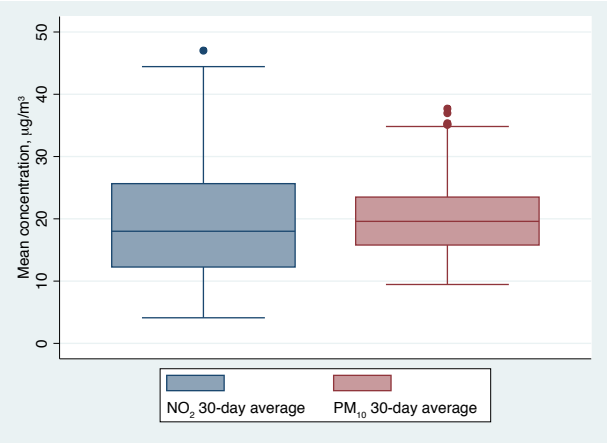
Notre étude repose sur la cohorte mère-enfants EDEN. L'examen Doppler réalisé à la fin du deuxième trimestre (artères utérines, ombilicale) et du troisième trimestre de grossesse (artère ombilicale, artère fœtale cérébrale) a permis d'estimer l'indice de résistance de chaque artère.

Les concentrations de PM_{10} et de NO_2 à proximité du domicile maternel dans des fenêtres temporelles allant de 1 à 90 jours avant l'examen Doppler ont été estimées à partir du modèle de dispersion atmosphérique décrit plus haut, à l'aide du logiciel ADMS-Urban. L'association entre pollution atmosphérique et mesures Doppler a été quantifiée par régression linéaire ou logistique ajustée sur le sexe du fœtus, l'âge de la mère, l'indice de masse corporel, la durée de gestation, le tabagisme actif et passif, le revenu mensuel du ménage, la parité, le centre, la saison de la mesure Doppler, la température extérieure, l'humidité extérieure et la pression atmosphérique.

3. Résultats

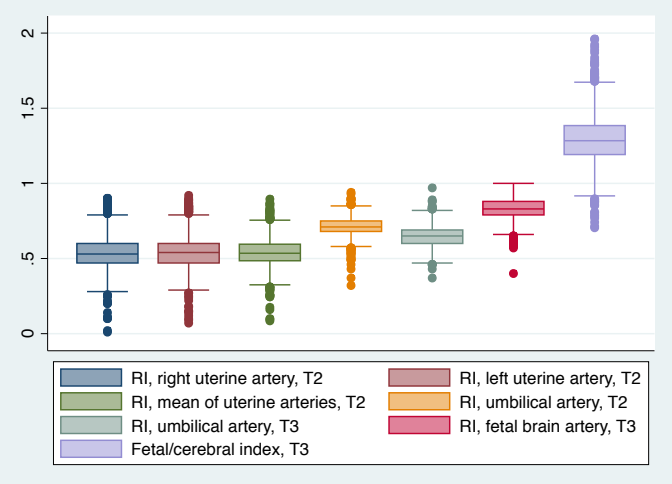
Les niveaux de NO_2 et PM_{10} moyens dans les 30 jours précédant l'examen étaient définis pour 900 femmes lors de l'échographie de fin de deuxième trimestre et 1026 femmes lors de l'échographie du troisième trimestre. La distribution des niveaux d'exposition est donnée Figure 16.

Figure 16 : Distribution des niveaux de NO_2 et PM_{10} moyens dans les 30 jours précédant l'échographie réalisée en fin de deuxième trimestre de grossesse. Les niveaux de pollution ont été estimés à partir du modèle de dispersion atmosphérique ADMS-Urban.



Les niveaux des indices de résistance (RI) des artères utérines (deuxième trimestre), ombilicale (deuxième et troisième trimestre) et fœtale cérébrale (troisième trimestre) ainsi que du ratio cérébro-placentaire sont donnés Figure 17. Comme attendu, l'indice de résistance de l'artère fœtale cérébrale était supérieur à celui de l'artère ombilical mesuré au même moment (ratio cérébro-placentaire généralement supérieur à 1).

Figure 17 : Distribution des mesures Doppler. RI : Indice de résistance (1-D/S, où D est la vitesse maximale télé-diastolique et S la vitesse maximale systolique) ; T2 : mesures faites à 20-24 semaines de gestation ; T3 : mesures faites à 30-34 semaines de gestation.



Comme attendu, la résistance de l'artère ombilicale diminuait avec l'âge gestationnel (non détaillé). Les associations entre les niveaux de pollution dans les 30 jours précédant l'examen Doppler et les paramètres Doppler, ajustés sur les facteurs de confusion potentiel et l'âge gestationnel lors de l'examen, sont décrites Tableau 12. Les associations étaient globalement concordantes pour les deux polluants (les valeurs différentes des paramètres s'expliquant par l'intervalle de variation plus important pour NO_2 que PM_{10}). Il n'y avait pas d'éléments en faveur d'un effet des polluants considérés sur les mesures Doppler en fin de deuxième trimestre de grossesse. Au troisième trimestre en revanche, les niveaux de pollution étaient associés à une diminution de l'indice de résistance de l'artère ombilicale, à une augmentation de la résistance de l'artère fœtale cérébrale et, de façon cohérente, à une augmentation de l'indice cérébro-placentaire (ratio des deux précédents paramètres).

Tableau 12 : Associations ajustées* entre les niveaux de pollution dans les 30 jours précédant l'examen Doppler et les mesures Doppler. Les valeurs des paramètres associés à l'exposition sont données en pourcent ; une valeur de 2,00 indique que l'indice de résistance augmente en moyenne de 0,02 pour chaque augmentation de 10 $\mu g/m^3$ de la concentration du polluant atmosphérique considéré.

	NO_2			PM_{10}		
Doppler measure	n	β*	95% CI	n	β*	95% CI
Second Trimester						
Right uterine artery RI	862	.03	-1.03; 1.08	862	.22	-1.38; 1.83
Left uterine artery RI	858	-.69	-1.74; 3.64	858	-6.70	-2.28; .94
Uterine arteries (average RI)	853	-.29	-1.19; .62	853	-1.94	-1.59; 1.20
Umbilical artery RI	895	.09	-.47; .66	895	-.33	-1.20; .54
Third Trimester						
Umbilical artery RI	994	-.95	-1.52; -.39	994	-1.89	-2.73; -1.05
Fetal brain artery RI	890	1.00	.32; 1.69	890	1.64	.63; 2.65
Brain/placental index	889	3.19	1.62; 4.76	889	5.53	3.23; 7.83

* β are reported for an increase by 10 $\mu g/m^3$ in exposure levels and have been adjusted for gestational age at measure (linear and quadratic terms), active smoking, pre-pregnancy maternal body mass index, season of conception, center, temperature, humidity and pressure averaged during 30 days before the examination.

Ces associations tendaient à être de sens opposé à celles observées (parfois seulement en tendance) pour le tabagisme actif maternel ; ainsi le tabagisme actif était associé à une *augmentation* de la résistance de l'artère ombilicale au troisième trimestre (p=0,01) et à une *diminution* du ratio cérébro-placentaire (p=0,08), ce qui est typique du *brain sparing effect*.

4. Discussion

Notre étude est une des toutes premières à caractériser l'effet des polluants atmosphériques sur les flux sanguins materno-placentaires et foeto-placentaires. A notre connaissance, une seule étude, s'appuyant sur la cohorte Generation R, a considéré un effet possible des polluants atmosphériques sur les flux sanguins materno-foeto-placentaires caractérisés par des mesures Doppler (van den Hooven, et al., 2012). Cette étude n'avait pas pris en compte les mesures de la résistance dans l'artère cérébrale fœtale, mais elle avait en revanche

étudié la survenue de *notch* (incisure lors de la diastole), événements trop peu fréquents pour être caractérisés avec l'effectif de notre cohorte. Malgré un effectif variant selon les analyses entre 3400 et 6000, cette étude n'avait pas mis en évidence d'association nette avec les niveaux de pollution atmosphérique estimés par un modèle de dispersion. Une tendance à la diminution de la résistance de l'artère ombilicale au deuxième (mais pas au troisième) trimestre de grossesse était observée en lien avec les niveaux de NO_2 et PM_{10} moyennés dans les deux mois précédant ou depuis le début de la grossesse.

Notre étude met en évidence une diminution de la résistance de l'artère ombilicale au troisième trimestre de grossesse en lien avec les niveaux de pollution dans le mois précédant. Cette diminution n'était pas conforme à notre hypothèse a priori, selon laquelle la pollution atmosphérique pourrait entraîner une augmentation de la résistance de l'artère ombilicale, augmentation qui est associée à une augmentation du risque de restriction de croissance fœtale. La résistance de l'artère cérébrale fœtale était, elle, augmentée avec les niveaux de pollution atmosphérique, ainsi que l'indice cérébro-placentaire. Les cliniciens ont tendance à considérer que c'est une diminution de cet indice cérébro-placentaire, qui indique une redistribution de la circulation sanguine fœtale au profit du cerveau, qui serait le signe d'une fonction placentaire altérée. Nos résultats indiquent que, si le tabagisme actif semble associé à un tel effet, ce n'est pas le cas des polluants atmosphériques, qui semblent eux associés à une augmentation de la résistance de l'artère fœtale cérébrale. Les conséquences éventuelles d'une telle augmentation de l'artère fœtale cérébrale sur le périmètre crânien et le neurodéveloppement de l'enfant semblent mal connues. Dans notre cohorte, des analyses préliminaires indiquaient qu'une augmentation de l'indice cérébroplacentaire était associé à une augmentation du périmètre crânien à la naissance, ce qui n'était pas en faveur de l'hypothèse selon laquelle l'effet de la pollution atmosphérique sur la diminution du périmètre crânien (voir II ci-dessus) serait en partie expliqué par une altération des échanges sanguins au niveau de l'artère fœtale cérébrale.

D. Communications scientifiques

I. Publications scientifiques

Le projet a à la date de rédaction de ce rapport fait l'objet de 7 publications dans les meilleures revues de santé environnementale, dont 4 soutenues par ce financement :

Hampel R, Lepeule J, Schneider A, Bottagisi S, Charles MA, Ducimetiere P, Peters A, Slama R. Short-term Impact of Ambient Air Pollution and Air Temperature on Blood Pressure Among Pregnant Women. *Epidemiology* 2011;**22:**671-679.

Lepeule J, Caini F, Bottagisi S, Galineau J, Hulin A, Marquis N, Bohet A, Siroux V, Kaminski M, Charles MA et al. Maternal exposure to nitrogen dioxide during pregnancy and offspring birth weight: comparison of two exposure models. *Environ Health Perspect* 2010;**118:**1483-1489.

Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Nybo Andersen AM, Ballester F, Beelen RMJ, Chatzi L, Cirach M, Danileviciute A, Dedele A, van Eijsden M, Estarlich M, Fernández-Somoano A, Fernández MF, Forastiere F, Gehring U, Grazuleviciene R, Gruzieva O, Heude B, Hoek G, de Hoogh K, van den Hooven EH, Håberg SE, Jaddoe V, Klümper C, Korek M, Krämer U, Lerchundi A, Lepeule J, Nafstad P, Nystad W, Patelarou E, Porta D, Postma D, Raaschou-Nielsen O, Rudnai P, Sunyer J, Stephanou E, Sørensen M, Thiering E, Tuffnell D, Varró MJ, Vrijkotte TJM, Wijga A, Wilhelm M, Wright J, Nieuwenhuijsen MJ, Pershagen G, Brunekreef B, Kogevinas M, Slama R. Ambient Air Pollution and Low Birth Weight: A European Cohort Study (ESCAPE). *The Lancet Respiratory Medicine* (*accepté*)

Rahmalia, A, L Giorgis-Allemand, J Lepeule, et al. Pregnancy exposure to atmospheric pollutants and placental weight: An approach relying on a dispersion model*. Environment international.* 2012;**48C**(47-55).

Ce dernier travail concernait l'impact de la pollution atmosphérique sur le poids de naissance, dans le cadre du projet européen ESCAPE, qui, grâce au financement Eden Air Plus a inclus les nouveau-nés de la cohorte Eden ; il a par ailleurs reçu le prix 2013 "Best abstract from a new researcher" de l'International Society of Environmental Epidemiology (ISEE).

Un article est en cours de révision :

Sellier Y, Galineau J, Hulin A, Caini F, Marquis N, Navel V, Bottagisi S,b, Giorgis-Allemand L, Jacquier C, Slama R, Lepeule J and the Eden mother-child cohort study group. Health effects of ambient air pollution: do different methods for estimating exposure lead to different results? (en révision à *Env Int*).

Les données de modélisation ont par ailleurs permis d'autres publications concernant :

- la santé respiratoire et le compromis entre biais et variance dans l'épidémiologie des effets de la pollution atmosphérique :

Pedersen M, Siroux V, Pin I, Charles MA, Forhan A, Hulin A, Galineau J, Lepeule J, Giorgis-Allemand L, Sunyer J, Annesi-Maesano I, Slama R; The 'EDEN Mother–Child' Cohort Study Group. Does Consideration of Larger Study Areas Yield More Accurate Estimates of Air Pollution Health Effects? An Illustration of the Bias-Variance Trade-off in Air Pollution Epidemiology, *Env Int*, 2013, **60C**:23-30.

- les effets de la pollution atmosphérique sur les niveaux de vitamine D dans le sang du cordon ombilical :

Baïz N, Dargent-Molina P, Wark JD, Souberbielle JC, *Slama R*, Annesi-Maesano I; EDEN Mother-Child Cohort Study Group. Gestational exposure to urban air pollution related to a decrease in cord blood vitamin d levels, *J Clin Endocrinol Metab*, **97**: 4087-95, 2012.

Une publication didactique dans une revue de langue française est parue :

Lepeule J, Caïni F, Marquis N, Hulin A, Galineau J, Navel V, Jacquier C, Giorgis-Allemand L, Charles MA, Slama R, Effets de l,exposition maternelle à la pollution atmosphérique sur le déroulement de la grossesse : résultats de la cohorte mère-enfant EDEN, *Particules*, 2012. Novembre, P.72-79.

D'autres publications sont en préparation.

II. Communications orales et posters

Galineau J, Hulin A, Marquis N, Estimation of exposure to urban air pollution in two cities using a Gaussian dispersion model: the Eden-Air project, Barcelone, *International ISEE Congress (International Society of Environmental Epidemiology), poster, septembre 2011 (abstract dans Env Health Perspect).*

Lepeule J, Caïni F, Galineau J, Hulin A, Marquis N, Bohet A, Thiébaugeorges O, Bottagisi S, Goua V, Kaminski M, Charles MA, Slama R, Maternal exposure to NO_2 during pregnancy and fetal growth: comparison of two exposure models, *International ISEE Congress (International Society of Environmental Epidemiology)*, Dublin, August 2009. *Epidemiology 2009;* **20**(6S): S79.

Lepeule J, Galineau J, Hulin A, Bottagisi S, Marquis N, Caïni F, Bohet A, Kaminski M, Charles MA, Slama R, Maternal exposure to urban air pollution during pregnancy assessed by a dispersion model and fetal growth, *International ISEE Congress (International Society of Environmental Epidemiology)*, Seoul, August 2010. *Epidemiology 2011;* **22**(1S): S121.

Sellier Y, Julien Galineau, Agnès Hulin, Fabrice Caïni, Nathalie Marquis, Sébastien Bottagisi, Lise Giorgis Allemand, Monique Kaminski, Marie-Aline Charles, Rémy Slama, Johanna Lepeule, Ambient air pollution models: Impact on estimated exposure and relationship with birth weight, Barcelone, *International ISEE Congress (International Society of Environmental Epidemiology), communication orale, septembre 2011 (abstract dans Env Health Perspect).*

III. Formation, stages

Les études présentées ici ont pour l'instant fait l'objet de trois stages de M2 recherche de l'Université Joseph Fourier Grenoble et de l'Ecole des Hautes Etudes en Santé Publique (Thomas Lloret, Yann Sellier, Annisa Rahmalia).

E. Références

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, Tsai M-Y, Künzli N, Schikowski T, Marcon A et al. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. *Atmospheric Environment* 2013;**72:**10-23.

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. A cohort study of traffic-related air pollution impacts on birth outcomes. *Environ Health Perspect* 2008;**116:**680-686.

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Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann HE, Heinrich J. Traffic-Related Atmospheric Pollutants Levels during Pregnancy and Offspring's Term Birth Weight: A Study Relying on a Land-Use Regression Exposure Model. *Environ Health Perspect* 2007;**115:**1283-1292.

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Slama R, Thiebaugeorges O, Goua V, Aussel L, Sacco P, Bohet A, Forhan A, Ducot B, Annesi-Maesano I, Heinrich J et al. Maternal Personal Exposure to Airborne Benzene and Intrauterine Growth. *Environmental Health Perspectives* 2009;**117:**1313-1321.

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Blood Pressure, and the Risk of Hypertensive Complications During Pregnancy: The Generation R Study. *Hypertension* 2011;**57:**406-412.

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ANNEXES

Principales publications

Hampel R, Lepeule J, Schneider A, Bottagisi S, Charles MA, Ducimetiere P, Peters A, Slama R. Short-term Impact of Ambient Air Pollution and Air Temperature on Blood Pressure Among Pregnant Women. *Epidemiology* 2011;**22:**671-679.

Lepeule J, Caini F, Bottagisi S, Galineau J, Hulin A, Marquis N, Bohet A, Siroux V, Kaminski M, Charles MA et al. Maternal exposure to nitrogen dioxide during pregnancy and offspring birth weight: comparison of two exposure models. *Environ Health Perspect* 2010;**118:**1483-1489.

Rahmalia, A, L Giorgis-Allemand, J Lepeule, et al. Pregnancy exposure to atmospheric pollutants and placental weight: An approach relying on a dispersion model*. Environment international.* 2012;**48C**(47-55).

(les autres publications sont disponibles à la demande).

Short-term Impact of Ambient Air Pollution and Air Temperature on Blood Pressure Among Pregnant Women

Regina Hampel,[a] *Johanna Lepeule,*[b,c] *Alexandra Schneider,*[a] *Sébastien Bottagisi,*[b,c] *Marie-Aline Charles,*[d,e] *Pierre Ducimetière,*[f] *Annette Peters,*[a] *and Rémy Slama*[b,c]

Background: Epidemiologic studies have reported inconsistent findings for the association between air pollution levels and blood pressure (BP), which has been studied mainly in elderly subjects. Short-term air pollution effects on BP have not been investigated in pregnant women, who may constitute a vulnerable population.

Methods: Between 2002 and 2006, 1500 pregnant women from a mother-child cohort study conducted in Nancy and Poitiers, France, underwent 11,220 repeated BP measurements (average, 7.5 measurements/woman). Nitrogen dioxide (NO_2), particulate matter with an aerodynamic diameter below 10 μm (PM_{10}), and meteorologic variables were measured on an hourly basis at permanent monitoring sites. We studied changes of BP in relation to short-term variations of air pollution and temperature with mixed models adjusted for meteorologic and personal characteristics.

Results: A 10°C decrease in temperature led to an increase in systolic BP of 0.5% (95% confidence interval = 0.1% to 1.0%). Elevated NO_2-levels 1 day, 5 days and averaged over 7 days before the BP measurement were associated with reduced systolic BP. The strongest decrease was observed for the 7-day NO_2 average (−0.4% [−0.7% to −0.2%] change for an 11 $\mu g/m^3$ increase in NO_2). PM_{10} effects on systolic BP differed according to pregnancy trimester: PM_{10} concentration was associated with systolic BP increases during the first trimester and systolic BP decreases later in pregnancy.

Conclusions: We observed short-term associations of air pollution and of temperature with BP in pregnant women. Whether such changes in BP have clinical implications remains to be investigated.

(*Epidemiology* 2011;22: 671–679)

There is evidence of an association between increased ambient air pollution levels and adverse cardiovascular health effects.[1,2] As high blood pressure (BP) is a risk factor for cardiac diseases, researchers have also investigated the influence of air pollution on BP, but with inconsistent findings.[3–7] Most of these epidemiologic studies were carried out in elderly participants, with or without underlying cardiovascular diseases. Very little attention has been given to effects on BP of pregnant women.[8]

Pregnant women may constitute a particularly susceptible population because of possible consequences for the fetus of any air pollution effect on maternal cardiovascular health.[9] Pregnancy is associated with major changes in maternal cardiovascular and endothelial function. In particular, among primipara, by gestational week 34, plasma volume increases by 50%. The increase in red blood cell mass is more limited, resulting in a physiologic anemia and reduced blood viscosity that creates a lower resistance to blood flow, and a thrombophilic state is induced. Cardiac output increases, although not enough to counterbalance the physiologic vasodilatation, and so a reduction in BP usually occurs.[9] Given these physiologic changes, the impact of air pollution on BP in pregnant women might differ from that among nonpregnant women. Furthermore, the sensitivity of the cardiovascular function of pregnant women to air pollution effects might vary during the course of pregnancy.

The question of air pollution effects on the cardiovascular function of pregnant women is also of interest in the context of the reported associations between air pollution and adverse pregnancy outcomes such as preterm birth and fetal growth.[10,11] Changes in the BP of pregnant women may alter maternal-placental oxygen and nutrient exchanges, and thereby alter fetal growth, as previously hypothesized.[12]

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The objective of our study was to analyze short-term effects of air pollution on BP in healthy pregnant women. As a secondary objective, we also aimed at characterizing possible effects of air temperature on BP during pregnancy.[13,14]

METHODS

Study Population and Clinical Measurements

This study was conducted in a subgroup of the EDEN (study of pre- and early postnatal determinants of the child's development and health) mother–child cohort.[11,15,16] The primary aim of this cohort is the investigation of prenatal and early postnatal nutritional, environmental, and social determinants of children's development and health. Between February 2003 and January 2006, pregnant women were recruited within 24 weeks of last menstrual period in obstetrical departments of the University Hospitals in Poitiers and Nancy, France. Exclusion criteria were multiple pregnancies, intention to deliver outside the University Hospital or to move out of the study region within the next 3 years, and inability to speak French. Among women who fulfilled these inclusion criteria, 55% agreed to participate (n = 2002). Between December 2002 and July 2006, 1871 of these women participated in up to 12 repeated antenatal visits as part of the normal follow-up of the pregnancy, and the corresponding information was extracted from the obstetric records. (Some of these visits took place before the start of the recruitment period.) Only women without hypertension before pregnancy and who had information on at least 2 visits were included in our analyses. Characteristics such as weight before pregnancy, number of previous pregnancies, disease, and smoking history were collected from the maternity records and by specific questionnaires during pregnancy. At each visit, systolic and diastolic BP were measured. Visit dates but not times were recorded. The study was approved by the relevant ethical committees (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin-Bicêtre University hospital, and Commission Nationale de l'Informatique et des Libertés). All women gave written consent.

Meteorologic and Air Pollution Data

Meteorologic variables (air temperature, relative humidity, and barometric pressure) were assessed hourly at one central site in each city (Météo France). Nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter $\leq 10\ \mu m$ (PM_{10}) were measured on an hourly basis at 28 NO_2 and 19 PM_{10} permanent background-monitoring sites (eFigure 1, http://links.lww.com/EDE/A490) by the air-quality-monitoring networks from Nancy (Airlor) and Poitiers (Atmo-PC). PM_{10} was measured by Tapered Element Oscillating Microbalance (TEOM) devices. Air pollution measurements of the monitoring station located closest to the woman's home address were used. Information on any residential move was available throughout the study period. Changes in home address were taken into account for exposure assessment. Analyses were restricted to women living less than 20 km from an air-quality-monitoring station. Twenty four-hour averages of air pollutants and meteorologic variables were calculated for the period before each BP measurement for each woman. We assumed that each visit took place at 8:00 AM, and we averaged air pollution levels from 9:00 AM one day before the visit up to 8:00 AM on the day of the visit (lag 0). Additionally, averages 24 to 47 hours (lag 1), 48 to 71 hours (lag 2), 72 to 95 hours (lag 3), 96 to 119 hours (lag 4), 120 to 143 hours (lag 5), and 144 to 167 hours (lag 6) before 8:00 AM on the day of the visit were estimated, as well as a 7-day average. In sensitivity analyses, we also tested the association between air pollution levels estimated by a dispersion model and BP. This model incorporated hourly meteorologic data, traffic, industrial, and other urban sources in Nancy and Poitiers urban areas, as well as hourly background air pollution levels measured from monitoring stations, and was implemented using ADMS-Urban software (CERC, Cambridge, United Kingdom).

Statistical Analyses

The longitudinal data were analyzed with SAS statistical package (version 9.1; SAS Institute Inc, Cary, NC) using additive mixed regression models with a compound symmetry covariance structure and a random intercept accounting for variations in individual BP levels between women. Selection of adjustment factors was conducted separately for systolic BP and diastolic BP. The following patient characteristics were all included in regression models: age, body mass index (BMI) before pregnancy, gestational age, number of previous pregnancies (none, 1, $\geq$2), smoking, and passive smoking. We defined woman-specific variables for smoking or passive smoking in the first trimester of pregnancy, as well as visit-specific variables for smoking or passive smoking during the trimester when the visit took place. Variables for active smoking were coded linearly (number of smoked cigarettes), categorically (0, 1–10, 11–20, >20 cigarettes), or as an indicator (yes vs. no). Only single variables for smoking and passive smoking were entered in each regression model, selecting the variables that minimized Akaike's Information Criterion (AIC). Models on air pollutant effects were additionally adjusted for long-term time trends (counts of the days during the study period, to take into account seasonal variations in BP), air temperature, and relative humidity. Barometric pressure and day of the week were included only if they decreased AIC. For continuous confounders, the shape (linear, polynomial, or restricted cubic spline) and the lag (for meteorologic variables) that minimized AIC were chosen. When investigating the effects of temperature, we adjusted models for the same clinical characteristics and with the same shape of long-term time trend as used in the air pollution models. Additionally, we included relative humidity and

barometric pressure with the same lag as the analyzed temperature lag. We tested the shape of the association between temperature and BP by coding temperature with restricted cubic splines. There was no evidence for a deviation from linearity for the relationship between temperature and BP so that temperature was included as a linear term in final models.

Linear effects of temperature and air pollution levels were estimated in adjusted mixed models, including one exposure lag at a time. For each monitoring station, interquartile ranges (IQR) of air pollution measurements during the study period and the median of these station-specific IQRs were calculated for NO_2 and PM_{10} using 24-hour and 7-day averages. Associations are presented as percent changes of the outcome mean per median IQR increase in air pollutant or per 10°C decrease in temperature, as in previous studies of temperature effects on cardiovascular health.[17,18]

Effect Modification

In further analyses, categorical interaction variables were added to the models to estimate whether temperature and air pollution effects were modified by specific characteristics. Potential effect modifiers were center (Nancy vs. Poitiers), smoking in the first trimester of pregnancy (yes vs. no), season (April–September vs. October–March), and trimester of pregnancy at the time of the examination (1st vs. 2nd vs. 3rd trimester). Trimester of pregnancy was considered a potential effect modifier because of the important changes in cardiovascular function throughout pregnancy.[9]

Sensitivity Analyses

We repeated the estimation of temperature effects adjusting for NO_2 or PM_{10} levels (with the same lag as the temperature lag). To check the robustness of the estimated air pollution effects, we conducted several sensitivity analyses: (1) Instead of using the time lags of meteorologic variables leading to the best model fit, we included meteorologic variables with the same lag as the analyzed air pollution lag. (2) We excluded visits that took place on the weekend, assuming that these were unplanned visits due to concerns of the women. (3) We excluded women who developed gestational diabetes. (4) We restricted our analyses to women living within 10 km, 5 km, or 1 km from the closest air-quality-monitoring station. (5) Instead of a mixed model with compound symmetry, we used a "spatial" covariance structure.[19] The elements of this covariance matrix decrease with increasing elapsed time between 2 visits. (6) Instead of using the air pollution measurements of the station closest to the woman's home address, we used an alternative exposure metric that averaged measurements of several monitoring sites in 3 areas: the urban and the suburban background (20-km buffer around the center, excluding the urban area) of Nancy, and the urban background (20-km buffer around the center) of Poitiers. Missing values on the aggregated level were replaced as described by Berglind et al.[20] Averages were calculated only for women living within 20 km from the city centers of Nancy or Poitiers. (7) In a further sensitivity analysis regarding exposure modeling, we characterized the association between 7-day averages of NO_2 and PM_{10} levels estimated with a dispersion model and BP.

RESULTS

Study Population and Clinical Measurements

Of the 1871 women with repeated antenatal visits, we excluded 37 women (2%) who had hypertension before pregnancy and 61 women (3%) with missing values in clinical characteristics. We also excluded 273 women (15%) because they lived more than 20 km from the closest PM_{10} and NO_2 monitoring stations. The remaining 1500 women had 11,220 visits (mean: 7.5 visits/woman, 5th–95th percentiles: 4–11 visits/woman) with BP measurements. The time elapsed between 2 consecutive visits was on average 27 days (5th–95th percentiles: 5–43 days).

Table 1 describes the clinical characteristics of the participants. Average diastolic BP was lower in Nancy compared with Poitiers, whereas systolic BP was higher in Nancy. The differences in BP between the study centers remained after adjustment for patient characteristics and meteorologic variables (data not shown). Mean values of systolic and diastolic BP were 117.0 mm Hg (standard deviation (SD) = 12.9) and 64.9 mm Hg (9.2), respectively, in winter, and 116.3 mm Hg (12.3) and 65.1 mm Hg (9.2) in summer, respectively. Averaged systolic BP measurements were lower during the second trimester of pregnancy (mean = 115.4 mm Hg [SD = 12.2]) compared with the first (118.2 mm Hg [13.0]) and third trimesters (117.2 mm Hg [12.8]). The same pattern was observed for diastolic BP (data not shown).

Meteorologic and Air Pollution Data

A description of the 24-hour averages of meteorologic and air pollution variables for each monitoring site can be found in eTable 1 (http://links.lww.com/EDE/A490). Medians of these site-specific descriptive measures are shown in Table 2. Mean temperature in summer was 16.5°C and in winter 5.4°C.

Air Temperature and Blood Pressure

A 10°C decrease in temperature was associated with an immediate (lag 0) increase in systolic BP by 0.5% (95% confidence interval [CI = 0.1% to 1.0%]) and a delayed (lag 6) increase in systolic BP by 0.4% (0.0% to 0.9%) (Fig. 1A). These percent changes correspond to an immediate increase in systolic BP of 0.6 mm Hg (0.1 to 1.1 mm Hg) and a delayed increase of 0.5 mm Hg (0.0 to 1.0 mm Hg) in association with a 10°C decrease in temperature. When we additionally adjusted for NO_2, the sample size decreased by about 10% but temperature effects were stronger for lags 1, 2, and 5 and for the 7-day average (Fig. 1A). Temperature effects on systolic BP were not affected by adjustment for PM_{10} (data not shown). For all time

TABLE 1. Clinical Characteristics[a] and Blood Pressure Measurements of 1500 Women From EDEN (Study of Pre- and Early Postnatal Determinants of the Child's Development and Health) Cohort Living Less Than 20 Km From an Air Quality Monitoring Station

	All	Poitiers	Nancy
Based on number of women			
	(n = 1500)	**(n = 657)**	**(n = 843)**
Age (years); mean (SD)	29.2 (4.9)	29.0 (5.0)	29.3 (4.9)
Height (cm); mean (SD)	163.6 (6.1)	162.9 (6.1)	164.2 (6.1)
Weight before pregnancy (kg); mean (SD)	61.9 (12.5)	62.1 (12.7)	61.7 (12.3)
Body mass index before pregnancy (kg/m^2)			
Distribution			
<25	1124 (75)	473 (72)	651 (77)
25–29.9	258 (17)	122 (19)	136 (16)
≥30	118 (8)	62 (9)	56 (7)
Mean (SD)	23.1 (4.5)	23.4 (4.6)	22.9 (4.4)
Gestational hypertension			
Yes	75 (5)	24 (4)	51 (6)
No	1425 (95)	633 (96)	792 (94)
Gestational diabetes			
Yes	94 (6)	40 (6)	54 (6)
No	1406 (94)	617 (94)	789 (94)
Previous pregnancies			
0	673 (45)	312 (48)	361 (43)
1	558 (37)	230 (35)	328 (39)
≥2	269 (18)	115 (17)	154 (18)
Smoking in the 1st trimester of pregnancy			
Yes	384 (26)	189 (29)	195 (23)
No	1116 (74)	468 (71)	648 (77)
Passive smoking in the 1st trimester of pregnancy			
Yes	472 (31)	189 (29)	283 (34)
No	1028 (69)	468 (71)	560 (66)
Based on number of antenatal visits			
	(n = 11220)	**(n = 4697)**	**(n = 6523)**
Trimester			
1st (0–13 weeks)	1849 (16)	436 (9)	1413 (22)
2nd (14–27 weeks)	4587 (41)	1855 (39)	2732 (42)
3rd (>27 weeks)	4784 (43)	2406 (51)	2378 (36)
Weekend visit			
Yes	322 (3)	275 (6)	47 (1)
No	10898 (97)	4422 (94)	6476 (99)
Season of visit			
Winter (Oct–Mar)	5744 (51)	2137 (45)	3607 (55)
Summer (Apr–Sep)	5476 (49)	2560 (55)	2916 (45)
Smoking in the trimester of the visit			
Yes	2008 (18)	887 (19)	1121 (17)
No	9212 (82)	3810 (81)	5402 (83)
Passive smoking in the trimester of the visit			
Yes	3256 (29)	1228 (26)	2028 (31)
No	7964 (71)	3469 (74)	4495 (69)
Gestational age of visit (days); mean (SD)	172.9 (66.8)	189.3 (61.8)	161.1 (67.8)
Diastolic blood pressure (mm Hg); mean (SD)	65.0 (9.3) (n = 11209)	67.1 (9.0) (n = 4693)	63.5 (9.2) (n = 6516)
Systolic blood pressure (mm Hg); mean (SD)	116.6 (12.6) (n = 11218)	114.2 (10.9) (n = 4697)	118.3 (13.4) (n = 6521)

[a]No. (%), unless otherwise indicated.

lags, temperature effects were much stronger in April–September than in October–March (Fig. 1B). We observed no main effects of temperature on diastolic BP, but interaction analyses revealed a statistically significant increase in diastolic BP in association with temperature decrements in summer (data not shown). Temperature effects were not modified by center, smoking, or trimester of pregnancy.

Air Pollution and Blood Pressure

The medians of the station-specific interquartile ranges for 24-hour and 7-day averages were 14.4 and 11.4 $\mu g/m^3$, respectively, for NO_2 and 11.3 and 7.7 $\mu g/m^3$ for PM_{10}, respectively. Figure 2A shows the associations between NO_2 and systolic BP, adjusted for the variables listed in eTable 2 (http://links.lww.com/EDE/A490). An IQR increase in NO_2 in the 24 hours preceding the visit was associated with a change in systolic BP of −0.3% (−0.5% to −0.1%) or −0.4 mm Hg (−0.6 to −0.1 mm Hg). Similar decreases were also observed with lags of 1, 5, and 6 days. Increases in the 7-day average for both NO_2 (−0.4% [−0.7% to −0.2%] or −0.5 mm Hg [0.8% to −0.2% mm Hg]) and PM_{10} (−0.3% [−0.5% to 0.0%] or −0.3 mm Hg [−0.6% to 0.0%]) were associated with the strongest reductions in SBP. Effect estimates for NO_2 on systolic BP seemed to be stronger than PM_{10} effects in analyses considering pregnancy as a whole. We detected no clear associations between air pollutants and diastolic BP (Fig. 2B).

Effect Modification of Air Pollution Effects

Air pollution effect estimates were similar for the 2 cities (eFigure 2, http://links.lww.com/EDE/A490). There was a consistent pattern of effect modification by season, with a tendency to weaker negative effects of air pollutants in the April–September, compared with the October–March periods (Fig. 3A–3B). This effect modification reached statistical significance only for PM_{10} concentrations with a 2-day lag (−0.3% [−0.7% to −0.0%] in October–March versus 0.1% [−0.2% to 0.5%] in April–September, P value of interaction = 0.04). NO_2 effects on systolic BP tended to be more pronounced in nonsmoking compared with smoking women (lowest P value of interaction = 0.12; eFigure 3, http://links.lww.com/EDE/A490).

We detected a strong modification of PM_{10}, but not of NO_2 effects, on systolic BP by trimester of pregnancy (Fig. 3C–D). The strongest modification was observed with the

TABLE 2. Description of the 24-hour Averages of Meteorologic Conditions and Air Pollution Levels in Nancy and Poitiers Areas From December 2002 to July 2006

	No. Sites	Mean (SD)	Minimum	25%	Median	75%	Maximum	IQR
Air temperature (°C)	2	11.0 (7.7)	−9.1	4.9	11.0	16.9	31.4	12.0
Relative humidity (%)	2	76.2 (13.5)	25.7	67.0	78.4	87.1	98.3	20.1
Barometric pressure (mm Hg)	2	1018.1 (7.7)	984.0	1013.6	1018.3	1023.0	1039.7	9.4
NO_2 ($\mu g/m^3$)	31	21.1 (10.7)	2.5	13.0	18.8	26.7	71.5	14.0
PM_{10} ($\mu g/m^3$)	23	19.1 (9.1)	2.1	13.1	17.5	23.8	74.0	11.1

IQR indicates interquartile range.

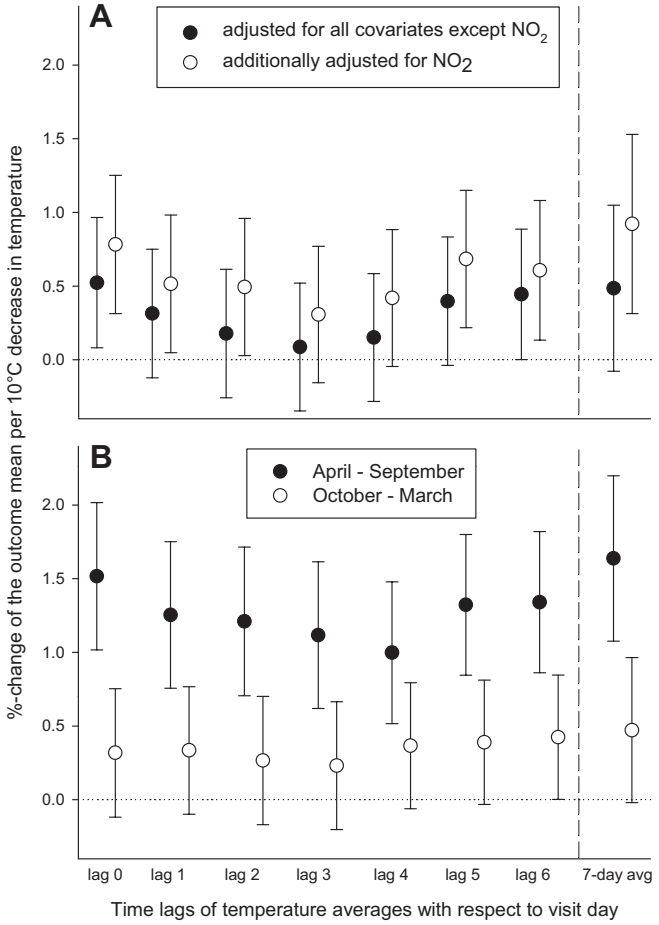

FIGURE 1. Adjusted changes in systolic blood pressure during pregnancy associated with a 10°C decrease in 24-hour and 7-day air temperature averages by (A) adjustment variables and (B) season.

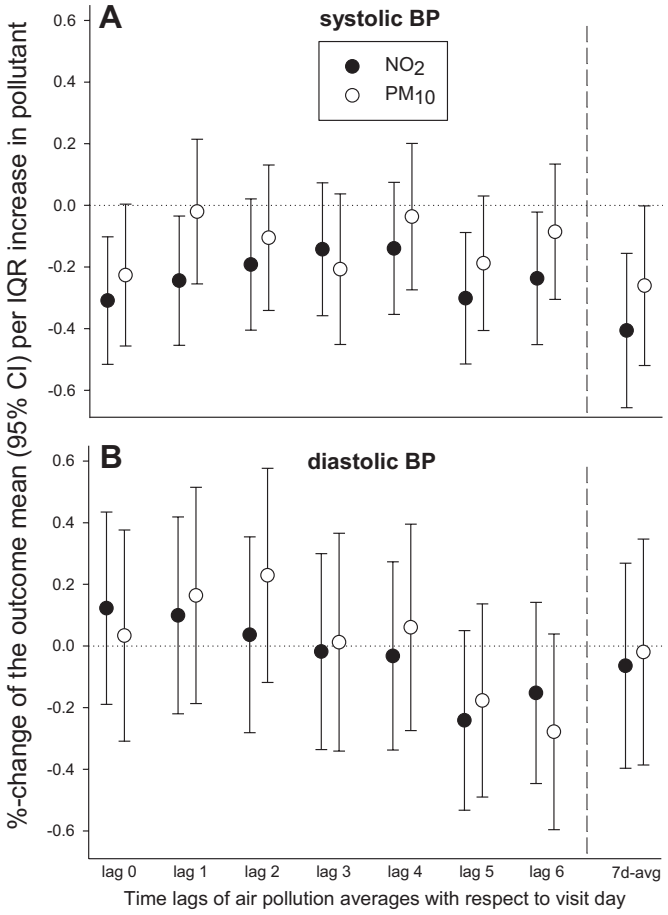

FIGURE 2. Adjusted associations between 24-hour and 7-day averages of NO_2 and PM_{10} and (A) systolic and (B) diastolic blood pressure during pregnancy. Associations are reported for an increase in air pollutants corresponding to the interquartile range.

4-day lag, which showed a 1.0% (0.5% to 1.5%) change in systolic BP associated with PM_{10} during the first trimester and changes of −0.3% (−0.6% to 0.0%) and −0.2% (−0.6% to 0.2%) during the second and third trimesters, respectively (P value of interaction <0.001).

Increases in PM_{10} (lag 0) were associated with a positive change in diastolic BP during the first trimester (1.1% [0.3% to 1.8%]), little change during the second trimester (0.2% [−0.3% to 0.8%]), and a negative change during the third trimester (−0.5% [−0.9% to 0.0%]).

Sensitivity Analyses

Air pollution effects were similar when we included meteorologic variables with the same lag as the analyzed air

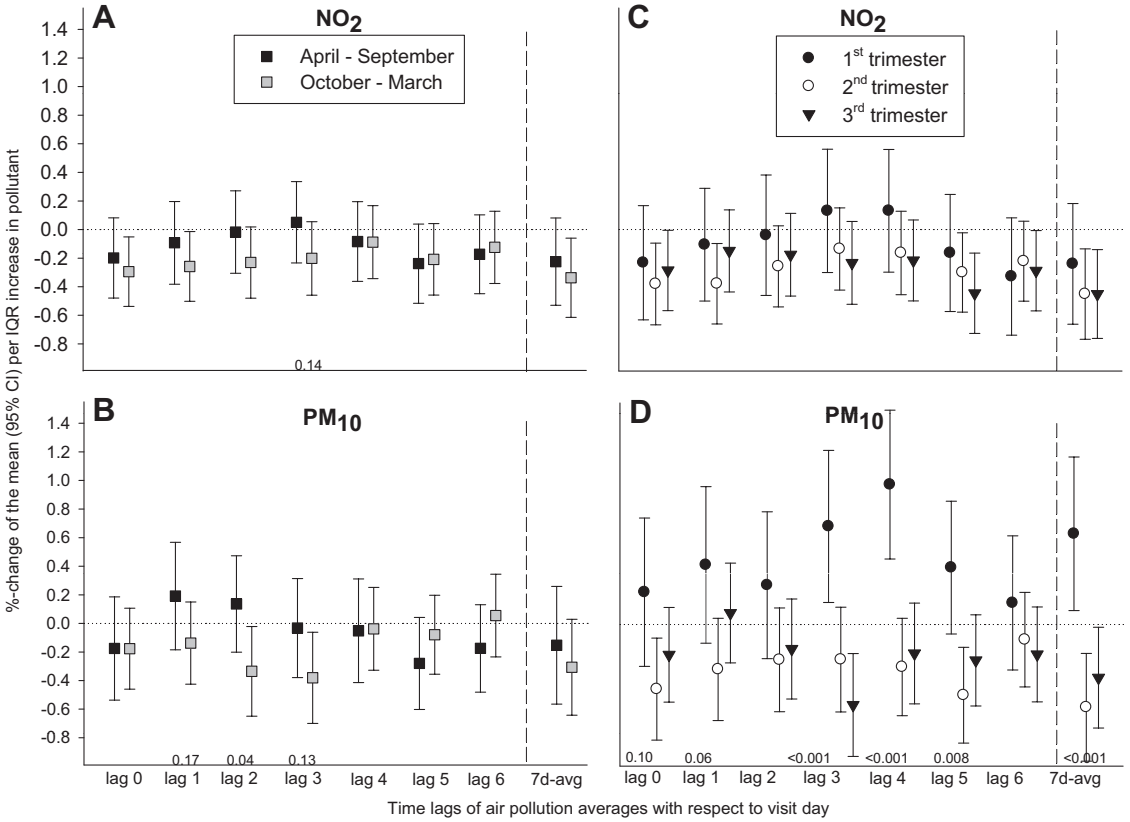

FIGURE 3. Adjusted associations between 24-hour and 7-day NO_2 (A and C) and PM_{10} (B and D) averages and systolic blood pressure (interquartile range increases), modified by season and trimester of pregnancy. Only *P* values <0.2 for interaction terms are indicated.

pollution lag, after the exclusion of visits during the weekend or of the 46 women who developed gestational hypertension (data not shown). NO_2 effects (lags 0, 1, and 2) slightly strengthened when we reduced the study population to women living $\leq$10 km from the closest monitoring station (NO_2 effects with a lag of 0, 1, and 2 days were -0.4% [-0.6% to -1.5%], -0.3% [-0.6% to -0.1%], and -0.3% [-0.5% to -0.0%], respectively) or within 5 km (-0.4% [-0.7% to -0.2%], -0.4% [-0.7% to -0.1%], and -0.4% [-0.6% to -0.1%]) (eFigure 4A, http:links.lww.com/EDE/A490). When we included only the 220 women (with 1439 systolic BP measurements) living within a radius of 1 km to the closest NO_2 station, no associations were observed and CIs were considerably widened. PM_{10} effect estimates did not change when we included only women living closer to the next monitoring station, but CIs widened (not shown). The air pollution effects on systolic BP were not altered when we used a spatial instead of a compound symmetry covariance structure. In the case of diastolic BP, convergence problems occurred, and a comparison between the models with different covariance structures was not possible. Using averaged air pollution measurements of several monitoring stations resulted in a smaller sample size but similar air pollution effects (eFigure 4B, http://links.lww.com/EDE/A490). Dispersion model estimates were available for 1155 women (eFigure 5, http://links.lww.com/EDE/A490). Seven-day averages of NO_2 estimated with the dispersion model exhibited a similar (somewhat weaker) association with BP than when estimated with the closest station approach, with wider CIs. When the entire duration of pregnancy was considered, the effect of PM_{10} on systolic BP was stronger with the dispersion approach compared with the closest-station approach (eFigure 6, http://links.lww.com/EDE/A490). We found no interaction between trimester and PM_{10} when using the dispersion model (P value of interaction $= 0.37$, compared with $P < 0.001$ using the closest-station approach).

DISCUSSION

In our cohort of healthy pregnant women with no previous history of hypertension, we observed short-term reductions in systolic BP in association with increasing NO_2 levels. This association was detected in all 3 trimesters of pregnancy. PM_{10} concentrations were positively associated with systolic and diastolic BP in the first trimester of pregnancy and tended to be negatively associated with both measures of BP later in pregnancy. This was not found with

the alternative (dispersion) exposure model. We detected a short-term increase in systolic BP associated with decrements in temperature. These temperature effects persisted after adjustment for NO_2, indicating at least partially independent associations of temperature and air pollution with systolic BP. The lack of associations between either temperature or air pollution and diastolic BP might be because diastolic BP is less accurately assessed than systolic BP.

Air Temperature and Blood Pressure

Elderly participants exhibit a higher BP in winter than in summer.[13,21] We observed a slightly higher systolic BP in winter among pregnant women; air temperature effects on BP were more pronounced in summer. Among adults aged 35–64 years, Barnett et al[14] reported an increase in average systolic BP of 0.19 mm Hg in association with a 1°C decrease in temperature. We also observed an immediate but weaker increase in systolic BP of 0.06 mm Hg with a 1°C decrease in temperature. Halonen et al[22] reported increases in systolic BP of 0.6%–1.3% associated with decreases in apparent temperature among elderly men living in Boston. Furthermore, they detected elevated diastolic BP levels associated with decreases in air temperature and apparent temperature. However, in these studies, effects of apparent temperature might also partly reflect the association between relative humidity (or air pollution) and BP. Temperature effects in our study were weaker, and we did not find an association with diastolic BP.

Seasonal variation in BP might be explained by changes in blood viscosity favoring a decreased systemic pressure in summer compared with colder seasons.[23] Furthermore, exposure to cold temperatures may activate the sympathetic nervous system and increase secretion of catecholamine. This possibly results in an increased heart rate and peripheral vascular resistance, and thus to increased BP with lower temperature.[13,23]

Air Pollution and Blood Pressure

The association between air pollution and BP has been characterized mainly in elderly participants[5,24,25] and in people with underlying cardiovascular diseases.[3,4,7] Findings are not consistent, perhaps due to misclassification of BP, differing confounder adjustment, or random associations because of multiple testing. Exposure misclassification and diversity in chemical composition of PM might also contribute to the inconsistent findings. Accordingly, Brook et al[26] found no association of BP with $PM_{2.5}$ estimated by ambient monitors, but did with personally measured $PM_{2.5}$ levels. Only one study, based on Generation R cohort,[8] has investigated the influence of air pollution on BP in pregnant women. BP was estimated once per trimester and exposure was averaged over each trimester of pregnancy. The Generation R study contrasts with ours by its focus on longer-term effects of air pollution, and on between-subject rather than within-subject variations in exposure. Van den Hooven and colleagues[8] observed a positive association between trimester averages of PM_{10} and systolic BP only in the second and third trimesters of pregnancy; we observed a positive association with 1-day to 1-week PM_{10} averages only in the first trimester. Since the PM_{10} effect based on our dispersion model was not modified by trimester of pregnancy, the increase in systolic BP associated with first trimester PM_{10} levels from the closest station in our study should be considered with caution. Disregarding issues related to exposure misclassification, the gradual and profound changes in cardiovascular function during pregnancy[27] make it plausible that environmental stressors could have different effects during different trimesters of pregnancy. Although we detected negative short-term NO_2 effects on systolic BP, van den Hooven et al[8] found an elevated systolic BP in association with trimester-specific NO_2 increases. Differences in time scale and design make comparisons between these 2 studies difficult; taken together (and assuming that these findings cannot be explained by biases), these studies suggest that air pollutants could have different effects on the shorter- and longer-terms. Differences such as those between estimated effects of NO_2 and PM_{10} are common in air pollution epidemiology. Such differences might be explained by the fact that these pollutants capture different dimensions of atmospheric pollutants, with PM_{10} coming in primarily from long-range pollution while NO_2 levels come from predominantly local sources.

Potential Mechanisms

A positive association between PM and BP could be mediated by an activation of the sympathetic nervous system due to a stimulation of nerve endings in the human airways by inhaled particles.[2] Furthermore, PM might trigger a systemic inflammation and oxidative reactions promoting vascular dysfunction.[2] An inhalation chamber study with 27 participants found an increase in the endothelium-dependent vasoconstrictor endothelin-1 induced by diesel exhaust particles.[28] Ultrafine particles, which are usually highly correlated with NO_2, can pass alveolar walls and might directly influence endothelial cell structure and endothelial function, possibly leading to vasoconstriction and increased BP.[2,29]

Other authors have raised alternative hypotheses to explain a negative association between air pollution levels and BP. Cheng et al,[30] who found a decreased BP in hypertensive rats exposed to concentrated particles, suggested that particles may cause airway irritation leading to increases of parasympathetic tone of the heart and peripheral vascular system. This hypothesis is supported by Zareba et al,[31] who exposed 12 participants to ultrafine particles and observed such changes in electrocardiogram parameters as QT-shortening and ST-elevation, indicating an increase in parasympathetic tone.

Whether one of these mechanisms could apply to pregnant women remains to be investigated. Indeed, pregnant women are a very specific population. Pregnancy-related

changes include hormonal changes, increases in blood volume and heart rate over the course of pregnancy, and decreasing BP in the second trimester of pregnancy.[27] For these reasons, pregnant women may have different susceptibility to air pollution than nonpregnant and elderly subjects, and our results cannot be generalized to the whole population. Additionally, these considerable cardiac and hormonal changes throughout pregnancy could modify air pollution effects throughout pregnancy, as supported by the possible effect modification of PM_{10} by trimester of pregnancy in our population.

Implications

Changes in BP might act as an intermediate step between exposure to air pollution and adverse pregnancy outcomes, such as preterm birth and reduced fetal growth.[11] Warland and McCutcheon[32] reviewed the association between hypotension and poor pregnancy outcomes and concluded that low BP might result in preterm birth, perinatal mortality, and low birth weight. However, Zhang and Klebanoff[33] suggested that the association between low BP during pregnancy and poor perinatal outcomes is due to confounding by other risk factors. Consequently, it is unclear whether the decreases in systolic BP reported in our study in association with air pollution could affect pregnancy outcome. High BP during pregnancy is a risk factor for preterm birth and low birth weight,[34,35] and an increase in systolic BP in the first trimester associated with PM_{10} might have consequences for pregnancy outcomes.

Strengths and Limitations

The main strength of our study is the large number of women who participated in repeated BP measurements. This enabled us to analyze intraindividual variations in BP, avoiding bias due to potential confounders constant over time. A further strength is the availability of clinical characteristics, allowing us to efficiently control for these variables and perform subgroup analyses. BP is a highly variable parameter which is affected by such characteristics as age, medication, smoking, and weather. However, we could control our models for most of these factors. Moreover, we performed several sensitivity analyses that did not change our findings. A limitation is the lack of information on the exact times of BP measurements. BP has its own diurnal rhythms. This is unlikely to have induced confounding but may have caused exposure misclassification. The extent of misclassification is probably limited for the 7-day exposure averages, because these averages are unlikely to differ strongly if they end at 8 AM or, say, 3 PM on the visit day. Only ambient exposure was measured, although people usually spend a lot of time indoors. NO_2 effects tended to vary according to the buffer size considered around monitoring stations. Because population size varied with buffer size, the relative contribution of exposure misclassification and selection effects to these variations in estimated NO_2 effects cannot easily be determined.

In conclusion, we observed a reduced systolic BP in pregnant women in association with elevated levels of NO_2 and third trimester PM_{10} levels, and an increased systolic BP with higher PM_{10} levels during the first trimester of pregnancy. The consequences of such BP effects on pregnancy-related outcomes require further investigations. Additionally, our study observed decreases in systolic BP with increasing temperatures.

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SUPPLEMENTAL MATERIAL

eTable 1. Description of 24h-averages (9:00 A.M. to 8:00 A.M on the following day) of NO_2, PM_{10} and meteorological variables, from December 2002 to July 2006 (Nancy and Poitiers areas, France).

Area	Location	Station type	Variable	N	Mean	SD	Min	25%	Median	75%	Max	IQR
Nancy	Tomblaine	Peripheral	NO_2 (µg/m³)	1301	18.1	8.3	3.1	11.8	16.4	23.0	62.2	11.2
Nancy	Nancy-Kennedy	Urban	NO_2 (µg/m³)	1319	38.1	13.1	10.6	29.0	36.7	45.5	89.4	16.5
Nancy	Nancy-Brabois	Peripheral	NO_2 (µg/m³)	1310	22.4	11.9	1.0	13.1	20.9	29.7	76.2	16.6
Nancy	Fléville	Peripheral/Industrial	NO_2 (µg/m³)	1303	26.0	11.3	3.0	17.6	24.9	32.6	77.6	15.0
Nancy	Fléville	Peripheral/Industrial	PM_{10} (µg/m³)	1292	20.1	9.1	3.7	13.5	18.6	25.0	70.4	11.5
Nancy	Epinal	Urban	NO_2 (µg/m³)	1271	21.3	11.6	1.8	12.4	18.8	28.4	75.2	16.0
Nancy	Remiremont	Urban	NO_2 (µg/m³)	1306	23.6	10.5	2.7	15.9	21.9	29.8	66.3	13.8
Nancy	Gérardmer	Urban	NO_2 (µg/m³)	1308	22.9	12.9	2.5	14.4	18.9	28.4	86.4	14.0
Nancy	Vittel	Peripheral	NO_2 (µg/m³)	1276	12.2	7.6	0.1	6.8	10.7	16.1	63.8	9.3
Nancy	St-Nicolas-de-Port	Industrial	NO_2 (µg/m³)	1315	21.1	9.7	4.7	13.8	19.1	26.7	65.5	12.9
Nancy	Neuves-Maisons	Urban	NO_2 (µg/m³)	1326	19.8	10.6	1.6	11.7	17.9	26.4	64.9	14.8
Nancy	Neuves-Maisons	Urban	PM_{10} (µg/m³)	1303	25.8	15.2	2.1	15.4	22.1	32.3	113.0	17.0
Nancy	Frolois	Industrial	PM_{10} (µg/m³)	1298	23.1	10.4	3.7	15.6	21.1	29.2	84.3	13.5
Nancy	Héming	Industrial	NO_2 (µg/m³)	1325	16.1	9.3	1.2	9.5	14.2	20.3	64.6	10.8
Nancy	Héming	Industrial	PM_{10} (µg/m³)	1296	18.9	8.6	2.7	12.7	17.1	23.8	70.5	11.0
Nancy	Bar-Le-Duc	Urban	NO_2 (µg/m³)	1316	23.0	11.2	2.2	14.2	21.2	30.0	73.1	15.8
Nancy	Bar-Le-Duc	Urban	PM_{10} (µg/m³)	1296	19.8	9.1	2.0	13.5	18.5	24.6	72.3	11.1
Nancy	Jonville	Rural	NO_2 (µg/m³)	1289	9.5	8.7	0.0	3.5	7.1	12.1	67.9	8.6
Nancy	Jonville	Rural	PM_{10} (µg/m³)	1284	19.7	9.0	1.8	13.4	18.0	24.5	79.5	11.0
Nancy	Nancy-CharlesIII	Urban	NO_2 (µg/m³)	716	27.6	12.1	2.6	18.4	26.7	36.1	85.2	17.7
Nancy	Nancy-CharlesIII	Urban	PM_{10} (µg/m³)	694	20.0	9.8	2.0	13.4	18.0	24.4	78.5	11.0
Nancy	Nancy-Poincaré	Urban	NO_2 (µg/m³)	614	55.3	17.9	16.0	42.0	54.8	68.0	122.2	26.0
Nancy	Nancy-Poincaré	Urban	PM_{10} (µg/m³)	618	29.0	14.2	5.8	19.3	27.2	35.5	135.5	16.2
Nancy	Longlaville	Peripheral	NO_2 (µg/m³)	1262	19.9	11.2	2.2	12.0	16.9	25.0	80.9	13.0

Nancy	Longlaville	Peripheral	PM_{10} (µg/m³)	1267	19.2	11.8	1.8	11.0	16.6	23.7	86.6	12.6
Nancy	Moyeuvre	Peripheral	NO_2 (µg/m³)	968	13.2	10.4	0.3	5.8	10.3	16.9	71.5	11.0
Nancy	Moyeuvre	Peripheral	PM_{10} (µg/m³)	971	15.3	15.1	0.2	5.4	11.9	21.3	207.6	15.9
Nancy	Blénot lès Pont-à-Mousson	Peripheral/Industrial	NO_2 (µg/m³)	1266	18.1	11.1	0.6	9.3	15.8	24.5	63.8	15.1
Nancy	Metz-Sablon	Urban	NO_2 (µg/m³)	830	29.0	14.3	4.0	18.3	26.7	37.2	107.9	18.9
Nancy	Metz-Sablon	Urban	PM_{10} (µg/m³)	1150	13.1	11.5	0.0	3.9	10.9	18.7	74.0	14.8
Nancy	Scy-Chazelles	Peripheral	PM_{10} (µg/m³)	1303	18.2	8.6	1.4	11.9	16.8	23.1	65.8	11.3
Nancy	Thionville-Piscine	Urban	NO_2 (µg/m³)	1222	28.2	13.7	4.8	17.4	24.9	37.0	83.1	19.5
Nancy	Thionville-Piscine	Urban	PM_{10} (µg/m³)	1302	10.3	9.4	0.0	3.0	7.4	15.3	66.7	12.3
Nancy	Thionville-Centre	Urban	NO_2 (µg/m³)	1131	30.6	14.2	3.6	20.1	27.8	39.0	92.1	18.9
Nancy	Thionville-Centre	Urban	PM_{10} (µg/m³)	1163	18.5	12.2	0.0	9.9	16.2	24.6	103.0	14.8
Nancy	Thionville-Garche	Urban	NO_2 (µg/m³)	1012	19.5	10.7	0.7	11.4	17.2	25.4	59.0	14.0
Nancy	St-Avold Centre	Urban	NO_2 (µg/m³)	1312	25.8	12.8	2.6	16.0	24.7	33.9	75.0	18.0
Nancy	St-Avold Centre	Urban	PM_{10} (µg/m³)	1285	19.1	8.9	2.2	12.9	17.6	24.0	89.9	11.1
Nancy	Averaged measurements of several monitoring sites.	Peripheral	NO_2 (µg/m³)	1334	20.4	9.8	3.7	13.0	18.5	26.3	65.2	13.3
Nancy	Averaged measurements of several monitoring sites.	Peripheral	PM_{10} (µg/m³)	1308	24.5	12.1	3.5	15.8	22.0	30.8	98.6	15.0
Nancy	Averaged measurements of several monitoring sites.	City center	NO_2 (µg/m³)	1334	26.2	10.5	6.2	18.3	24.9	32.4	69.5	14.1
Nancy	Averaged measurements of several monitoring sites.	City center	PM_{10} (µg/m³)	1292	20.1	9.1	3.7	13.5	18.6	25.0	70.4	11.5
Nancy			Air temperature (°C)	1333	10.0	8.0	-9.1	3.4	10.3	16.2	31.4	12.8
Nancy			Relative humidity (%)	1333	76.3	14.3	25.7	66.7	79.3	88.1	98.3	21.4
Nancy			Barometric pressure (hPa)	1333	1018.0	7.7	985.9	1013.5	1018.1	1023.0	1039.7	9.5
Poitiers	Airvault	Industrial	NO_2(µg/m³)	1311	11.5	6.5	1.0	6.7	9.8	15.0	50.2	8.3
Poitiers	Les Couronneries	Peripheral	NO_2(µg/m³)	1276	16.0	9.7	0.9	9.1	13.7	21.1	84.7	12.0
Poitiers	Les Couronneries	Peripheral	PM_{10}(µg/m³)	1254	17.5	8.1	2.1	11.8	15.9	21.3	89.9	9.5
Poitiers	Place du Marché	Urban	NO_2(µg/m³)	1288	34.7	15.6	5.0	22.7	33.8	44.4	107.6	21.7
Poitiers	Place du Marché	Urban	PM_{10}(µg/m³)	1316	18.9	7.7	2.8	13.5	17.5	22.5	81.0	9.0

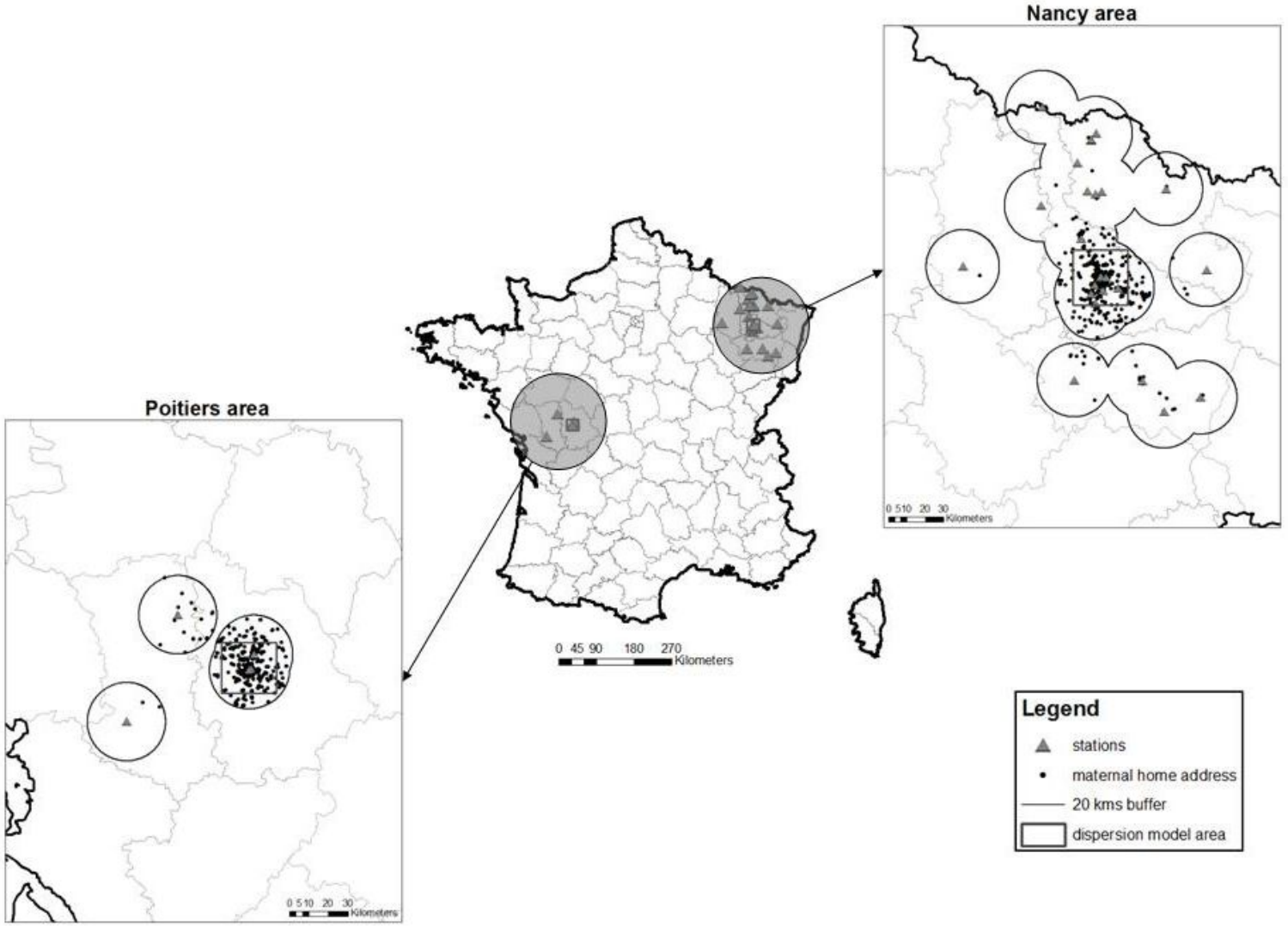
Poitiers	Chasseneuil	Peripheral	NO_2(µg/m³)	1295	14.3	8.0	1.1	8.7	12.2	18.1	59.1	9.4
Poitiers	Chasseneuil	Peripheral	PM_{10}(µg/m³)	1312	18.7	7.7	1.9	13.1	17.2	22.8	72.4	9.7
Poitiers	J.Ferry	Urban	NO_2 (µg/m³)	1301	21.3	10.0	4.5	13.9	19.1	26.8	70.8	12.9
Poitiers	J.Ferry	Urban	PM_{10} (µg/m³)	1296	18.7	7.0	4.0	13.9	17.2	22.0	57.8	8.1
Poitiers	Averaged measurements of several monitoring sites.	City center	NO_2(µg/m³)	1334	21.6	10.4	4.1	13.8	20.0	27.5	83.1	13.7
Poitiers	Averaged measurements of several monitoring sites.	City center	PM_{10}(µg/m³)	1334	18.3	7.6	2.3	13.0	17.0	22.1	81.1	9.1
Poitiers			Air temperature (°C)	1335	11.9	7.3	-6.0	6.3	11.7	17.5	30.4	11.2
Poitiers			Relative humidity (%)	1335	76.0	12.7	29.7	67.2	77.9	86.1	98.0	19.0
Poitiers			Barometric pressure (hPa)	1335	1018.2	7.6	984.0	1013.6	1018.4	1023.1	1039.3	9.5

eTable 2. Adjustment factors selected in mixed models of associations between air pollutants and SBP and DBP.

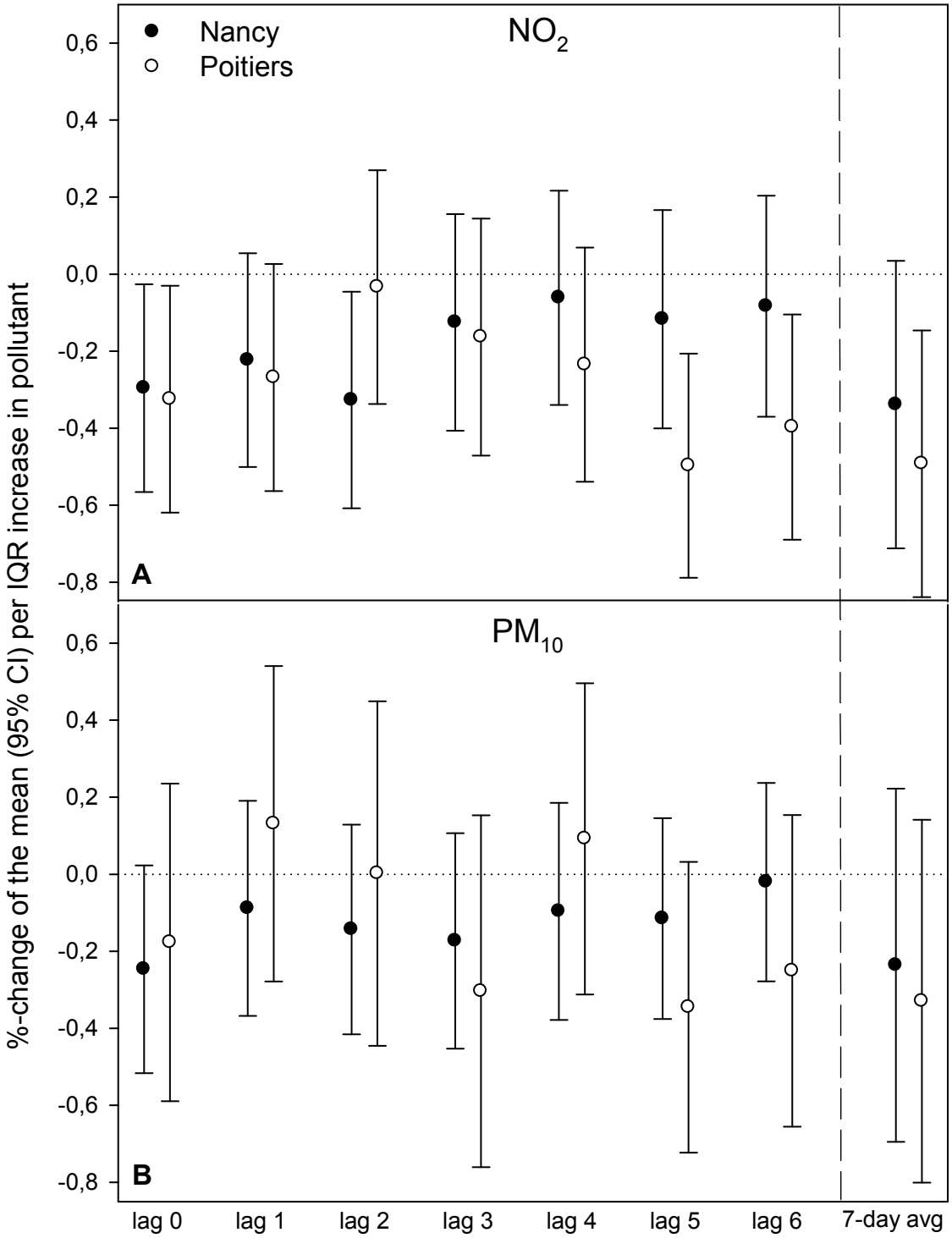
Outcome	Covariate	Shape
SBP		
	Gestational age (weeks)	Cubic
	BMI before pregnancy	Linear
	Previous pregnancies	Categorical
	Age	Cubic
	Smoking (first trimester)	Yes vs. no
	Passive smoking (first trimester)	Yes vs. no
	Time trend	Cubic
	Month	Categorical
	Air temperature	Lag 0, linear
	Relative humidity	Lag 4, quadratic
DBP		
	Gestational age (weeks)	Cubic
	BMI before pregnancy	Linear
	Previous pregnancies	Categorical
	Age	Cubic
	Smoking (first trimester)	Yes vs. no
	Passive smoking (first trimester)	Yes vs. no
	Time trend	Linear
	Month	Categorical
	Air temperature	Lag 4, linear
	Relative humidity	Lag 3, linear
	Barometric pressure	Lag 1, linear
	Weekday	Categorical

SBP: Systolic blood pressure, DBP: diastolic blood pressure, BMI: Body Mass Index.

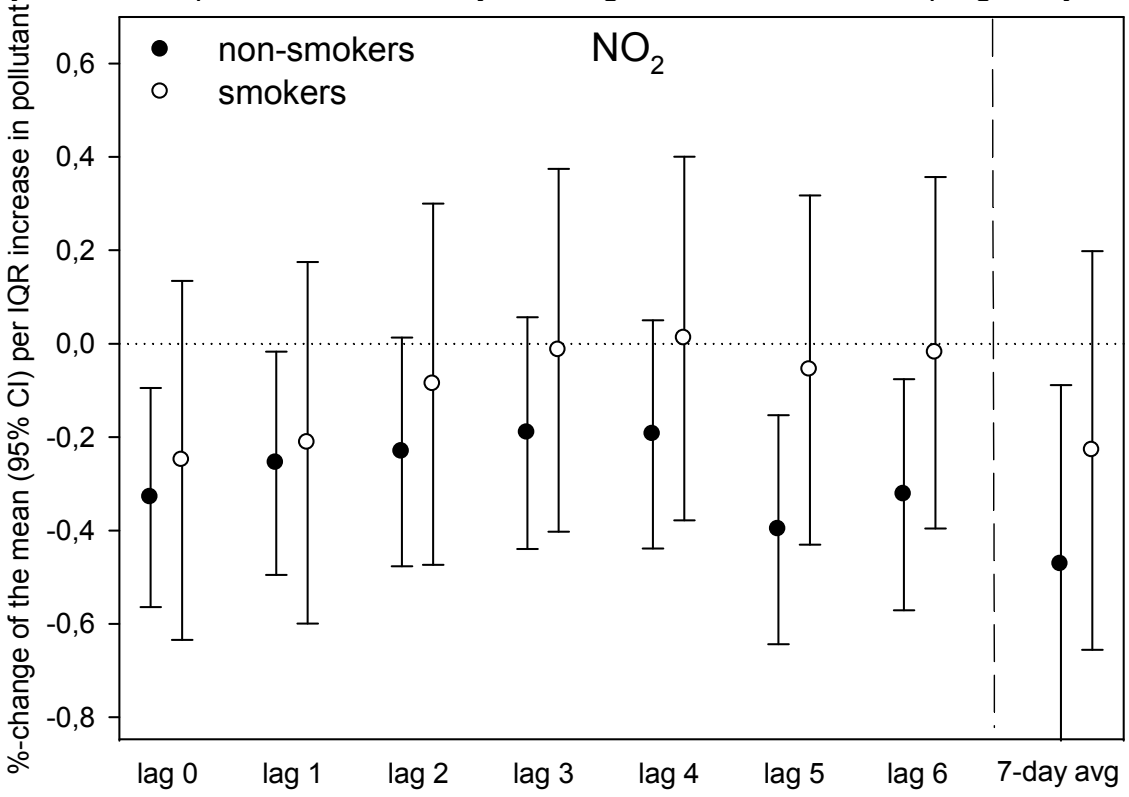
eFigure 1: Location of the air pollution monitoring stations in Poitiers and Nancy areas, respectively.



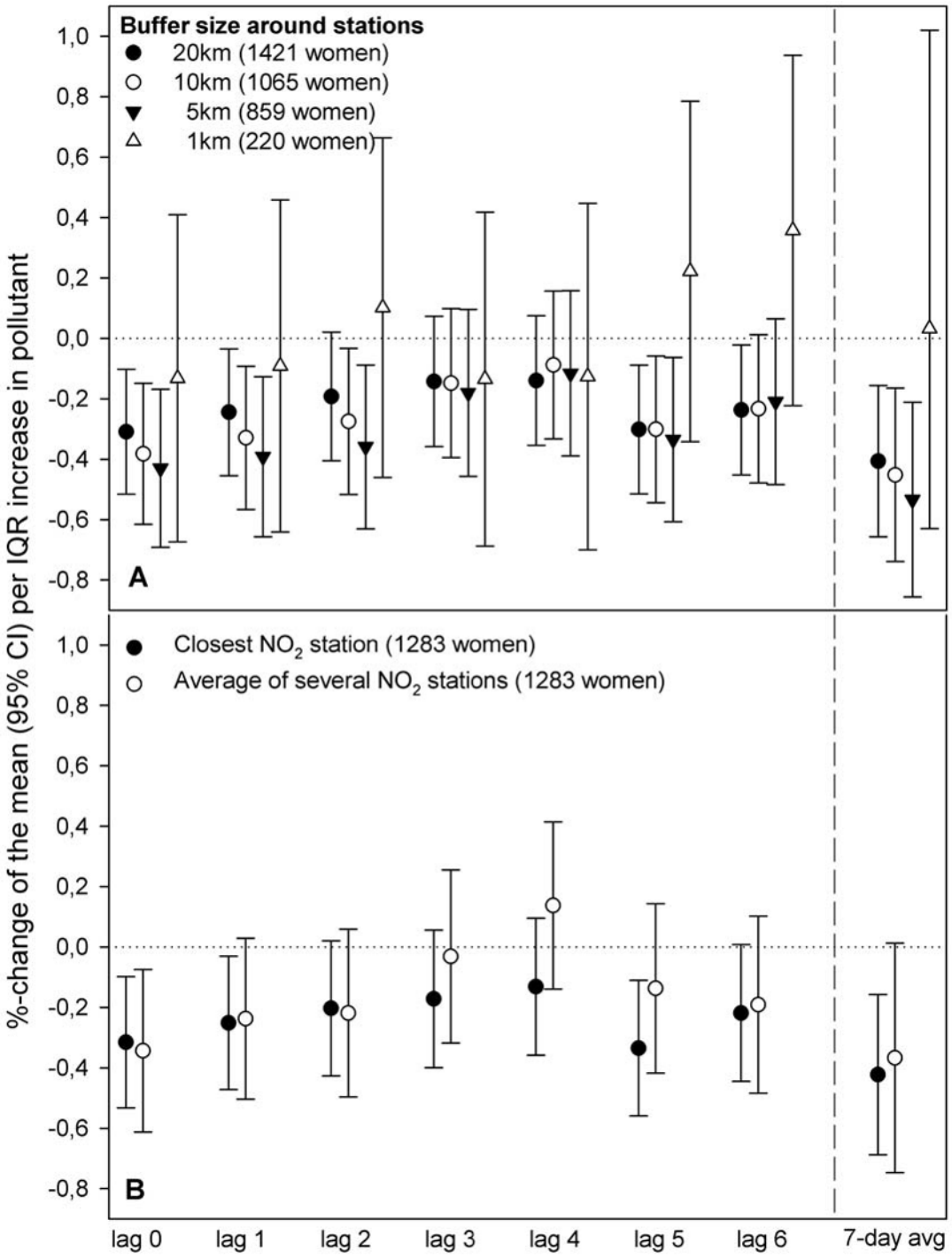
eFigure 2. Adjusted associations between 24-hour and 7-day NO_2 and PM_{10} averages and systolic blood pressure (interquartile range increases) modified by study center.



eFigure 3. Adjusted associations between an increase in 24h-averages of NO_2 on systolic blood pressure modified by smoking in the 1st trimester of pregnancy.

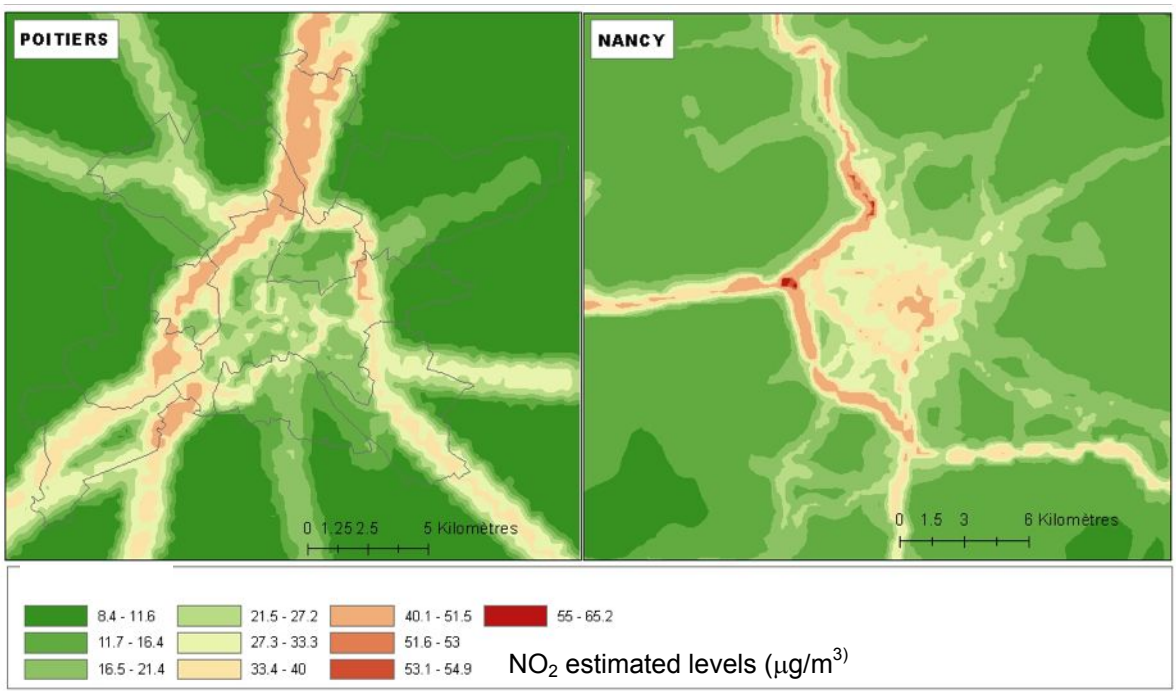


eFigure 4. A) Adjusted associations between an increase in 24h-averages of NO_2 on systolic blood pressure (SBP) in pregnant women living less than 20 km, 10 km, 5 km, and 1 km to the closest station. B) Adjusted associations between an increase in 24h-averages of NO_2 on SBP in pregnant women estimating NO_2 either from the closest air quality monitoring station or from an average of all stations from the area (based on the same women).

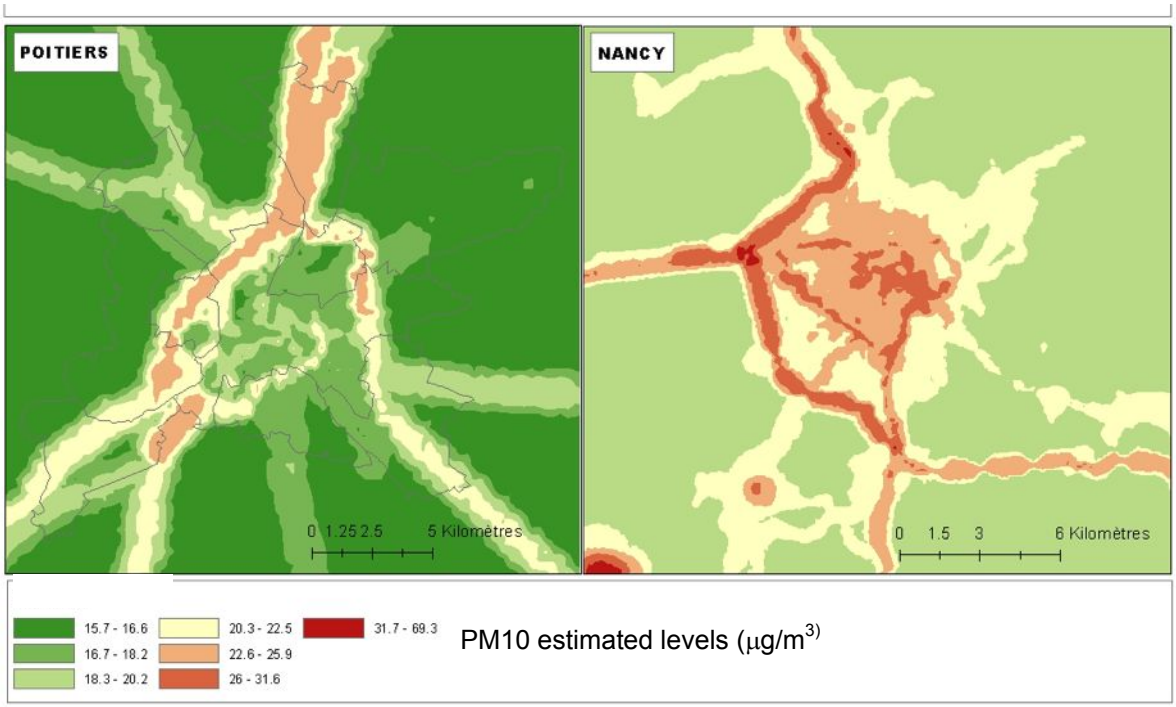


eFigure 5: Modeled NO_2 (A) and PM_{10} (B) concentrations estimated by dispersion modeling in Poitiers and Nancy areas. Concentrations are yearly estimates for the year 2005; the model was implemented with ADMS-Urban software (CERC, Cambridge, UK). A. Hulin, V. Navel, F. Caïni, Atmo Poitou-Charentes and J. Galineau, Airlor.

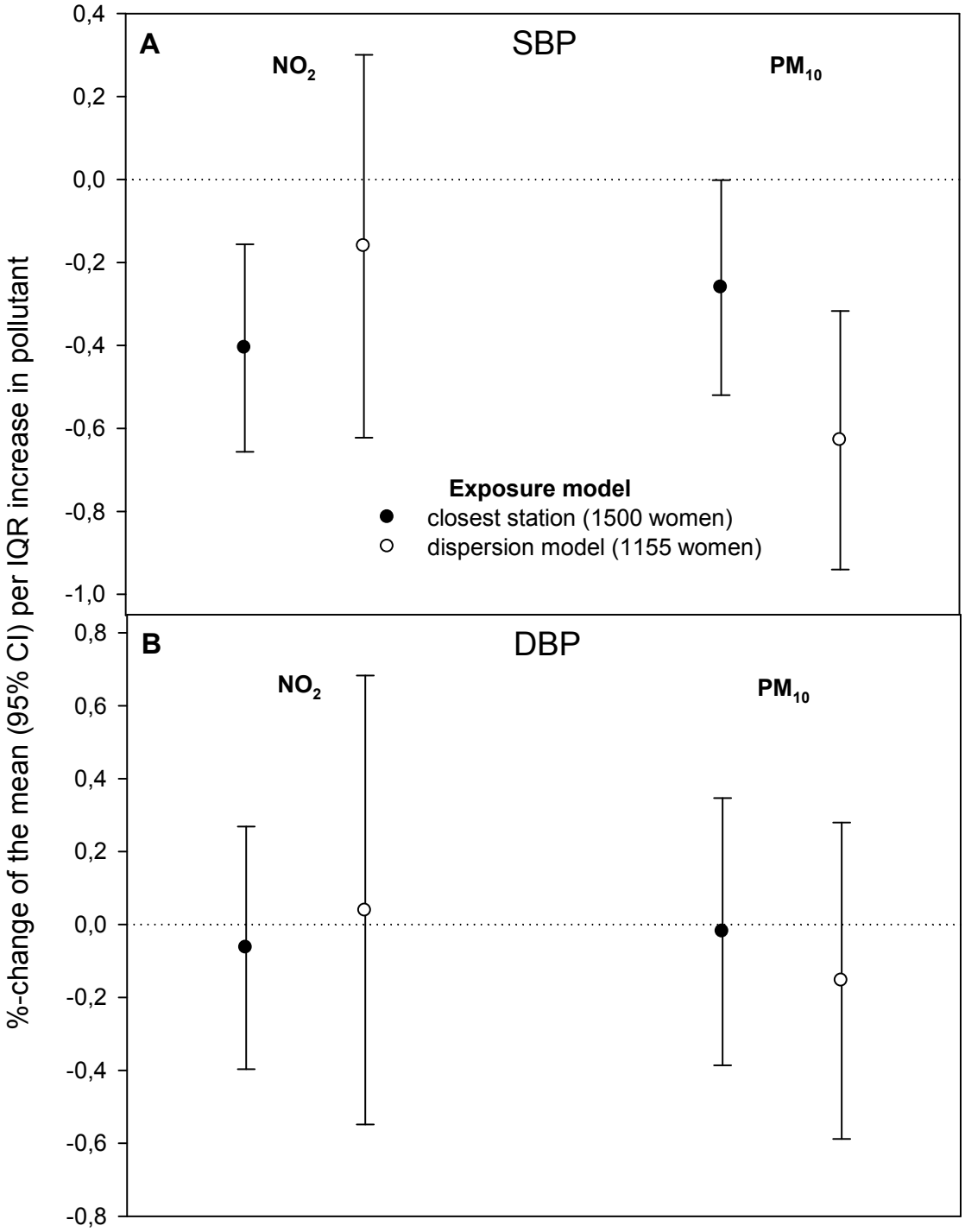
A



B



eFigure 6. Adjusted associations between air pollutants (7-day averages, as estimated from the closest monitoring station or from a dispersion model) on blood pressure in pregnant women.



Maternal Exposure to Nitrogen Dioxide during Pregnancy and Offspring Birth Weight: Comparison of Two Exposure Models

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Background: Studies of the effects of air pollutants on birth weight often assess exposure with networks of permanent air quality monitoring stations (AQMSs), which have a poor spatial resolution.

Objective: We aimed to compare the exposure model based on the nearest AQMS and a temporally adjusted geostatistical (TAG) model with a finer spatial resolution, for use in pregnancy studies.

Methods: The AQMS and TAG exposure models were implemented in two areas surrounding medium-size cities in which 776 pregnant women were followed as part of the EDEN mother–child cohort. The exposure models were compared in terms of estimated nitrogen dioxide (NO_2) levels and of their association with birth weight.

Results: The correlations between the two estimates of exposure during the first trimester of pregnancy were r = 0.67, 0.70, and 0.83 for women living within 5, 2, and 1 km of an AQMS, respectively. Exposure patterns displayed greater spatial than temporal variations. Exposure during the first trimester of pregnancy was most strongly associated with birth weight for women living < 2 km away from an AQMS: a 10-μg/m^3 increase in NO_2 exposure was associated with an adjusted difference in birth weight of –37 g [95% confidence interval (CI), –75 to 1 g] for the nearest-AQMS model and of –51 g (95% CI, –128 to 26 g) for the TAG model. The association was less strong (higher p-value) for women living within 5 or 1 km of an AQMS.

Conclusions: The two exposure models tended to give consistent results in terms of association with birth weight, despite the moderate concordance between exposure estimates.

Key words: atmospheric pollution, birth weight, cohort, exposure modeling, geostatistical, measurement error, monitoring station, nitrogen dioxide, spatial variation, temporal variation. *Environ Health Perspect* 118:1483–1489 (2010). doi:10.1289/ehp.0901509 [Online 14 May 2010]

Several epidemiologic studies have reported associations between maternal exposure to nitrogen dioxide (NO_2) during pregnancy and fetal growth assessed by birth weight, taking into account gestational duration (e.g., Bell et al. 2007; Liu et al. 2007; Ritz and Wilhelm 2008; Slama et al. 2008; Wilhelm and Ritz 2003). Various approaches may be used to estimate exposure, from the use of biomarkers of exposure to personal dosimeters and environmental models. Most previous studies have been based on measurements from permanent air quality monitoring stations (AQMSs), using data from the AQMS closest to the subject's home address or interpolating data for neighboring monitors, for which measurements are averaged over the entire pregnancy or over each trimester of pregnancy. This approach has the advantage of making use of readily available exposure data, being simple to implement and, because pollutants are assessed on an hourly or at least weekly basis, being highly flexible in terms of the temporal exposure window considered. However, the spatial density of AQMS networks is generally low, and studies have shown that the data provided by permanent AQMSs are representative only of air pollution levels in the close vicinity of the station (Lebret et al. 2000). Studies based on AQMS measurements assume that air pollution levels are homogeneous within a buffer of several kilometers around each monitor or, at least, that exposure misclassification introduces no major bias into the estimated exposure–response relationship. However, studies based on the simultaneous use of several exposure models have demonstrated that the amplitude of the measurement error may be large (Nerriere et al. 2005; Nethery et al. 2008; Sarnat et al. 2005). Moreover, at least for respiratory or cardiovascular outcomes, measurement error may have a large impact on the exposure–response relationship (Miller et al. 2007; Van Roosbroeck et al. 2008). This issue has very little been studied in the context of reproductive outcomes (Brauer et al. 2008).

We aimed to compare the exposure model based on the nearest AQMS and a temporally adjusted geostatistical (TAG) model based on measurement campaigns with a fine spatial resolution, and also focusing on background pollution, in the context of a mother–child cohort. We compared these models in terms of estimated NO_2 levels and the estimated association between NO_2 levels and birth weight.

Materials and Methods

Study population and data collection. This study was conducted in a subgroup of the French EDEN (study of pre- and early postnatal determinants of the child's development and health) mother–child cohort. Pregnant women at < 26 weeks of gestation were recruited from the maternity wards of Poitiers and Nancy university hospitals (France) between September 2003 and January 2006. Gestational age was assessed from the date of the last menstrual period (Slama et al. 2009). Exclusion criteria were a personal history of diabetes, multiple pregnancy, intention to deliver outside the university hospital or to move out of the study

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region within the next 3 years, and an inability to speak and read French. The birth weights of the infants were extracted from the maternity records. Information on maternal active and passive smoking, height, weight, and educational level were collected by interview between 24 and 28 weeks of gestation, and by questionnaire after birth. The study was approved by the relevant ethical committees (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin-Bicêtre University Hospital, and Commission Nationale de l'Informatique et des Libertés), and all participating women gave informed written consent for their own participation and that of their children. More details of this study can be found elsewhere (Drouillet et al. 2009; Slama et al. 2009; Yazbeck et al. 2009).

Exposure to NO_2. We restricted the cohort to pregnant women living in two areas, one of 165 km^2 around Nancy and the other of 315 km^2 around Poitiers, in which air quality measurement campaigns have been conducted. We then further restricted the study area to the immediate vicinity of an AQMS, focusing on circular buffers with a radius of 5, 2, and 1 km around each AQMS (Figure 1B,D). The detailed addresses of all women were geocoded in ArcGIS (version 9.3; ESRI, Redlands, CA, USA). For both models, changes of home address between inclusion and delivery were taken into account by calculating time-weighted means of exposure over the relevant time windows [whole pregnancy, and each trimester (92 days per trimester if no delivery) of pregnancy].

Nearest-AQMS model (model 1). We obtained air pollution data from the Airlor (Nancy) and Atmo-Poitou-Charentes (Atmo-PC)(Poitiers) AQMS networks. All permanent AQMS measuring NO_2 concentrations during the study period and located within 2.5 km of the limits of the study areas were considered (three in the Poitiers area and six in the Nancy area) (Figure 1A,C), excluding those labeled as traffic (i.e., located < 5 m from a road with traffic levels of > 10,000 vehicles/day) (Agence de l'Environnement et de la Maîtrise de l'Energie 2002) or industrial stations. For each woman i, hourly measures of NO_2 concentration by the AQMS j closest to her home address were averaged over each time window Δ_t^i considered (noted Δ_t for convenience), to obtain our exposure estimate $E1^i_{j,\Delta_t}$.

TAG model (model 2). NO_2 measurement campaigns with a Palmes diffusive sampler (Palmes et al. 1976) were conducted in the urban and periurban areas of both cities. The diffusive samplers were located so as to give measurements of background pollution in each area (61 locations in the Poitiers area, 98 locations in the Nancy area). The campaigns lasted 14 days (Poitiers) or 10–15 days (Nancy) and were repeated throughout the year to capture seasonal variations. Nine campaigns were performed in 2005 in the Poitiers area, and 10 were performed in 2002 in the Nancy area (Airlor 2004; Atmo-PC 2007). In each area, for each passive sampler, the AQMS giving the measurements most strongly correlated with the measurements of the passive sampler during campaigns was used to estimate mean annual concentration at each measurement location. These estimated annual concentrations were smoothed over the whole area with kriging techniques (Chilès and Delfiner 1999) on a 50 × 50 m grid, with Isatis software version 6.06 (Géovariances, Fontainebleau, France) (Figure 1B,D). This corresponded to our estimate of C^i_{yearly}, the mean NO_2 concentration at the home address, for the year 2005 in Poitiers and 2002 in Nancy (spatial component of the model).

The estimated annual NO_2 concentrations were then combined with time-specific measurements from the permanent AQMS to capture temporal variations in concentrations. This approach has previously been used in the context of land use regression (LUR) models (Slama et al. 2007). The hourly NO_2 measures of all AQMSs from the area were averaged over each time window Δ_t considered ($S^i_{\text{all},\Delta_t}$) and also over the year in which the measurement campaign was performed ($S_{\text{all, yearly}}$). The ratio

$$\left(\frac{S^i_{\text{all},\Delta_t}}{S_{\text{all,yearly}}}\right)$$

was the temporal component of the model. The temporally adjusted estimate of NO_2 exposure $E2^i_{\Delta_t}$ for woman i was the product of the spatial and temporal components, or

$$E2^i_{\Delta_t} = C^i_{\text{yearly}} \times \left(\frac{S^i_{\text{all},\Delta_t}}{S_{\text{all,yearly}}}\right). \quad [1]$$

Statistical analyses. For each model, we assessed the relative contribution of spatial (or temporal) variations in exposure contrasts by Pearson's correlation coefficient between the exposure estimate and its spatial (or temporal) component. We also carried out variance decomposition. The nearest-AQMS model could be broken down as

$$E1^i_{j,\Delta_t} = \overline{E1_{\Delta_t}} + \left(S^i_j - \overline{E1_{\Delta_t}}\right) + \left(E1^i_{j,\Delta_t} - S^i_j\right), \quad [2]$$

with $\overline{E1_{\Delta_t}}$ the mean level of exposure of all women during the time window Δ_t, and S^i_j the NO_2 concentration at AQMS j averaged over the entire study period, so as to obtain a spatial component $S^i_j - \overline{E1_{\Delta_t}}$ dependent solely on the address of the woman. This corresponded to our estimate of the spatial component of the AQMS model; $E1^i_{j,\Delta_t} - S^i_j$ corresponded to our estimate of the temporal component of the model. The TAG model was log-transformed and expressed as

$$\log\left(E2^i_{\Delta_t}\right) = \log\left(C^i_{\text{yearly}}\right) + \log\left(\frac{S^i_{\text{all},\Delta_t}}{S_{\text{all,yearly}}}\right) \quad [3]$$

for the variance analysis. These analyses were restricted to women who did not change address during pregnancy.

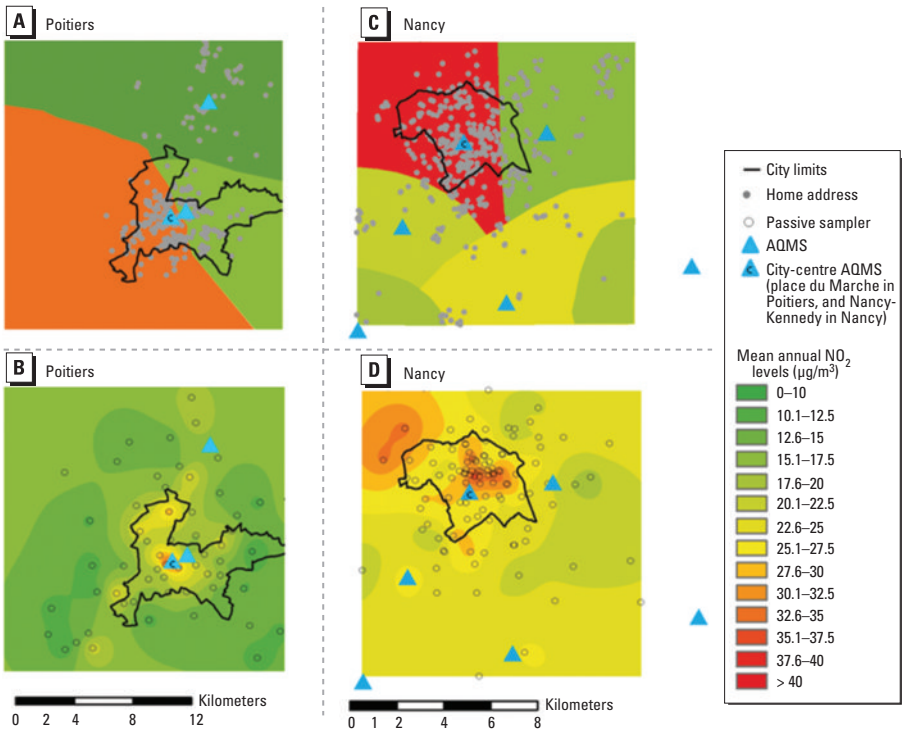

Figure 1. Mean annual NO_2 levels estimated by the nearest-AQMS model in Poitiers (*A*) and Nancy areas (*C*) and by the TAG model in Poitiers (*B*) and Nancy areas (*D*).

For comparison of the exposure estimates generated by each model, exposure estimates for the two models were compared by Kruskal–Wallis rank tests and by calculating correlation coefficients (r). The distributions of the exposures estimated by the nearest-AQMS model and by the TAG model were plotted as a function of the AQMS closest to woman's home address, with and without excluding the AQMS located in the city center. We also assessed the concordance between the estimates generated by the two models, classified into tertiles, by determining percentage concordance and the κ coefficient. Bland–Altman plots were used to estimate the magnitude of the systematic error between the two exposure models (Bland and Altman 1986).

For exposure–response relationships, we studied the relationship between birth weight and NO_2 exposure during each exposure window in linear regression models taking into account gestational age and adjustment factors. Linear trend tests were performed with a categorical variable, the value of which corresponded to the category-specific median NO_2 concentration. The adjustment factors were selected on the basis of *a priori* knowledge (Rothman et al. 2008). We adjusted for active and passive smoking during the second trimester of pregnancy, because these factors were more strongly associated with birth weight than were exposures during the first trimester, the third trimester, or all three trimesters combined. We also adjusted for sex of the newborn, maternal height (as a continuous variable), prepregnancy weight (broken stick model with a knot at 60 kg), birth order, maternal age at end of education, center, and trimester of pregnancy. Statistical analyses were carried out with STATA statistical software (Stata SE version 10.1; StataCorp LP, College Station, TX, USA). Analyses were repeated for the three buffers considered (< 5, 2, or 1 km from an AQMS).

Results

Population. Of the 1,893 women from the cohort with a known offspring birth weight, 776 lived in the study area, < 5 km from an AQMS, during at least one trimester of pregnancy (431 and 158 women lived within 2 and 1 km of an AQMS, respectively). Mean birth weight was 3,284 g (25, 50, 75th percentiles: 3,005, 3,310, 3,620 g). Table 1 shows the characteristics of the study population.

Exposure to air pollutants. Estimates of exposure to NO_2 were higher in Nancy than in Poitiers, whatever the exposure model and exposure window considered (Figure 1, Tables 1 and 2). The nearest-AQMS model estimate during pregnancy was more strongly correlated with the spatial component of the TAG model (r = 0.61, 0.68, and 0.84, for the 5-, 2-, and 1-km buffers, respectively) than with its temporal component (r = 0.35, 0.35, and 0.45, respectively). For both models, exposure estimates throughout pregnancy were subject to strong spatial variation (accounting for > 90% of the variance of exposure; Table 3). Temporal variations made a greater contribution to total variation when we considered trimester-specific windows

Table 1. Characteristics of women living < 5 km away from an AQMS and their associations with NO_2 levels averaged during pregnancy (n = 776).

		Mean (median) NO_2 level (μg/m^3)			
Characteristic	n (%)	Nearest-AQMS model	p-Value[a]	TAG model	p-Value[a]
Sex of offspring			0.97		0.28
Male	395 (51)	28.6 (32.3)		23.6 (23.8)	
Female	381 (49)	28.6 (32.5)		23.9 (23.9)	
Gestational duration (weeks)			0.37		0.17
30–36	48 (6)	30.2 (33.4)		24.7 (23.1)	
37–38	151 (20)	29.1 (32.6)		24.3 (24.1)	
39–40	407 (52)	28.1 (32.2)		23.4 (23.6)	
≥ 41	170 (22)	29.2 (32.8)		23.8 (24.3)	
Birth order			0.71		0.14
First birth	367 (47)	28.8 (33.4)		23.9 (23.9)	
Second birth	263 (34)	28.7 (31.7)		23.9 (24.0)	
Third birth or more	145 (19)	28.0 (32.2)		23.0 (23.1)	
Missing value	1				
Trimester of conception of the child			$< 10^{-4}$		$< 10^{-4}$
January–March	167 (21)	25.7 (25.3)		21.5 (21.9)	
April–June	184 (24)	29.1 (33.6)		23.5 (24.0)	
July–September	226 (29)	31.2 (35.2)		25.9 (25.7)	
October–December	199 (26)	27.7 (31.3)		23.3 (23.5)	
Maternal age at conception (years)			$< 10^{-2}$		$< 10^{-2}$
< 25	187 (24)	26.7 (26.3)		22.8 (22.7)	
25–29	289 (37)	30.0 (33.8)		24.3 (24.3)	
30–34	203 (26)	28.7 (32.1)		24.2 (24.0)	
≥ 35	97 (13)	27.9 (32.3)		22.9 (23.4)	
Maternal height (cm)			0.64		0.44
< 160	188 (24)	28.3 (32.0)		23.4 (24.0)	
160–169	460 (60)	28.6 (32.7)		23.8 (23.8)	
≥ 170	121 (16)	29.4 (33.1)		24.2 (24.2)	
Missing value	7				
Maternal prepregnancy weight (kg)			0.33		0.46
< 50	83 (11)	27.7 (28.8)		24.3 (24.1)	
50–59	333 (43)	28.6 (32.3)		23.8 (23.8)	
60–69	211 (27)	29.4 (33.5)		23.8 (24.0)	
70–79	87 (11)	29.0 (33.0)		23.6 (23.8)	
≥ 80	60 (8)	26.6 (25.9)		22.7 (22.0)	
Missing value	2				
Body mass index before pregnancy (kg/m^2)			0.39		0.07
< 18.5	82 (11)	29.6 (34.3)		25.0 (24.7)	
18.5–24.9	512 (67)	28.5 (32.1)		23.8 (23.9)	
25–29.9	111 (14)	29.4 (33.7)		23.3 (23.4)	
≥ 30	62 (8)	27.1 (30.6)		23.0 (22.4)	
Missing value	9				
Center			$< 10^{-4}$		$< 10^{-4}$
Poitiers	316 (41)	24.9 (18.8)		20.3 (19.2)	
Nancy	460 (59)	31.2 (34.4)		26.1 (25.7)	
Maternal age at end of education (years)			0.02		$< 10^{-3}$
≤ 16	52 (7)	29.6 (33.1)		24.0 (23.6)	
17–18	104 (13)	27.0 (29.6)		22.2 (21.9)	
19–20	124 (16)	27.1 (29.1)		23.2 (23.0)	
21–22	165 (21)	27.9 (30.0)		23.3 (23.5)	
23–24	174 (22)	29.3 (33.1)		24.5 (24.6)	
≥ 25	157 (20)	30.6 (34.5)		24.7 (24.6)	
Maternal active smoking (second trimester)			0.45		0.30
No	641 (83)	28.8 (32.7)		23.8 (24.0)	
Yes	133 (17)	28.1 (32.0)		23.3 (22.8)	
Missing value	2				
Maternal passive smoking (second trimester)			0.48		0.53
No	507 (66)	28.5 (32.1)		23.7 (23.9)	
Yes	264 (34)	29.0 (33.3)		23.9 (23.6)	
Missing value	5				

[a]p-Value comparing model-specific exposure estimates between categories (Student test for dichotomous variables) or among categories (Fisher's analysis of variance for variables with more than two categories). Tests were performed without including missing data as a separate category.

but remained smaller than spatial variations for the nearest-AQMS model (72–84% for spatial variation and 20–25% for temporal variation), whereas the contributions of the spatial and temporal variation components were similar for the TAG model (43–61% for spatial variation and 44–57% for temporal variation; Table 3). The buffer around the AQMS studied had no major effect on the relative contributions of spatial and temporal components of variation.

The levels and range of NO_2 concentrations estimated by the nearest-AQMS model were greater than those estimated by the TAG model (Table 2). Bland–Altman plots [see Supplemental Material, Figure 1 (doi:10.1289/ehp.0901509)] showed that the difference between the two models increased with mean exposure estimates. This pattern was principally due to between-model differences for women living in the city centers (mean NO_2 concentrations estimated by the nearest-AQMS model were higher and ranges were narrower than for the TAG model), rather than in the periurban areas. Indeed, the exposure distributions for the two models became more similar when we did not take into account city-center AQMS measurements (Figure 2). All this indicates that the overestimation of NO_2 exposure levels by the AQMS model with respect to the TAG model mainly concerned the women who were also the most exposed with the TAG model.

The correlation and concordance (κ) between the two exposure models were fair (0.40–0.74) when we considered all the women living within 5 km of an AQMS [Table 2; see also Supplemental Material, Figure 2 (doi:10.1289/ehp.0901509)] but were stronger if we restricted the study population to women living within 2 (0.37–0.79) or 1 km (0.59–0.87) of an AQMS. The correlation and concordance between the two exposure models also differed between the areas (Nancy/Poitiers) and between the city center and suburban areas [see Supplemental Material, Figure 2 (doi:10.1289/ehp.0901509)].

Associations between air pollutants and fetal growth. The patterns of association with birth weight identified were similar for the two exposure models, in terms of estimates of adjusted effects and confidence intervals (CIs), although these associations were stronger for the nearest-AQMS model [Figure 3; see also Supplemental Material, Table 1 (doi:10.1289/ehp.0901509)]. The first and third trimesters of pregnancy corresponded to the exposure windows most clearly associated with effects on birth weight, for both exposure models. For women living < 2 km from an AQMS, a 10-μg/m^3 increase in NO_2 concentration during the first trimester of pregnancy was associated with an adjusted change in mean birth weight of –37 g (95% CI, –75 to 1 g) for the nearest-AQMS model and of –51 g (95% CI, –128 to 26 g) for the TAG model. We obtained qualitatively similar results when we coded exposures in tertiles [see Supplemental Material, Table 1 (doi:10.1289/ehp.0901509)]. For the AQMS model, the parameter quantifying the association between NO_2 exposure and birth weight approached zero as buffer size increased. We obtained similar results if we made no adjustment for city center (data not shown).

Discussion

Our study is one of the first to describe associations between NO_2 exposure assessed with a TAG model and birth weight, and to compare this model with the more commonly used approach based on permanent AQMSs. We compared models in terms of both exposure estimates and association with birth weight. The nearest-AQMS model was influenced by the location of monitors. Variations in exposure were mostly attributable to spatial rather than temporal variations in both models, with temporal variation making a

Table 2. Maternal exposure to NO_2 (μg/m^3) and concordance between NO_2 levels [mean ± SD (5th, 50th, 95th percentiles)] estimated by the nearest-AQMS model and the TAG model, for various exposure windows and buffer sizes considered around AQMSs.

	Nearest-AQMS model (5-km buffer)		TAG model (5-km buffer)			Between-model agreement											
						Distance[a] < 5 km				Distance[a] < 2 km				Distance[a] < 1 km			
Area exposure window	*n*	NO_2 levels	*n*	NO_2 levels	*p*-Value[b]	*n*	*r*	*c*	κ	*n*	*r*	*c*	κ	*n*	*r*	*c*	κ
Both areas																	
First trimester	770	28.8 ± 10.8 (11.3, 30.1, 43.6)	773	23.7 ± 6.2 (13.6, 23.0, 34.6)	10^{-4}	767	0.67	61	0.41	429	0.70	62	0.43	158	0.83	75	0.63
Second trimester	771	29.0 ± 10.9 (11.5, 30.0, 43.9)	770	24.1 ± 6.5 (13.6, 23.6, 34.4)	10^{-4}	766	0.69	60	0.40	426	0.72	58	0.37	156	0.82	73	0.60
Third trimester	770	28.1 ± 11.1 (10.4, 29.4, 44.2)	772	23.3 ± 6.8 (12.5, 22.8, 34.7)	10^{-4}	767	0.74	63	0.44	428	0.79	68	0.52	155	0.87	79	0.68
Whole pregnancy	776	28.6 ± 10.0 (13.3, 32.4, 41.8)	770	23.7 ± 5.0 (16.1, 23.8, 32.3)	10^{-4}	770	0.65	63	0.44	428	0.70	64	0.46	157	0.85	73	0.59
Poitiers area																	
First trimester	310	25.6 ± 11.9 (9.3, 21.6, 43.0)	316	20.9 ± 6.3 (12.0, 20.4, 35.8)	$<10^{-3}$	310	0.61	59	0.38	181	0.65	57	0.36	75	0.89	83	0.74
Second trimester	311	25.2 ± 11.6 (10.1, 22.2, 42.7)	315	20.4 ± 6.1 (11.8, 19.9, 32.0)	10^{-4}	311	0.61	56	0.34	179	0.65	57	0.36	74	0.83	63	0.45
Third trimester	310	23.9 ± 11.3 (8.5, 21.7, 42.0)	315	19.5 ± 6.3 (11.5, 19.0, 30.8)	10^{-4}	310	0.66	62	0.43	179	0.72	67	0.51	73	0.86	78	0.67
Whole pregnancy	316	24.9 ± 10.6 (12.4, 18.8, 40.5)	316	20.3 ± 4.7 (14.7, 19.2, 30.0)	0.12	316	0.55	56	0.34	181	0.62	58	0.37	75	0.87	68	0.52
Nancy area																	
First trimester	460	31.0 ± 9.5 (13.6, 31.3, 44.1)	457	25.7 ± 5.2 (17.9, 25.5, 34.6)	10^{-4}	457	0.67	55	0.32	248	0.69	58	0.36	83	0.72	59	0.39
Second trimester	460	31.6 ± 9.6 (14.1, 32.0, 44.4)	455	26.7 ± 5.5 (18.5, 26.6, 35.6)	10^{-4}	455	0.70	58	0.37	247	0.73	65	0.48	82	0.74	66	0.49
Third trimester	460	30.9 ± 10.0 (13.5, 31.4, 45.0)	457	26.0 ± 5.8 (17.5, 25.7, 36.2)	10^{-4}	457	0.74	61	0.41	249	0.78	67	0.51	82	0.82	76	0.63
Whole pregnancy	460	31.2 ± 8.7 (16.9, 34.4, 42.4)	454	26.1 ± 3.7 (20.8, 25.7, 32.8)	10^{-4}	454	0.66	64	0.46	247	0.69	64	0.47	82	0.66	71	0.56

Abbreviations: *r*, Pearson correlation coefficient; *c*, concordance percentage (based on NO_2 levels categorized in tertiles); κ, kappa coefficient (based on NO_2 levels categorized in tertiles).
[a]Maximal distance between home address and the nearest AQMS (buffer size). [b]*p*-Value of Kruskal–Wallis rank test comparing the exposure levels from the two models.

Table 3. Variance component (%) of NO_2 exposure levels estimated by the nearest-AQMS model and by the TAG model for various exposure windows and buffer sizes considered around AQMSs.

	Distance < 5 km (*n* = 681)				Distance < 2 km (*n* = 383)				Distance < 1 km (*n* = 146)			
	Nearest-AQMS model		TAG model		Nearest-AQMS model		TAG model		Nearest-AQMS model		TAG model	
Exposure window	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal	Spatial	Temporal
First trimester	82	21	61	52	79	22	55	57	84	25	56	49
Second trimester	82	20	55	46	79	21	53	52	83	21	58	44
Third trimester	78	21	47	46	76	21	43	52	80	24	52	48
Pregnancy	95	7	92	14	91	8	92	17	97	9	92	13

The sum of variance components is > 100% because the data are not balanced as in experimental plans (i.e., the covariance is not null).

larger overall contribution to total variation in the TAG model than in the nearest-AQMS model. The concordance between NO_2 exposure estimates with the two models was fair when we considered the 5-km buffer. This concordance was stronger if we restricted the analysis to women living closer (< 2 km and, more clearly, < 1 km) to an AQMS. When we coded exposure as a continuous term, associations with birth weight for the TAG model were consistent with those obtained in analyses based on exposure estimated from the nearest-AQMS model, for the various buffers around AQMS and exposure windows.

The TAG model is thought to have a better spatial resolution than the nearest-AQMS model, because of the use of data from fine measurement campaigns, with no loss of temporal resolution, because we seasonalized TAG exposure estimates on the basis of AQMS measurements. The stronger contribution of the spatial component in the nearest-AQMS model than in the TAG model may at first glance appear counterintuitive, because the AQMS model could be considered to be essentially based on temporal variations. However, this finding may be accounted for by the considerable variation of the concentrations obtained with different AQMSs, some of which (in the city center) were influenced by traffic, despite meeting the criteria for background stations. This illustrates the extent to which the nearest-AQMS estimates depend on the location of the monitors, and the need for exposure models with a finer spatial resolution in studies with medium- or long-term exposure windows (3–9 months in our study). Because passive samplers were located at background sites less affected by traffic, the TAG approach led to a more purely background model than did the AQMS approach. The higher concentrations estimated by the nearest-AQMS model than by the TAG model (Table 2) may be accounted for by this feature. The TAG model may also smooth extreme exposure values, leading to an underestimation of the role of spatial variation.

One possible limitation of the TAG model stems from the approach used to seasonalize this model, in which we assumed that spatial differences in exposure remained constant over time. This assumption was found to be reasonable for a LUR model developed in Rome (Porta et al. 2009) but may not hold in other areas with different characteristics.

Several studies have evaluated the performance of AQMS for estimating exposure to air pollutants. Nerriere et al. (2005), Nethery et al. (2008), and Sarnat et al. (2005) reported poor concordance between AQMS estimates and personal monitoring data, which is not surprising because personal exposure is not expected to strictly correspond to background levels of air pollution at the home address. Marshall et al. (2008) reported correlations and κ-coefficients for estimates from the nearest-AQMS model (within 10 km) and estimates stemming from either an LUR (r = 0.61, κ = 0.42) or a dispersion model (r = 0.37, κ = 0.22). The concordance obtained with the LUR model was similar to that observed in our study with the TAG model for a 5-km buffer around the AQMS. However, Marshall et al.'s study is not directly comparable with ours because they used a larger buffer zone (10 km) and because the LUR and dispersion models incorporated all local sources of pollution, whereas our TAG model did not.

In this study, we focused on women living < 5 km from an AQMS, whereas previous studies on the effects of air pollution on birth weight have included women living > 8 km (5 miles) from a monitor (Basu et al. 2004; Brauer et al. 2008; Parker et al. 2005). Our results indicate that the size of buffer around monitors considered has a major effect on the concordance between models and the estimated association between NO_2 concentration and birth weight. We obtained higher levels of concordance between the models if we focused on women living within 2 km of a monitor, and higher still for women living within 1 km of a monitor. Associations between NO_2 levels and birth weight, although not statistically significant at the 5% level, tended to be stronger for the 2-km buffer around the AQMS than for the 5-km buffer (Figure 3). The findings were sometimes less clear for women living within 1 km of an AQMS, and the CIs were slightly larger

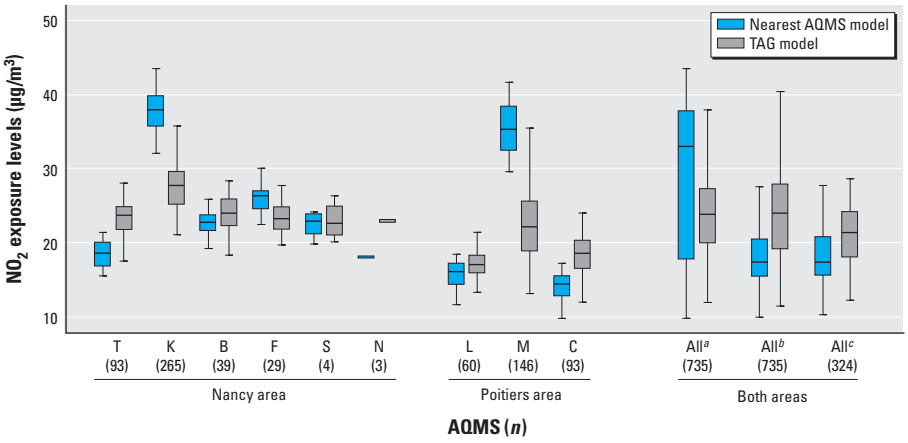

Figure 2. Box plots (25th, 50th, and 75th percentiles) of NO_2 exposure levels during the whole pregnancy as estimated by the nearest-AQMS model and by the TAG model, according to the AQMS closest to the residential address. The population was restricted to 735 women living < 5 km away from an AQMS without change of assigned station during pregnancy. Abbreviations: T, Tomblaine; K, Nancy-Kennedy; B, Nancy-Brabois; F, Fléville; S, St Nicolas de Port; N, Neuves-Maison; L, Les couronneries; M, Place du marché; C, Chasseneuil. Stations were located in the periurban area. K (Nancy) and M (Poitiers) are stations located in the city center.
[a]Exposures estimated taking into account all AQMS. [b]Exposures estimated taking into account all AQMS except K and M (city-center stations); for subjects initially assigned to one of these stations, the closest station has been replaced by the second AQMS nearest to the home address located outside the city center and < 5 km away from the home address, if any. [c]Exposures were estimated taking into account all AQMS except K and M, with all women for whom K or M was the closest station excluded from the analysis.

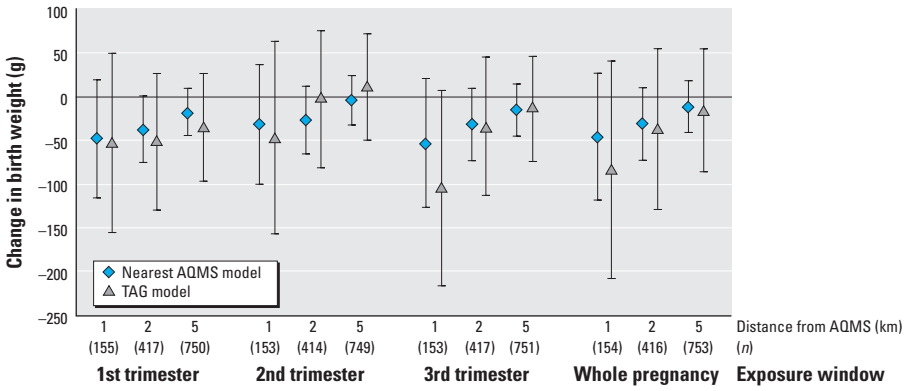

Figure 3. Change in mean birth weight (g) for a 10-µg/m^3 increase in NO_2 during pregnancy, as a function of the size of the buffer considered around each AQMS, adjusted for factors as described in "Materials and Methods." Error bars indicate 95% CIs.

than for the 2-km buffer, probably because of the small number of subjects. Previous studies with buffers of different sizes gave results similar to ours: Hansen et al. (2008) and Wilhelm and Ritz (2005) found negative associations between fetal growth and levels of exposure to carbon monoxide, coarse particulate matter (≤ 10 μm in aerodynamic diameter), sulfur dioxide, and ozone during pregnancy, as estimated from data from the nearest AQMS, that were stronger for women living within 2 km of a station than for those living up to 14 km away. The choice of the buffer size can probably be seen as a trade-off between bias and variance: The use of smaller buffers decreases sample size (increasing variance) but also probably decreases exposure misclassification (assuming that exposure is better assessed for subjects living closer to an AQMS). However, selection bias may also contribute to the increase in the absolute value of the regression parameter quantifying the association between exposure and birth weight when smaller buffers are considered. Indeed, for associations with third-trimester exposure (but less clearly for first-trimester exposure), the absolute value of the regression parameter also tended to increase as buffer size decreased for the TAG model. This is unlikely to stem from variations in exposure misclassification and might instead be attributed to differences in the selection effects associated with buffers of different sizes.

Most previous studies considering the effects of NO_2 have reported larger decreases in birth weight for exposure in the first and third trimesters of pregnancy (Bell et al. 2007; Gouveia et al. 2004; Ha et al. 2001; Liu et al. 2007; Mannes et al. 2005; Salam et al. 2005) than in the second trimester or over the entire pregnancy (Ha et al. 2001; Lee et al. 2003; Mannes et al. 2005). We observed a similar pattern in our study. A discussion of the biological relevance of the exposure window or the underlying mechanisms is beyond the scope of this article. Several potential mechanisms by which air pollution may affect fetal growth have been proposed (Kannan et al. 2006; Ritz and Wilhelm 2008; Slama et al. 2008), but none of these mechanisms has been validated.

It is generally difficult to predict the impact of an error in an exposure variable in terms of the potential for bias in the exposure–response relationship (Jurek et al. 2008). However, in the specific case of a Berkson-type error, the power of the study is reduced and CIs are widened, but no bias in linear regression coefficients is expected (Armstrong 2008; Zeger et al. 2000). Berkson-type error (Armstrong 2008) may occur when the exposure is measured at the population level and individual exposures levels vary because of differences in the time windows of exposure or time–activity patterns. The measurement error for the nearest-AQMS approach would be expected to have a Berkson-type error component, because the same proxy exposure is used for all women living in a circular area around a given monitor. The observation that exposure estimates for the nearest-AQMS model were at least as strongly associated with birth weight as those for the TAG model is consistent with the nearest-AQMS model being subject principally to Berkson-type error. Therefore, assuming that the observed association with birth weight was real, exposure misclassification seemed to have little impact on the dose–response relationship. If we accept that the TAG model cannot be seen as a gold standard, exposure mismeasurement seemed to affect both models in similar ways. In a study in Vancouver, Canada, Brauer et al. (2008) found significant negative associations between NO_2 exposure and fetal growth when they used an AQMS-based approach, but no association when they used an LUR model. They considered women living up to 10 km away from an AQMS, and the AQMS-based model corresponded to an inverse-distance weighting index, taking into account the three closest stations within 50 km.

Conclusion

Our study indicates that models of exposure to background NO_2 concentrations based on data from the nearest AQMS may entail large errors in estimated exposure, but that in some instances these errors have little impact on the exposure–birth weight relationship. The amplitude of exposure misclassification in AQMS-based models and of the resulting bias may be limited by restricting the size of the study area around each AQMS considered. Full quantification of the exposure error for each model would require consideration of the temporal and spatial activities of each subject. Our study cannot be interpreted as providing clear evidence that the nearest-AQMS approach yields unbiased estimates of the association between NO_2 concentrations and fetal growth. This question requires further consideration in other cohorts and in other countries, in which the siting of permanent monitors may follow different rules.

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Pregnancy exposure to atmospheric pollutants and placental weight: An approach relying on a dispersion model

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ABSTRACT

Background: Epidemiologic studies suggest an association between air pollution exposure and foetal growth. The possible underlying biological mechanisms have little been studied in humans, but animal studies suggest an impact of atmospheric pollutants on placental function.
Objectives: Our aim was to investigate the association between exposure to atmospheric pollutants' levels during pregnancy and placental weight, birth weight and the placental to foetal weights ratio (PFR). For comparison purposes, the effects of active smoking on the same measures at birth have also been estimated.
Methods: The study relies on women from Eden mother–child cohort recruited in the middle-sized cities of Poitiers and Nancy (France). Nitrogen dioxide (NO_2) and particulate matter with diameter <10 μm (PM10) home address levels during pregnancy were assessed using ADMS-Urban dispersion model. We characterized associations of NO_2, PM10 levels and active smoking with placental, birth weights and PFR by distinct linear regression models.
Results: Air pollution levels were higher and had greater variability in Nancy (5th–95th centiles, 19.9–27.9 μg/m^3 for PM10) than in Poitiers (5th–95th centiles, 14.3–17.8 μg/m^3). Associations differed by study area: in Nancy (355 births), air pollution levels were associated with decreased placental weight and PFR, while in Poitiers (446 births), opposite or null associations were observed. Cigarette smoking was not associated with placental weight while it was associated with a decrease in birth weight and an increase in PFR.
Conclusion: Results regarding air pollution estimated effects were not similar in both study areas and should therefore be taken with caution. The placental weight decrease observed with air pollutants in the more polluted area of Nancy is consistent with a recent epidemiological study. In this area, maternal active smoking and PM10 levels tended to have opposite effects on the PFR, suggesting different mechanisms of action of both pollutants on foetal growth.

1. Introduction

Epidemiologic studies have reported associations between prenatal exposure to atmospheric pollutants and foetal growth (Jedrychowski et al., 2004, Ritz and Yu, 1999, Slama et al., 2009) (reviewed e.g. by Choi et al., 2006, Ritz and Wilhelm, 2008, Shah and Balkhair, 2011, Slama et al., 2008). Although several hypotheses have been raised (Kannan et al., 2006, Ritz and Wilhelm, 2008, Slama et al., 2008), little toxicological research has been performed on this question (Veras et al., 2008) and the possible biological mechanisms whereby air pollution could impact reproductive outcomes have not been identified. Non exclusive hypotheses include an air pollution-mediated alteration of maternal cardiovascular function (Hampel et al., 2011, Lee et al., 2011, van den Hooven et al., 2011), of maternal-placental blood flow; air pollution effects on epigenetic marks in the zygote or placenta (Perera and Herbstman, 2011) or on the endocrine system. Several of these pathways could translate into alterations in placental development. Experimental studies in mice suggested that air pollution affects placental morphology (Veras et al., 2008).

Through its exchange, endocrine and metabolic functions, the placenta can be seen as playing for the foetus the role of several adult

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organs; it mediates circulation exchange between maternal and foetal blood and plays a key role in transport of nutriments, oxygen, immunoglobulins, waste and hormones to and from the foetus, as well as in metabolism (Evain-Brion and Malassiné, 2010; Gard, 2008, Korourian and De Las Casas, 2007); it has an endocrine activity, and also prevents an attack of the foetus from the maternal immune system. The placenta also has a central role in attenuating or mediating the effects of environmental factors on the foetus (Sood et al., 2006) and can be seen as a record of some in utero exposures and pregnancy troubles (Maccani and Marsit, 2009). These functions are aimed at achieving homeostasis in intrauterine environment and protect and support growth and development of the foetus (Schneider, 1996).

The gross weight and shape of the placenta at birth give information on placental development (Salafia et al., 2005) in relation to transfer of nutrients and oxygen to the foetus during pregnancy (Misra et al., 2009), one key determinant of infant birth weight. To our knowledge, only one study documented the possible impact of air pollution on placental development or growth in humans (Yorifuji et al., 2012); it reported decreases in placental and infant weight at delivery, and an increase in placental to foetal weights ratio in association with living within 200 m from a major road (Yorifuji et al., 2012).

Tobacco smoke presents some similarities with traffic-related air pollution in terms of exposure pathway, granulometry of their particulate phase and composition. Indeed, tobacco smoke particulate matter (PM) has an aerodynamic diameter typically in the 50–800 nm range (Kleeman et al., 1999), which overlaps with the 10–100 nm range, corresponding to fresh traffic-related PM (Schauer et al., 2002). Many families of combustions' by-products such as volatile organic compounds or polycyclic aromatic hydrocarbons are present in both mixtures. A notable difference is nicotine, which is present in tobacco smoke but not in traffic-related air pollution. In addition, one can note that the dose of fine particulate matter inhaled from smoking one cigarette per day is substantially higher than that stemming from living in an environment with an average concentration of PM2.5 (particulate matter with an aerodynamical diameter below 2.5 microns) of 30 $\mu g/m^3$ (Pope et al., 2011). A study has provided relative risks of lung cancer mortality (and cardiovascular mortality) associated with fine particulate matter from air pollution and from cigarette smoke (Pope et al., 2011), but such comparison has been seldom performed for other health outcomes. Regarding birth outcomes, studies tend to show that active smoking is associated with a decrease in offspring birth weight, is not associated with placental weight and, consequently, is associated with an increase in placental to foetal weights ratio (Williams et al., 1997, Yorifuji et al., 2012).

This study aims at investigating the association between pregnancy exposure to nitrogen dioxide (NO_2) and particulate matter with an aerodynamical diameter below 10 μm (PM10) and maternal smoking with placental weight, (infant) birth weight and placental to foetal weights ratio (PFR).

2. Population and methodology

2.1. Setting and study population

Our study is based on a part of EDEN (Etudes des Déterminants pré et postnatals précoces du développement et de la santé de l'ENfant) mother–child cohort, whose general aim is to characterize pre- and early postnatal determinants of foetus and infant development and health (Regnault et al., 2010; Slama et al., 2009). The study population was recruited at the maternity wards of two University hospitals in Poitiers and Nancy, France (Drouillet et al., 2009) before 28 weeks of pregnancy between February 2003 and January 2006. The women who carried multiple foetuses, known to have diabetes, not understanding French, or planning to deliver outside the university hospital or to move out from the study region within 3 years of recruitment were not eligible (Regnault et al., 2010).

2.2. Assessment of exposures to atmospheric pollutants

The exposures of interest are nitrogen dioxide (NO_2) and particulate matter with diameter <10 μm (PM10). NO_2 and PM10 ambient air levels were estimated using a dispersion model implemented with ADMS-Urban software (CERC, Cambridge, UK)(Galineau et al., 2011, Hampel et al., 2011). The input data of the dispersion model included spatial factors such as localization and characteristics of traffic, industrial and urban heating sources; temporal factors such as hourly meteorological parameters, daily traffic patterns and data from permanent monitoring stations (used to estimate background air pollution levels). The model output was constituted by hourly air pollution levels at each of the cohort subjects' home addresses during the study period.

Maternal exposure during pregnancy was estimated as the average of the hourly estimates from the dispersion model at the home address during specific time windows (pregnancy trimesters, whole pregnancy). For women who changed home address during pregnancy, exposure was estimated as the average of exposures at each home address during the relevant periods weighted by the number of days spent at each address. Women whose average exposure level estimate had more than 25% missing daily values during the considered exposure window were excluded.

The date of conception was estimated from the date of last menstrual period (LMP), or using the ultrasound-based estimate when LMP date was missing or yielded a gestational duration of above 44 weeks (Slama et al., 2009). To estimate trimester-specific exposure averages, we defined the first trimester as spanning from the date of conception to day 91, the second trimester as days 92–183 and the third trimester as days 184 to delivery (if delivery took place after day 184).

2.3. Assessment of active smoking

Data on maternal active smoking during the two first trimesters of pregnancy were collected at the questionnaire filled in during the interview with the study midwife taking place at 24–28 gestational weeks. Information on smoking during the last trimester was collected in the questionnaire filled in after delivery by the woman.

2.4. Assessment of outcomes

The outcomes of interest were placental and birth weight at delivery (obtained from maternity records) and placental to foetal weights ratio (PFR, placental weight/infant weight at birth). Placental weight is not systematically collected in French maternity clinics; it was more frequently missing in Nancy than in Poitiers (Table 1). In Nancy, the proportion of births with missing placental weight information was much higher (76 out of 96 births, 79%) for infants born through assisted delivery (forceps or vacuum extraction) compared to unassisted vaginal births or Caesarean sections (39% of missing data). We therefore decided to exclude the remaining 20 infants from Nancy born with assisted delivery from the analyses (not excluding them did not alter our conclusions; not detailed). In Poitiers, the frequency of missing data for placental weight was below 8% for assisted deliveries, Caesarean sections and vaginal births.

2.5. Statistical analysis

Linear regression models (Stata SE version 10.1; StataCorp., College Station, TX, USA) have been used to investigate the association between levels of NO_2 and PM10 and either infant or placental weights at birth or PFR. All analyses were conducted on the same population of newborns with simultaneously available information on infant, placental weight and exposure. NO_2 and PM10 levels were considered separately as continuous variables; we reported the weight change for every increase of NO_2 or PM10 of 10 $\mu g/m^3$.

Table 1
Characteristics of Eden cohort mother–child pairs with placental weight data and of pairs with missing information on placental weight (1154 singleton deliveries with information on birth weight and air pollution exposure from Eden mother child cohort).

Variables	Overall (N = 1154) N (%)	Information on placental weight, N (%)		p-value[a]
		Non-missing (N = 888)	Missing (N = 266)	
Centre				$<10^{-3}$
Poitiers	566 (100)	526 (95)	30 (5)	
Nancy	598 (100)	362 (61)	236 (39)	
Maternal age at end of education				0.04
≤16 years	62 (100)	48 (77)	14 (23)	
17–18 years	151 (100)	118 (78)	33 (22)	
19–20 years	201 (100)	169 (84)	32 (16)	
≥21 years	735 (100)	548 (75)	187 (25)	
Maternal age at conception				0.10
<25 years	261 (100)	206 (79)	55 (21)	
25–29 years	421 (100)	336 (80)	85 (20)	
30–34 years	332 (100)	241 (73)	91 (27)	
≥35 years	140 (100)	105 (75)	35 (25)	
Birth order				0.10
First birth	518 (100)	413 (80)	105 (20)	
Second birth	422 (100)	318 (75)	104 (25)	
Third birth or more	212 (100)	155 (73)	57 (27)	
Maternal smoking during trimester 1				0.11
0	845 (100)	645 (76)	200 (24)	
1–5 cig./day	136 (100)	111 (82)	25 (18)	
6–10 cig./day	109 (100)	88 (81)	21 (19)	
≥10 cig./day	61 (100)	41 (67)	20 (33)	
Maternal smoking during trimester 2				0.49
0	948 (100)	726 (77)	222 (23)	
1–5 cig./day	114 (100)	93 (82)	21 (18)	
6–10 cig./day	74 (100)	56 (76)	18 (24)	
≥10 cig./day	15 (100)	10 (67)	5 (33)	
Maternal smoking during trimester 3				0.37
0	950 (100)	729 (77)	221 (23)	
1–5 cig./day	101 (100)	81 (80)	20 (18)	
6–10 cig./day	68 (100)	54 (79)	14 (24)	
≥ 10 cig./day	32 (100)	21 (66)	11 (33)	
Infant sex				0.61
Male	597 (100)	463 (78)	134 (22)	
Female	557 (100)	425 (76)	132 (24)	
Mode of delivery				0.001
Vaginal [b]	910 (100)	682 (75)	228 (25)	
Assisted deliveries	62 (100)	59 (95)	3 (5)	
Caesarean section	181 (100)	146 (81)	35 (19)	
Gestational duration				0.99
<37 weeks	69 (100)	53 (77)	16 (23)	
37–38 weeks	220 (100)	169 (77)	51 (23)	
39–40 weeks	610 (100)	469 (77)	141 (23)	
≥41 weeks	255 (100)	197 (77)	58 (23)	
	Mean (5–50–95th centiles)	Mean (5–50–95th centiles)	Mean (5–50–95th centiles)	
Birth weight (g)	3286 (2470–3303–4050)	3297 (2500–3330–4070)	3248 (2380–3265–4000)	0.18 [c]
Placental weight (g)	538 (350–540–730)	538 (350–540–730)	–	
NO_2 level, pregnancy (Poitiers), μg/m^3	16.1 (10.2–14.9–25.9)	16.1 (10.3–14.9–26.1)	16.0 (9.6–15.5–24.0)	0.89 [c]
NO_2 level, pregnancy (Nancy), μg/m^3	24.8 (14.3–24.5–38.5)	24.9 (14.9–24.3–38.4)	24.7 (13.7–25.4–38.5)	0.85 [c]
PM10 level, pregnancy (Poitiers) μg/m^3	16.2 (14.2–16.2–17.8)	16.2 (14.3–16.2–17.8)	16.1 (14.0–16.5–17.4)	0.87 [c]
PM10 level, pregnancy (Nancy), μg/m^3	23.3 (19.9–22.8–28.1)	23.3 (19.9–22.8–27.9)	23.4 (20.1–22.8–28.1)	0.80 [c]

[a] *p*-Value of chi-square test, unless otherwise specified.
[b] Vaginal births without medical assistance.
[c] *p*-Value of Student's *t*-test.

The choice and coding of adjustment factors follow the approach previously defined in our cohort (Slama et al., 2009). Regression models were adjusted for gestational duration (linear and quadratic terms), infant sex, maternal height (continuous), maternal pre-pregnancy weight [coded using a broken stick model with a knot at 60 kg (Slama and Werwatz, 2005)], parity (3 categories), maternal age at end of education (categories), second trimester smoking (continuous) and season of last menstrual period. Centre of recruitment was a predictor of exposure. Our a priori choice was therefore to adjust for centre, but also to report results of analyses stratified on centre and to discuss results adjusted for centre only if the estimated effect of air pollution on the health parameters were similar in both centres. Effects of active smoking were estimated on the same population as that for which air pollution effects are reported, with the same set of adjustment factor (excluding smoking); a separate regression model was run for each trimester-specific exposure variable.

3. Results

3.1. Study population

The EDEN cohort included 2002 pregnant women. Information on infant birth weight was available for 1893 singleton live births. Out of these, 1223 lived in the geographical area where we developed the exposure model (Fig. 1) and had information on exposure to NO_2 and PM10 based on this dispersion model; the characteristics

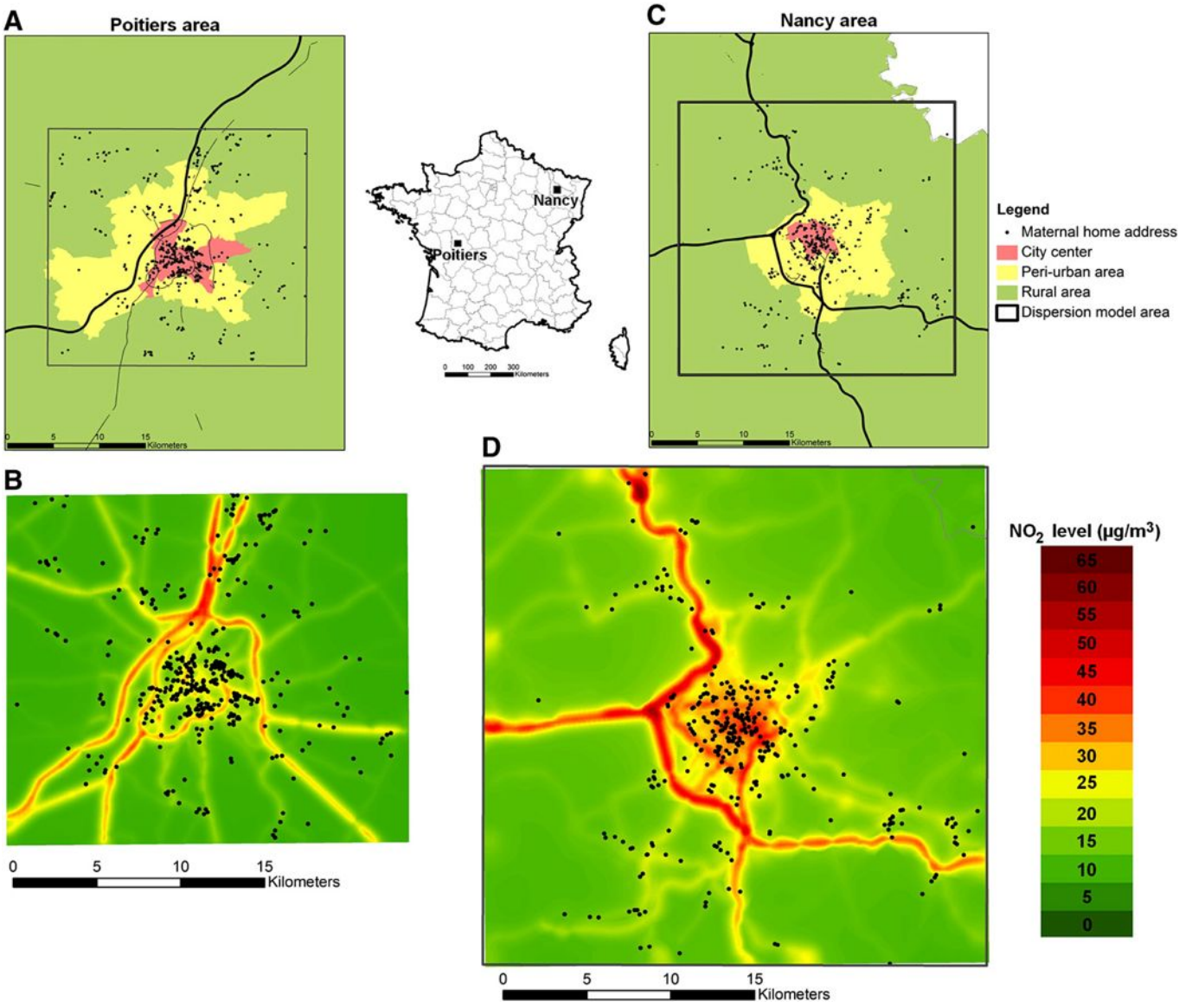

Fig. 1. Map of Nancy and Poitiers areas and of modelled NO_2 levels. The squares in the inlets A) and C) represent the areas included in the dispersion modelling. The black dots in the inlets correspond to the home addresses of the study population. B) and D) indicate the modelled NO_2 yearly levels in Poitiers and Nancy area, respectively.

of these subjects are compared to those of subjects with missing information on air pollution in supplementary Table 1. Placental weight has been collected for 901 of them (74%); after exclusion of assisted births from Nancy, the final number of observations available for analysis was 888.

The proportion of liveborns with available information on placental weight was 95% in Poitiers and 61% in non-assisted births from Nancy. We found no difference in maternal age at pregnancy start, maternal smoking, infant sex, birth weight and gestational duration (*t*-test, Chi-square test or Wilcoxon rank test; all *p*-values >0.10) between observations with and without information on placental weight (Table 1). Within each centre, air pollution levels did not differ between observations with and without available placental weight ($p>0.8$ for each pollutant) (see supplementary Tables S2 and S3 for a comparison of subjects with and without placental weight information in Poitiers and Nancy, respectively). In adjusted analyses in which availability of placental weight information was the dependent variable, apart from centre, only the mode of delivery was associated with placental weight information availability, with placental weight being more often available for Caesarean than for vaginal births.

Mean birth weight was 3297 g (5th–95th percentiles, 2500–4070 g), while mean placental weight was 538 g (5th–95th percentiles, 350–730 g) and mean PFR 0.164 (5th percentile, 0.119 and 95th percentile, 0.219). The correlation coefficient between infant and placental weights at birth was $r=0.61$ ($p<0.001$, Supplementary Figure S1); PFR had a coefficient of correlation of −.20 with birth weight and of .64 with placental weight (both $p<0.001$).

For the whole pregnancy exposure window, mean NO_2 level was 24.9 µg/m^3 in Nancy (5th–95th centiles, 14.9 to 38.4 µg/m^3) and 16.1 µg/m^3 in Poitiers (5th–95th centiles, 10.3 to 26.1 µg/m^3); mean PM10 level was 23.3 µg/m^3 in Nancy (5th–95th centiles, 19.9 to 27.9 µg/m^3) and 16.2 µg/m^3 in Poitiers (5th–95th centiles, 14.3 to 17.8 µg/m^3). PM10 variability was thus very limited in Poitiers and PM10 levels very little overlapped between both cities.

3.2. PM10 and birth outcomes

PM10 pregnancy level was associated with an average adjusted placental weight change by −30 g (95% CI, −64 to 4 g) for each increase by 10 µg/m^3 (Table 2). This estimate was strongly driven by results in

Table 2
Associations between PM10 levels and placental weight, birth weight, and placental to foetal weights ratio (PFR).

PM10 (μg/m³)	Unadjusted regression models						Adjusted regression models [a]					
	Placental weight (g)		Birth weight (g)		PFR (%)		Placental weight (g)		Birth weight (g)		PFR (%)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
First trimester exposure (N=882)												
<16.4	Referent		Referent		Referent		Referent		Referent		Referent	
16.4–21.2	−4.0	−23.3 to 15.3	−26	−110 to 58	.04	−.45 to .52	−1.2	−22.0 to 19.7	6	−66 to 78	−.05	−.59 to .48
>21.2	−20.2	−39.4 to−.9	−51	−135 to 33	−.39	−.87 to .09	−10.1	−44.8 to 24.6	10	−109 to 130	−.35	−1.24 to .54
Continuous [b]	−28.7	−45.9 to−11.6	−75	−150 to −1	−.52	−.95 to−.09	−26.3	−54.0 to 1.4	−8	−104 to 88	−.78	−1.49 to −.07
Second trimester exposure (N=876)												
<16.7	Referent		Referent		Referent		Referent		Referent		Referent	
16.7−21.1	6.1	−13.2 to 25.4	−36	−120 to 48	.39	−.10 to .87	16.5	−4.0 to 37.0	3	−68 to 74	.50	−.03 to 1.02
>21.1	−17.4	−36.7 to 1.9	−58	−143 to 26	−.27	−.75 to .22	0.9	−33.7 to 35.5	−20	−140 to 100	.14	−.75 to 1.02
Continuous [b]	−27.5	−45.9 to −9.0	−91	−171 to −10	−.41	−.88 to .05	−8.8	−38.1 to 20.5	−4	−105 to 97	−.32	−1.07 to .43
Third trimester exposure (N=788)												
<16.3	Referent		Referent		Referent		Referent		Referent		Referent	
16.3–20.7	18.6	−.6 to 37.8	71	−12 to 155	.13	−.35 to .61	19.2	−1.7 to 40.0	44	−28 to 116	.30	−.24 to .83
>20.7	−17.9	−37.1 to 1.3	−46	−129 to 37	−.39	−.88 to .09	−13.1	−46.4 to 20.2	−36	−151 to 79	−.32	−1.17 to .54
Continuous [b]	−26.7	−44.4 to −9.0	−55	−132 to 21	−.59	−1.04 to −.15	−26.2	−54.7 to 2.2	−18	−116 to 80	−.76	−1.48 to −.03
Whole pregnancy average exposure (N=868)												
<16.4	Referent		Referent		Referent		Referent		Referent		Referent	
16.4−21.2	.5	−18.8 to 19.9	−46	−131 to 38	.34	−.14 to .83	9.9	−10.2 to 30.0	21	−48 to 91	.24	−.27 to .76
>21.2	−26.9	−46.3 to −7.6	−92	−176 to −7	.35	−.84 to .13	−28.9	−64.3 to 6.4	−63	−185 to 59	−.52	−1.43 to .38
Continuous [b]	−32.6	−51.6 to −13.6	−90	−173 to −7	−.58	−1.05 to -.10	−29.6	−63.6 to 4.4	−6	−124 to 111	−.93	−1.80 to −.06

[a] PM10 estimated effect adjusted for gestational duration (linear and quadratic terms), infant sex, centre, maternal height (continuous), pre-pregnancy weight (broken stick model with a knot at 60 kg (Slama and Werwatz, 2005), maternal age at the end of education, parity, smoking during second trimester (number of cigarettes/day) and season of last menstrual period.
[b] Parameters are reported for an increase by 10 μg/m³ of PM10.

Nancy, where PM10 variability was larger. Indeed, in centre-specific analyses, PM10 levels were associated with a placental weight change by 68 g in Poitiers (95% CI, −29 to 166) and by −45 g in Nancy (−85 to −4, Table 3, *p* for interaction, .04). For Nancy, among all trimesters, the amplitude of the placental weight decrease associated with PM10 levels tended to be strongest for the 3rd trimester exposure window. Birth weight tended to be adjusted with PM10 in unadjusted analyses, an association that disappeared after adjustment for gestational duration and sex of the offspring. In adjusted analyses, birth weight was not associated with PM10, the trend corresponding to a birth weight decrease with increasing PM10 levels in both cities, with very wide confidence intervals. PFR decreased by 1.3% for each increase by 10 μg/m³ of PM10 pregnancy average in Nancy (95% CI, −2.3 to −.3) while an opposite trend was observed in Poitiers (+2.2%, 95% CI, −.5 to 4.7%). CIs were generally very wide for subjects from Poitiers, and associations with placental weight and PFR had an opposite direction than for Nancy (Table 3). Associations between PM10 levels and placental weight in Nancy area remained similar when using log-transformed PM10 levels instead of untransformed PM10 levels, and after excluding the 7 observations with a PM10 pregnancy average above 35 μg/m³ (not detailed).

3.3. NO_2 and birth outcomes

In Nancy, the pattern of associations with NO_2 was similar to that with PM_{10}, with placental weight tending to decrease with exposure (the association being strongest for 3rd trimester NO_2 levels) and PFR tending to decrease (the association being again strongest for 3rd trimester NO_2 levels, Table 3). In Poitiers, associations with NO_2 had, again, an opposite direction compared to estimates for the subjects recruited in Nancy, with very wide confidence intervals. Table 4 indicates

Table 3
Adjusted associations between air pollution levels (for an increase of 10 μg/m³) and placental weight, birth weight, and placental to foetal weights ratio (PFR), stratified on centre.

Pollutant and exposure window	Poitiers [a] (n=489)						Nancy [a] (n=354)					
	Placental weight (g)		Birth weight (g)		PFR (%)		Placental weight (g)		Birth weight (g)		PFR (%)	
	β [b]	95% CI	β [b]	95% CI	β [b]	95% CI	β [b]	95% CI	β [b]	95% CI	β [b]	95% CI
PM10												
1st trimester	−5.0	−63.4 to 53.3	−148	−361 to 64	.58	−.98 to 2.14	−33.9	−69.7 to 1.9	8	−109 to 126	−1.09	−1.96 to −0.22
2nd trimester	62.1	2.4 to 121.8	−10	−229 to 210	2.05	.45 to 3.65	−33.3	−70.5 to 4.0	−7	−130 to 116	−1.05	−1.96 to −.14
3rd trimester	21.3	−37.8 to 80.4	162	−53 to 378	−.30	−1.88 to 1.28	−42.8	−78.3 to −7.4	−75	−192 to 42	−.94	−1.81 to −.01
Whole pregnancy	68.3	−29.2 to 165.9	−15	−341 to 372	2.15	−0.45 to 4.74	−44.6	−84.8 to −4.3	−22	−155 to 111	−1.30	−2.28 to −.32
NO_2												
1st trimester	5.6	−11.3 to 22.6	−18	−81 to 43	.31	−.14 to .76	−10.8	−26.5 to 4.8	2	−50 to 53	−.36	−.74 to .02
2nd trimester	15.5	−2.4 to 33.4	28	−37 to 94	.38	−.10 to .86	−10.3	−25.8 to 5.3	3	−48 to 54	−.38	−.76 to−.01
3rd trimester	15.5	−3.3 to 34.2	58	−10 to 127	.18	−.32 to .68	−23.2	−38.8 to −7.5	−36	−88 to 16	−.58	−.96 to−.20
Whole pregnancy	13.5	−6.2 to 33.1	25	−47 to 97	.34	−.18 to .87	−15.3	−31.8 to 1.2	−8	−62 to 46	−.47	−.87 to−.01

[a] Adjusted for gestational duration (linear and quadratic terms), infant sex, centre, maternal height (continuous), pre-pregnancy weight (broken stick model with a knot at 60 kg (Slama and Werwatz, 2005), maternal age at the end of education, parity, smoking during second trimester (number of cigarettes/day) and season of last menstrual period. Each pollutant was considered in a separate linear regression model.
[b] Parameters are reported for an increase of 10 μg/m³ of PM10 or NO_2.

Table 4
Association between NO_2 levels and placental weight, birth weight, and placental to foetal weights ratio (PFR).

NO_2 (μg/m^3)	Unadjusted regression models						Adjusted regression models [a]					
	Placental weight (g)		Birth weight (g)		PFR (%)		Placental weight (g)		Birth weight (g)		PFR	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
First trimester exposure (N=882)												
<15.0	Referent		Referent		Referent		Referent		Referent		Referent	
15.0–22.4	−6.6	−25.9 to 12.6	−88	−171 to −4	2.94	−.19 to .78	2.1	−17.7 to 21.8	−45	−113 to 23	.31	−.20 to −.81
>22.4	−23.6	−42.9 to −4.4	−132	−216 to −49	.01	−.28 to .20	−11.5	−33.7 to 10.7	−41	−118 to 36	−.14	−.71 to .43
Continuous [b]	−11.5	−21.0 to −2.1	−59	−100 to −17	.02	−.08 to .11	−4.1	−15.2 to 7.0	−3	−42 to 35	−.11	−.39 to .18
Second trimester exposure (N=876)												
<15.1	Referent		Referent		Referent		Referent		Referent		Referent	
15.1–22.4	5.7	−13.7 to 25.1	25	−59 to 110	.01	−.48 to .49	15.8	−4.7 to 36.3	66	−5 to 136	.19	−.33 to .72
>22.4	−6.4	−25.8 to 12.9	−7	−91 to 77	−.21	−.70 to .27	13.7	−10.0 to 37.4	60	−21 to 142	.12	−.49 to .73
Continuous [b]	−9.0	−18.1 to 0.1	−23	−63 to 16	−.18	−.40 to .05	−1.5	−12.7 to 9.8	11	−28 to 50	−.12	−.41 to .17
Third trimester exposure (N=810)												
<14.0	Referent		Referent		Referent		Referent		Referent		Referent	
14.0–22.2	10.3	−9.0 to 29.6	61	−22 to 145	−.03	−.51 to .46	11.9	−8.5 to 32.2	63	−7 to 133	.05	−.47 to .57
>22.2	−6.0	−25.3 to 13.4	23	−61 to 106	−.36	−.84 to .12	0.0	−24.4 to 24.2	45	−39 to 128	−.25	−.87 to .37
Continuous [b]	−10.3	−19.3 to −1.3	−16	−55 to 23	−.27	−.49 to −.04	−10.3	−21.9 to 1.2	−3	−43 to 37	−.34	−.63 to −.04
Pregnancy average exposure (N=868)												
<15.4	Referent		Referent		Referent		Referent		Referent		Referent	
15.4–21.5	−4.1	−23.5 to 15.4	−19	−104 to 65	.06	−.43 to .55	6.0	−13.8 to 25.9	47	−22 to 115	.04	−.47 to .55
>21.5	−12.0	−31.5 to −7.5	−55	−140 to 30	−.08	−.57 to .41	3.5	−19.4 to 26.4	3	−76 to 82	.14	−.45 to .72
Continuous [b]	−12.7	−23.0 to −2.4	−41	−86 to 4	−.19	−.45 to .07	−5.8	−18.0 to 6.4	4	−38 to 46	.21	−.52 to .10

[a] NO_2 estimated effect adjusted for gestational duration (linear and quadratic terms), infant sex, centre, maternal height (continuous), pre-pregnancy weight (broken stick model with a knot at 60 kg (Slama and Werwatz, 2005), maternal age at the end of education, parity, smoking during second trimester (number of cigarettes/day) and season of last menstrual period.
[b] Parameters are reported for an increase of 10 μg/m^3 of NO_2.

association with NO_2 for mother–child pairs for both cities considered simultaneously.

3.4. Cigarette smoking and placental and birth weights

In the same population of newborns as for the analysis on atmospheric pollutants, the effect of maternal active smoking on birth weight appeared strongest for smoking during the second (compared to first or third) trimester (Table 5). An increase in maternal smoking during the second trimester by 5 cigarettes/day was associated with a birth weight change by −127 g (95% CI, −172 to −82, $p<0.01$) and a change in PFR by .4% (95% CI, 0.1% to 0.8%, $p=0.01$). Placental weight was not associated with cigarette smoking (estimated change, −8 g, 95% CI −21 to 5, $p=0.25$). These associations were similar after stratification on centre (e.g., the PFR change associated with an increase by 5 cigarettes/day in maternal 2nd trimester smoking was .48% in Poitiers and .38% in Nancy) or after adjustment for PM10 pregnancy level (not detailed). Fig. 2 shows effect estimates associated with PM10 levels and maternal second trimester smoking for newborns from Nancy centre.

4. Discussion

We characterized associations between air pollution levels during pregnancy and placental weight at birth and PFR, the ratio of placental to foetal weights at birth, in a mother–child cohort conducted in two areas. Associations differed according to the recruitment area, with PM10 (and to a lesser extent, NO_2) concentrations being associated with decreases in placental weight and in PFR in Nancy area, an urban area of about 258,000 inhabitants located in the East of France with a population density of 1816 inhabitants/km^2; associations were statistically weaker and generally had an opposite direction for mother–child pairs recruited in Poitiers. Poitiers is a smaller and less densely populated urban area of about 129,000 inhabitants (population density, 746 inhabitants/km^2), with PM10 levels much lower than in Nancy: indeed, the 95th percentile of PM10 pregnancy level in women from Poitiers was lower than the 5th percentile of PM10 pregnancy level in Nancy.

4.1. Comparison with the epidemiological literature

To our knowledge, only one previous published study considered placental weight as an outcome of interest in relation to air pollution

Table 5
Association between maternal active smoking during pregnancy and placental weight, birth weight, and placental to foetal weights ratio (PFR).

Active smoking	Active smoking, n		Adjusted regression models [a]					
			Placental weight (g)		Birth weight (g)		PFR (%)	
	No (%)	Yes (%)	β	95% CI	β	95% CI	β	95% CI
1st trimester[b]	628 (73)	235 (27)	2.6	−5.7 to 11.0	−50	−79 to −20	.34	.12 to .55
2nd trimester[b]	709 (82)	154 (18)	−7.6	−20.6 to 5.3	−127	−172 to −82	.43	.10 to .76
3rd trimester[b]	712 (83)	151 (17)	−2.4	−13.9 to 9.2	−86	−126 to −46	.37	.07 to .66

[a] Estimated effect of maternal active smoking during pregnancy adjusted for gestational duration (linear and quadratic terms), infant sex, centre, maternal height (continuous), pre-pregnancy weight (broken stick model with a knot at 60 kg (Slama and Werwatz, 2005), maternal age at the end of education, parity, and season of last menstrual period.
[b] Parameters are reported for an increase of 5 cigarettes/day.

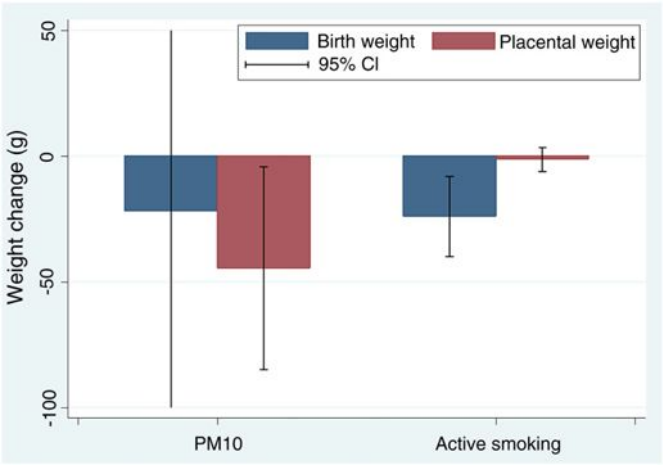

Fig. 2. Adjusted changes in placental and infant weight at birth associated either with an increase in PM10 pregnancy level or with maternal second trimester smoking during pregnancy (Nancy area only). Changes are reported for an increase of 10 μg/m^3 in PM10 and, for reading convenience, for an increase by 1 cigarette smoked/day (354 newborns from Nancy).

exposure (Yorifuji et al., 2012). This study was based on records from a hospital in Shizuoka prefecture, Japan, including 14,189 singletons born between January 1997 and December 2008. Exposure assessment was based on distance between the home address at the time of delivery and the closest major road (>50,000 vehicles/day on a week day, a traffic density reached for one single freeway in our study, with only 7 women living <200 m from this freeway). After adjustment, placental weight at birth decreased by 13 g (95% CI, −21 to −4) and infant birth weight by 82 g (95% CI, −120 to −43) in the 813 newborns whose mother lived less than 200 m away from a major road, compared to the remaining 13,376 observations. This resulted in an increase in PFR in association with exposure (Yorifuji et al., 2012). Our results cannot be directly compared because of the much lower number of subjects living in vicinity to high traffic, and because they are based on a dispersion modeling of NO_2 and PM10 levels, that takes into account temporal variations in addition to fine scale spatial variations in air pollution (whereas the study by Yorifuji et al. was based only on spatial exposure contrasts); moreover, our dispersion model took into account all urban sources of pollution, including e.g. heating and long-range pollution transport, whereas the study by Yorifuji et al. was based only on locally-emitted traffic-related air pollution. In terms of direction of associations, and disregarding the differences related to exposure assessment, the placental weight decrease observed in the Japan study was coherent with results from our study concerning births from Nancy, but not from Poitiers. The increase in PFR observed in the Japan study in association with air pollution levels was not clearly observed in our study in Nancy, where PFR tended to decrease in association with air pollution levels.

Maternal smoking was not strongly associated with placental weight; it had a strong negative association with infant weight at birth and was associated with a PFR increase, a result coherent with the Japanese study (Yorifuji et al., 2012) and an Australian study (Williams et al., 1997). Maternal pregnancy smoking was associated with an increase in PFR by 0.2% (95% CI, 0.1 to 0.3%) in the Australian and by 1.3% in the Japanese study (95% CI, 0.9 to 1.7), a result coherent with our estimate of 0.4% associated with an increase by 5 cigarettes/day in active smoking during pregnancy (95% CI, 0.06 to 0.73%). If reflecting causal associations, the different patterns of associations of birth and placental weights with either air pollution levels or active smoking in our study in Nancy centre (Fig. 2) might be seen as suggesting different mechanisms of action of atmospheric pollutants and cigarette smoke on the developing foetal-placental unit. In particular, cigarette smoking seems to impact on birth weight without affecting placental weight at birth, whereas urban atmospheric pollutants might affect placental weight. Whether the placenta reacts differently to the tobacco smoke mixture and to traffic-related air pollutants warrants further investigation.

In our study, in Nancy area, PM10 levels were associated with decreases in placental weight, whereas associations with birth weight were statistically much weaker. This may imply that placental weight change is a more sensitive indicator than birth weight in association with exposure to atmospheric pollutants (but not to maternal tobacco smoke). However, our sample size was limited so that the uncertainties in the effect estimates on birth weight and placental weight were large; moreover, this hypothesis is not clearly supported by the Japanese study, where vicinity to traffic was associated to both birth weight and placental weight decreases (Yorifuji et al., 2012).

4.2. Strengths and limitations

The main strengths of our study were the availability of placental weight, its prospective design, our ability to control for a variety of potential confounders, the fine spatial resolution of our exposure model and the fact that we took into account changes of home address during pregnancy, which has so far seldom been done in epidemiological studies of atmospheric pollutants on pregnancy outcomes (Lepeule et al., 2010, Madsen et al., 2010). Limitations included the fact that outdoor air pollution estimated at the home address was used as an exposure estimate (without explicitly considering exposure in traffic or at the workplace); because the collection of placental weight was not planned as part of the cohort protocol, many observations were missing in Nancy maternity clinic, where this information is not routinely collected.

4.3. Study population

The number of newborns with missing information on placental weight within Nancy population of the EDEN cohort was high, raising concern for a potential selection bias. Adjustment for a number of potential confounders possibly limited such a bias (Hernan et al., 2004), although adjustment may not be fully efficient at correcting selection bias, in particular if selection is due to unidentified factors.

The association between air pollution levels and placental weight differed according to area. Subjects from both areas strongly differed in terms of mean exposure levels, which were lower and had a much more limited range of variation in Poitiers compared to Nancy area; for example, the 5th and 95th percentiles of PM10 pregnancy levels were 14.3 and 17.8 μg/m^3 in Poitiers, compared to 19.9 and 27.9 μg/m^3 in Nancy. This weak variability limited our ability to highlight any association between PM10 and birth outcomes in Poitiers. In a previous study on the association of maternal personal benzene exposure on head circumference, associations tended to be stronger in subjects from Nancy compared to subjects from Poitiers (Slama et al., 2009), but exposure levels more widely overlapped between both areas, possibly because of the use of personal monitors, taking into account exposure indoors and during commuting. The current study, based only on outdoor air pollution levels and disregarding variations in exposure due to behaviours and indoor levels, could not take these sources of variability in exposure into account. Major differences in outcome assessment between areas are a less likely explanation because maternal smoking showed similar patterns of adjusted association with birth weight and PFR in both cities.

4.4. Possible biological mechanisms

Human placenta is quite different from that of rodents (Carter, 2007) and comparison with animal studies should therefore be done cautiously. In mice, exposure to traffic-related air pollution was associated with a decrease of maternal circulatory volume and

an increase of foetal circulatory space area in the placenta, as well as decreases in trophoblast thickness and in foetal weight, but no change in placental volume, which is a proxy of placental weight (Veras et al., 2008). Another mouse study found placental structural and functional disruption due to *intravenous* injected engineered nanoparticles (silica and titanium dioxide) (Yamashita et al., 2011). These studies did not directly assess placental weight.

Placental weight is a simple marker of placental functional efficiency. Other placental measurements such as the shape, diameters, or disk thickness are potential useful indicators of placental efficiency (Salafia et al., 2008), but so far no study described their association with environmental factors and these have not been assessed in our cohort.

5. Conclusion

We did not highlight a coherent pattern of association between air pollutants and placental weight in the two areas investigated. In the more polluted Nancy area, NO_2 and PM10 pregnancy levels tended to be associated with decreases in placental weight and in the placental to foetal weights ratio. In this area, the association with placental weight was of similar amplitude than the (weak) association with birth weight, which, due to a much larger weight of the foetus, may imply a greater sensitivity of the placenta to air pollution, as if the placenta was buffering air pollution effects. Such associations were not observed in Poitiers area; we hypothesize that this was due to the much lower air pollution levels in this area, implying a very limited statistical power, but we cannot discard alternative hypotheses such as residual confounding by unmeasured environmental or behavioural factors in either area, or random fluctuation. Since the only other study on the topic relied on an exposure model not taking temporal variations in exposure into account and since our approach to assess exposure also had limitations, caution is needed regarding a possible impact of atmospheric pollutants on placental size. Future research may need to focus on investigating the effects of air pollution on other (finer) placental measures, and rely on exposure assessment tools taking into account time space activity.

In Nancy area, air pollution estimated effects on the foeto-placental unit differed from the effects of active cigarette smoking (which impacted infant birth weight without affecting placental weight, hence increasing the ratio of placental to infant weights); this suggests that atmospheric pollutants and cigarette smoke may act on foetal growth via different mechanisms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2012.06.013.

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