



Environmental and psychological factors and childhood asthma

Cailiang Zhou

► To cite this version:

Cailiang Zhou. Environmental and psychological factors and childhood asthma. Agricultural sciences. Université Pierre et Marie Curie - Paris VI, 2014. English. NNT : 2014PA066044 . tel-01077906

HAL Id: tel-01077906

<https://theses.hal.science/tel-01077906>

Submitted on 27 Oct 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

THESE DE DOCTORAT DE
L'UNIVERSITE PIERRE ET MARIE CURIE

Sp  cialit  
  pid  miologie

ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS : EPIDEMIOLOGIE ET SCIENCES
DEL'INFORMATION BIOMEDICALE

Pr  sent  e par

M. Cailiang ZHOU

Pour obtenir le grade de

DOCTEUR de l'UNIVERSIT   PIERRE ET MARIE CURIE

Sujet de la th  se :

**Facteurs environnementaux et psychologiques et asthme infantile
(Environmental and psychological factors and childhood asthma)**

soutenue le 10 Mars 2014

Devant le jury compos   de :

Mme Isabella Annesi-Maesano	Directrice de th��se
M Denis BARD	Rapporteur
M Jacques DE BLIC	Rapporteur
Mme Annick CLEMENT	Examineur
M Pascal CHANEZ	Examineur
Mme Marie-Jos��phe SAUREL-CUBIZOLLES	Examineur

Thèse réalisée dans l'unité INSERM UMR-S 707 : Epidémiologie, Systèmes d'informationModélisation" au sein de l'équipe EPAR "Epidémiologie des maladies Allergiques et Respiratoires".

Acknowledgements

Formost, i would like to express my deepest gratitude to my advisor, Dr. Isabella Annesi-Maesano, for her continuous and kindly support in everyday life and her patience, motivation, enthusiasm, and immense knowledge in the guidance of the research. I could not have imagined a better advisor and mentor for my Ph.D study.

I would also like to extend my appreciation to my committee members: Dr. Denis Bard; Dr. Jacques De Blic; Dr. Pascal Chanez; Dr. Annick Clement and Dr. Marie-Josèphe Saurel-Cubizolles for their attendance in my thesis defending, their encouragement, and insightful comments on my thesis manuscript.

My sincere appreciation also goes to Dr. Zheng XIE and Dr. Tuohong ZHANG for their help and guidance in Peking University and their great support of my Ph.D study.

Special thanks to my colleagues: Soutrik Banerjee, Nour Baïz, Hassani Youssouf, Wideline Jacques, Malek Bentayeb, Cécile Billionnet, Hulin-Flamant Marion, Vibert Franck, and Fatima Benaissa for their assistance and discussions on the research projects, and my best friends of Gaurav Kumar and Chea Sopheap for their helps in my everyday life.

I would also extend my greatest gratitude to the fellowship of Erasmus Mundus External Cooperation Window (EM ECW) for China, lot 14 coordinated by Lund University.

Last but not the least, i would like to thank my family: my grandmother, my parents, my parents-in-law, my wife and my elder sisters for their spiritually supporting and encouragement during my Ph.D study.

RÉSUMÉ LONG

Introduction

Dans les dernières décennies, la prévalence de l'asthme infantile a constamment augmenté dans les pays développés et a maintenant atteint un plateau dans certains pays. Cependant, l'étiologie de cette augmentation et la complexité de l'asthme présentant différents phénotypes provoqués par une variété de facteurs de risque doivent encore être étudiées. La pollution de l'air (environnement physique) et les facteurs psychologiques (environnement social) ont été considérés comme des facteurs importants pour le développement de l'asthme infantile.

Bien que des politiques aient été mis en œuvre pour réduire la pollution de l'air dans les pays européens, le trafic, les centrales électriques, l'industrie et les activités agricoles continuent à émettre des quantités importantes de polluants. Pour la pollution de l'air extérieur, il s'agit de la pollution de l'air liée au trafic, particules dont $PM_{2.5}$ (de particules d'un diamètre aérodynamique inférieur à $2,5\ \mu m$) et PM_{10} (de particules d'un diamètre aérodynamique inférieur à $10\ \mu m$), NO_x (oxyde d'azote), CO (monoxyde de carbone), COV (composés organiques volatils), SO_2 (dioxyde de soufre), O_3 (ozone), benzène et de la pollution dérivée de la combustion du charbon et d'autres combustibles dans des installations industrielles ainsi que des pollens et des moisissures. Pour la pollution de l'air intérieur, il s'agit de polluants caractéristiques de l'habitation, du lieu de travail, école, des centres de soins de jour, des bars... Les polluants de l'air intérieur incluent des composants de la fumée de tabac ambiante, NO_x , NO_2 (dioxyde d'azote), COV, $PM_{2.5}$ et PM_{10} , moisissures et allergène. Les principales sources de polluants de l'air intérieur sont : fumée du tabac, de l'humidité dans la maison ou à l'école, chauffage domestique, cuisine, peintures, et le contact avec les animaux. Fait à noter, la corrélation entre les polluants de l'air extérieur et les polluants de l'air intérieur par le biais du transfert lors de l'ouverture des fenêtres. Les polluants de l'air extérieur et intérieur peuvent être mesurés objectivement et subjectivement.

Plusieurs études font état d'un lien entre l'exposition à court terme à la pollution de l'air extérieur et dans la cas de l'asthme infantile l'augmentation des crises, les hospitalisations et l'utilisation des médicaments de l'asthme, tandis que l'exposition à long terme à la pollution de l'air extérieur est liée à l'augmentation de la prévalence et l'incidence de l'asthme infantile et des hospitalisations. Les expositions à court terme à des polluants de l'air intérieur sont associées à une augmentation des exacerbations d'asthme, et à une augmentation de la prévalence. Cependant, l'association entre l'exposition à long terme aux polluants de l'air intérieur et le développement de l'asthme infantile n'est pas entièrement établie. Les résultats les plus consistants sont ceux sur les relations entre l'asthme et la fumée de tabac dans l'environnement, l'humidité ou les moisissures et la proximité résidentielle à une route très fréquentée en termes de trafic.

En ce qui concerne les facteurs psychologiques, ils comprennent plusieurs niveaux micro ou individuel, méso et macro. Pour les facteurs psychologiques au niveau micro, ils se composent de stress perçu, de dépression, d'anxiété, des événements de la vie, des problèmes de comportement, alors que le niveau méso inclut le stress dans la famille, la violence dans la famille, la violence dans la communauté, et le soutien social. Enfin, les facteurs au niveau macro sont associés à la structure sociale. Cependant, aucune étude épidémiologique ou clinique n'a trouvée de relation significative pour les relations entre les facteurs psychologiques du niveau macro et l'asthme infantile. Des relations, en revanche, ont été trouvées dans le cas du stress et de la dépression de la mère.

Bien que les données sur les relations entre l'exposition aux polluants atmosphériques et l'asthme d'un côté et entre les facteurs psychologiques et l'asthme de l'autre soient en augmentation, peu d'études ont investigué l'impact des interactions entre l'exposition aux polluants atmosphériques et les caractéristiques psychologiques sur l'asthme infantile. Les objectifs de cette thèse sont d'examiner l'hypothèse selon laquelle les caractéristiques psychologiques constituent un modificateur de la relation entre l'exposition polluants atmosphériques et l'asthme infantile.

A cet effet, nous avons utilisé les données de l'Etude des 6 villes, avec dessein transversales, et l'étude de cohorte mère-enfant de type longitudinale EDEN (Étude sur les Déterminants pré et postnatals du développement de la santé l'ENfant) pour examiner cette hypothèse.

Population et les méthodes d'étude

L'Etude des 6 villes est la phase II de l'étude internationale de l'asthme et des allergies dans l'enfance (International Study of Asthma and Allergies in Childhood) menée en France entre Mars 1999 et Octobre 2000. Cette étude a recruté 9615 enfants âgés en moyenne de 10 ans dans 6 villes (Créteil, Reims, Marseille, Strasbourg, Clermont-Ferrand, Bordeaux) de la France métropolitaine. Les enfants venaient de 108 écoles sélectionnées au hasard dans les six villes. Dans la thèse, nous n'avons inclus que les enfants qui résidaient à leur adresse actuelle depuis plus de 3 ans et qui avaient rempli le échelles sur les problèmes d'émotion et de comportement (échantillon total de 4209). La concentration en polluant de benzène, CO, NO₂, NO_x, PM₁₀ (de particules d'un diamètre aérodynamique inférieur à 10 µm), et COV aux 108 adresses des écoles ont été estimées par un modèle de dispersion via le logiciel STREET® 5, en utilisant les données de la moyenne des polluants de 3 ans (1998-2000). Les facteurs psychologiques, à savoir les problèmes d'émotion et de comportement, ont été mesurées par deux échelles (symptômes émotionnels et les problèmes de comportement) du questionnaire Point-forts – Point faibles (SDQ-Fra). Obtenir un score total entre 0 et 8 a été défini comme des « problèmes émotionnels et de comportement (PEC) », tandis qu'obtenir un score entre 9-20 a été défini comme « aucune émotion et aucun problèmes de comportement (Non PEC) ». Les symptômes et maladies ont été déterminés à l'aide de réponse à un questionnaire standardisé. Le sifflement actuel a été défini par une réponse « oui » à la question « Au cours des 12 derniers mois, votre enfant a-t-il eu des sifflements dans la poitrine ? ». L'asthme diagnostiqué actuel a été défini par : (i) une réponse « oui » à la question « Est-ce que l'asthme de votre enfant a été diagnostiquée par un médecin », (ii) crise de sifflement au cours des 12 derniers mois et (ou) utilisation de médicaments pour soigner l'asthme au cours des 12 derniers mois. Nous avons également inclus l'eczéma actuel, car hautement lié à l'asthme. L'eczéma actuel a été défini comme démangeaisons dans les zones de flexion (les plis des coudes, derrière les genoux, en avant des chevilles, sous les fesses, autour du cou, autour des yeux ou de oreilles) au cours des 12 derniers mois.

L'étude EDEN est une étude de cohorte en cours qui a recruté (< 24 semaines d'aménorrhée (SA)) 2002 femmes enceintes à Nancy et à Poitiers en 2003 (<https://eden.vjf.inserm.fr>). Les critères de non- inclusion étaient les suivants: 1) grossesse gémellaire; 2) diabète maternel avant la grossesse; 3) quittant la région au cours des 3 prochaines années ; 4) ne pas parlant ou lisant le français . Nous avons mené la première enquête par questionnaire standardisé lorsque les femmes étaient à 24-28 SA. Nous avons ensuite suivi les paires mère-enfant à la naissance, 4 mois 8 mois, 12 mois, 2 ans, 3 ans, 4 ans et 5 ans, 8 ans (données pas montrées pour cette dernière période) de l'enfant. Le nombre total de couples mère-enfant suivi aux âges de 1, 2, 3, 4, et 5 ans de l'enfants était 1765, 1436, 1313, 1228, et 1139, respectivement. Dans la thèse, nous avons inclus les enfants ne se déplaçant pas hors de la région dans la première année de la vie et sans données manquantes sur l'exposition aux polluants de l'air extérieur *in utero* et la première année de la vie, et la dépression maternelle pendant la grossesse (échantillon total de 1222 dans le premier 3 ans, et 722 dans les 5 premières années). Les expositions précoces de la vie au tabagisme parental, la pollution de l'air liée au trafic, l'humidité, les moisissures, les agents de blanchiment, les acariens, les animaux domestiques et le chauffage domestique ont été évaluées par des questionnaires remplis par les parents des enfants. Les concentrations en polluant de benzène , CO, NO₂, SO₂, PM₁₀ et de COV aux adresses résidentielles *in utero* et à la première année de la vie ont été estimées par un modèle de dispersion via le logiciel STREET® 5, en tenant compte des données de la pollution de l'air ambiant, les caractéristiques de la circulation véhiculaire, et les caractéristiques topographique et météorologique de l'adresse. Le facteur psychologique que nous avons évaluée dans l'étude EDEN sont la dépression maternelle prénatale, qui a été évaluée à l'aide de l'Échelle d'évaluation de l'état dépressif du Centre d'études épidémiologiques (CES-D), contenant 20 éléments. Le score total va de 0 à 60 pouvait être obtenu. Les scores totaux entre 0-2 ont été exclus de l'analyse parce que ces scores extrêmement bas sont considérés comme un déni de symptômes dépressifs. Dans les analyses, la dépression maternelle prénatale a été définie comme une variable binaire: présence de dépression maternelle (score total

≥ 16) et absence de dépression maternelle (score total < 16). Les événements de santé ont été évalués par questionnaire standard. Les «sifflements dans la vie» a été défini par une réponse «oui» à la question de «Votre enfant a-t-il eu des sifflements dans la poitrine?». L'asthme diagnostiqué dans la vie a été définie par une réponse «oui» à la question de «Votre enfant a-t-il eu un asthme diagnostiqué par un médecin?». L'eczéma diagnostiqué par un médecin a été identifié par «oui» aux toutes questions : «Votre enfant a-t-il eu un eczéma diagnostiqué par un médecin?», «Votre enfant a-t-il eu sur la peau une éruption (plaques rouges , boutons ...) qui démange (envie de se gratter), et qui apparaît et disparaît par intermittence», et «Cette éruption qui démange, a-t-elle, touché l'une des zones suivantes: les plis des coudes, derrière les genoux, en avant les chevilles, sous les fesses, autour du cou, autour des yeux ou des oreilles?». La rhino-conjonctivite allergique a été identifiée par des réponses positives aux questions suivantes : «Votre enfant a-t-il eu des éternuements, le nez qui coule ou le nez bouché alors qu'il n'avait pas d'infection respiratoire (ni rhume, ni rhinopharyngite, ni grippe...)», et «ces problèmes de nez étaient-ils accompagnés de larmoiements (pleurs) ou de démangeaisons (envie de se gratter) des yeux?». L'état de santé de l'enfant a été évalué dans les vagues de l'enquête menée lorsque les enfants avaient 4 mois, 8 mois, 12 mois, 2 ans, 3 ans , 4 ans, et 5 ans respectivement. Dans chaque vague, la prévalence et l'incidence de l'événement de santé ont été calculées.

Les résultats ont été présentés par des moyens et écarts-types lorsque les variables étaient continues, et par des pourcentages lorsque les variables étaient catégoriques. Une régression logistique multivariée a été utilisée pour analyser les relations entre l'exposition aux polluants de l'air ou les caractéristiques psychologiques et les événements de santé, en cas d'exposition évaluée en même temps que la santé, après ajustement sur les facteurs de confusion potentiels. Les modèles marginaux ont été appliqués pour la prise en compte de la non-indépendance des données des enfants mesurées à maintes reprises dans les différentes vagues de l'enquête lors de leur suivi longitudinal, ou dans le cas d'enfants qui vivaient dans la même communauté ou fréquentaient la

même école/class. Les modèles les marginaux ont été estimés par la méthode de Generalized Estimation Equation (GEE), en utilisant les matrices de corrélation échangeables. Les odds ratios ajustés (aOR) et l'intervalle de confiance de 95 % (IC) ont été utilisés pour estimer les relations entre l'exposition aux polluants de l'air ou les facteurs psychologiques et les résultats de santé. L'impact de chaque exposition sur la santé a été estimé par le risque attribuable de population ajusté (aPAR), la fraction de la morbidité a connu dans la population qui n'aurait pas eu lieu si l'effet associé au facteur de risque d'intérêt était absent. Le prise en compte des interactions entre la pollution de l'air et les facteur psychologiques a été faite en incluant le produit des deux dans les modèles. Nous présentons dans la thèse les aPARs avec signification statistique. Une exposition élevée à la pollution a été définie par une augmentation interquartile de la concentration des polluants.

Résultats

Les données ont montré qu' à la fois les polluants atmosphériques mesurés subjectivement et les polluants atmosphériques mesurés objectivement étaient associés à l'asthme infantile, avec une augmentation du risque d'asthme chez les enfants qui étaient exposés à des niveaux élevés de divers polluants atmosphériques. Dans l'Etude des 6 villes, les polluants de l'air ambiant (benzène, CO, NO₂, NO_x, SO₂, PM₁₀ et COV) évalués par le modèle de dispersion étaient associés à l'asthme infantile. Dans la première année de vie des enfants de l'étude EDEN, plusieurs phénotypes de l'asthme étaient corrélés positivement au tabagisme parental, à la pollution de l'air liée au trafic et à l'humidité, mais négativement au contact avec les chats et au chauffage au bois domestique. L'exposition au trafic dans la vie *in utero* et pendant la première année de vie avaient un impact plus important que les autres polluants sur les phénotypes de l'asthme chez les enfants. Pour les expositions relevant de la première année de vie, les aORs pour la pollution de l'air liée au trafic étaient les plus élevés (1,71 (95% IC: 1,08-2,72)) pour l'asthme diagnostiqué, bronchiolite avec sifflement (1,44 (95% IC: 1,05-1,99)), et l'asthme diagnostiqué avec une histoire de la bronchiolite (2,01 (95 % IC: 1,23-3,30)). Les aPARs sur la base de ces aORs étaient 13,52% , 9,39% et 17,78 %, respectivement. Les résultats persistaient dans le cas du tabagisme maternel prénatal et du trafic dans la vie *in utero*, bien que des associations statistiquement significatives aient été observées seulement avec le phénotype de bronchiolites.¹

En considérant les 5 premières années de vie de l'enfant de l'étude EDEN, le tabagisme maternel pendant la grossesse était lié au développement des sifflements dans les 5 années (aOR=1,24, 95% IC: 1,01-1,52; aPAR=4,54, 95% IC: 0,23-8,03), tandis que l'exposition *in utero* à la pollution de l'air du trafic était liée au développement des sifflements (aOR=1,23, 95% IC: 1,01-1,50; aPAR=5,38, 95% IC: 0,28-9,29) et de la rhino-conjunctivitis allergiques (aOR=1,71, 95% IC: 1,16-2,52; aPAR=13,72, 95% IC: 4,56-19,88) à 5 ans. Cependant, aucune relation significative n'était observée entre les polluants de

¹ **Zhou C**, Baiz N, Zhang T, Banerjee S, Annesi-Maesano I. Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. BMC Public Health. 2013 May 24;13(1):506.

l'air ambiant mesuré objectivement (benzène, CO, NO₂, SO₂, PM₁₀ et de COV) et le développement de l'asthme et des allergies au cours des 5 premières années (papier soumis).

Les analyses sur les relations entre les facteurs psychologiques et de l'asthme infantile ont montré une association entre les problèmes comportementaux et la prévalence de l'asthme et de l'eczéma, l'asthme sévère et l'apparition de l'asthme précoce dans l'Etude des 6 villes. Les enfants présentant des symptômes émotionnels anormaux ou des problèmes de comportement étaient plus asthmatiques que les autres ($P < 0,01$). Par rapport à la normalité, les symptômes émotionnels anormaux et les problèmes de comportement étaient liés à l'asthme persistant léger à modéré (aOR = 1,55 (95 % IC: 1,26-1,90) et 1,42 (95 % IC: 1,17-1,71), respectivement) et à l'asthme à début précoce (risque relatif ajusté par modèle de Cox = 1,60 (95 % IC: 1,27-2,01) et 1,34 (95 % IC: 1,05-1,70)).² Dans l'étude EDEN, la dépression pendant la grossesse a été trouvée associée avec le développement de la rhino-conjonctivite allergique (aOR = 1,87, 95 % IC: 1,33-2,62) dans les 5 premières années de vie. Aucune relation significative n'a été trouvée entre la dépression maternelle pendant la grossesse et les sifflements, l'asthme diagnostiqué et l'eczéma diagnostiqué (aOR = 1,12 (95 % IC = 0,91-1,39), 1,23 (95 % IC = 0,81-1,85) et 1,17 (95 % IC = 0,86-1,61, respectivement).³

La prise en compte des interactions entre les polluants de l'air et les facteurs psychologiques ont montré que les relations entre les polluants de l'air et l'asthme infantile étaient modifiées par des facteurs psychologiques. Les enfants ayant des problèmes d'émotion et de comportement avaient odds ratios ajustés de 1,17 à 1,51 fois plus élevés pour les associations entre les polluants de l'air ambiant (benzène, CO, NO₂, NO_x, PM₁₀, COV), et les phénotypes de l'asthme et de l'eczéma actuel que les enfants sans problèmes émotionnels et de comportement dans le cas de l'Etude des 6 villes. Le terme d'interaction entre les symptômes émotionnels et les problèmes de comportement et les

² Annesi-Maesano I, **Zhou C**, Baiz N, Banerjee S, André Charpin D, Caillaud D, de Blay F, Raherison C, Lavaud F. Externalizing and internalizing behavioural problems related to asthma in school children. *Allergy* 2013; 68: 1471–1474.

³ **Zhou C**, Baiz N, Banerjee S, Charpin DA, Caillaud D, de Blay F, Raherison C, Lavaud F, Annesi-Maesano I. The relationships between ambient air pollutants and childhood asthma and eczema are modified by emotion and conduct problems. *Ann Epidemiol.* 2013 Dec;23(12):778-83.

polluants de l'air ambiant étaient significatifs (P -valeur interaction $<0,20$ pour phénotypes de l'asthme et d'eczéma respectivement). Une augmentation interquartile des expositions à benzène, NO_x et COV a été mise en relation avec les sifflements actuels (aOR=1,22 (95 % IC : 1,00-1,50), 1,35 (95 % IC : 1,06-1,72) et 1,43 (95 % IC : 1,03-2,00), respectivement), alors que l'exposition à NO_x a été liée aussi à l'asthme diagnostiqué actuel (aOR=1,30 (95 % IC : 1,01-1,67)), chez les enfants avec problèmes émotionnels et de comportement. Cependant, aucune relation n'a été trouvée entre les polluants de l'air ambiant et les phénotypes de l'asthme chez les enfants sans problèmes émotionnels et de comportement. De même, l'eczéma actuel était associé à une augmentation interquartile des expositions à benzène, CO, NO_2 , NO_x , PM_{10} et de COV (aOR=1,48 (95 % IC : 1,24-1,75), 1,42 (95 % IC : 1,24-1,62), 1,52 (95 % IC : 1,31-1,77), aOR=1,55 (95 % IC : 1,30-1,85), 1,43 (95 % IC : 1,24-1,66), et 1,54 (95 % IC : 1,21-1,96), respectivement), chez les enfants avec les problèmes émotionnel et de comportement. Les relations persistaient chez les enfants sans problèmes émotionnels et de comportement en cas d'exposition à CO, NO_2 et PM_{10} (aOR=1,16 (95 % IC : 1,03-1,30), 1,24 (95 % IC : 1,08-1,43) et 1,18 (95 % IC : 1,04-1,34), respectivement). Chez les enfants de l'étude EDEN, une interaction était observée entre le tabagisme maternel pendant la grossesse et la dépression prénatale par rapport à l'asthme diagnostiqué au cours des 5 premières années de vie (aOR= 1,56, 95 % IC: 0,74-3,29 pour les enfants avec la dépression maternelle prénatale, aOR= 0,78, 95 % IC: 0,45-1,33 pour les enfants sans la dépression maternelle prénatale, P -valeur interaction: 0,14). Il y avait aussi une interaction entre l'exposition *in utero* à la pollution de l'air liée au trafic et la dépression pendant la grossesse dans le cadre du développement des sifflements au cours des 5 premières années de vie (aOR= 1,68, 95 % IC: 1,15-2,43 pour les enfants avec la dépression maternelle prénatale, aOR= 1,13, 95 % IC: 0,89-1,43 pour les enfants sans la dépression maternelle prénatale, P -valeur interaction: 0,08). En ce qui concerne les polluants de l'air mesuré objectivement dans l'étude EDEN, l'interaction n'était qu'entre l'exposition au benzène et la dépression pendant la grossesse par rapport à l'eczéma diagnostiqué au cours des 5 premières années de vie chez l'enfant (P -valeur interaction: 0,17).

Conclusions

En conclusion, nos résultats fournissent de nouvelles données sur les relations entre les polluants atmosphériques mesurés subjectivement et objectivement et/ou les facteurs psychologiques (problèmes comportementaux et de dépression maternelle pendant la grossesse) et l'asthme infantile, ce qui suggère de considérer les enfants ayant des problèmes psychologiques comme une population sensible aux effets néfastes des polluants atmosphériques et de prendre en compte ces facteurs simultanément dans le paradigme de la prévention de l'asthme infantile.

Mots clés: Enfants, pollution atmosphérique, facteurs psychologiques, asthme, allergies, interaction

RÉSUMÉ

Les objectifs de cette thèse est d'examiner l'hypothèses selon laquelle les caractéristiques psychologiques constituent modificateur de la relation entre l'exposition aux polluants atmosphériques et l'asthme infantile.

A cet effet, nous avons utilisé les données de l'Etude des 6 villes avec dessein transversale, et l'étude de cohorte mère-enfant de type longitudinale EDEN (Étude sur les Déterminants pré et postnatals du développement de la santé l'ENfant) pour examiner cette hypothèse.

Les données ont montré qu'à la fois les polluants atmosphériques mesurés subjectivement et les polluants atmosphériques mesurés objectivement étaient associés à l'asthme infantile. Les analyses sur les relations entre les facteurs psychologiques et de l'asthme infantile ont montré une association entre les problèmes comportementaux et la prévalence de l'asthme et de l'eczéma, l'asthme sévère et l'apparition de l'asthme précoce dans l'Etude des 6 villes et la dépression pendant la grossesse était associée au développement de la rhino-conjonctivite allergique au cours des 5 premières années de vie chez les enfants de l'étude EDEN. La prise en compte des interactions entre les polluants de l'air et les facteurs psychologiques ont montré que les relations entre les polluants de l'air et l'asthme infantile étaient modifiées par les facteurs psychologiques.

En conclusion, nos résultats fournissent de nouvelles données sur les relations entre les polluants atmosphériques mesurés subjectivement et objectivement et/ou des facteurs psychologiques (problèmes comportementaux et de dépression maternelle pendant la grossesse) et l'asthme infantile, ce qui suggère de considérer les enfants ayant des problèmes psychologiques comme une population sensible aux effets néfastes des polluants atmosphériques et de prendre en compte ces facteurs simultanément dans le paradigme de la prévention de l'asthme infantile .

Mots clés: Enfants, pollution atmosphérique, facteurs psychologiques, asthme, allergies, interaction

ABSTRACT

The purposes of this thesis are to examine the hypothesis according to which psychological features are a modifier of the relation between exposure to air pollution and childhood asthma.

To this extent, we used the data from the cross-sectional French 6 Cities Study and the longitudinal EDEN (Study of pre- and post-natal determinants of children's growth and development) mother-child cohort study to examine the hypothesis.

The data show that both subjectively and objectively measured air pollutants were related to childhood asthma. The analyses on the relationships between psychological factors and childhood asthma and allergies yielded that children with behavioral problems had a higher odds ratio in relation to prevalences of asthma and eczema, asthma severity and early asthma onset in the French 6 Cities study and maternal depression during pregnancy was associated with the development of allergic rhinoconjunctivitis in the first 5 years of life in children of the EDEN mother-child cohort study. Taking into account the interactions between air pollutants and psychological factors, results showed that the relationships between air pollutants and childhood asthma were modified by psychological factors.

In conclusion, our results add new evidence on the relationships between subjectively and objectively measured air pollutants and/or psychological factors (behavioral problems and maternal depression during pregnancy) and childhood asthma and imply to consider children with psychological problems as a population susceptible to the detrimental effects of air pollutants and take into account these factors simultaneously into the paradigm of childhood asthma prevention.

Keywords: Children, air pollutants, psychological factors, asthma, allergies, interaction

Valorisation des travaux de thèse

Articles publiés

- 1 **ZHOU C**, BAIZ N, ZHANG T, BANERJEE S, ANNESI-MAESANO I; EDEN Mother-Child Cohort Study Group. Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. BMC Public Health. 2013 May; 13(1):506.
- 2 **ZHOU C**, BAIZ N, BANERJEE S, CHARPIN D, CAILLAUD D, BLAY F, RAHERISON C, LAVAUD F, ANNESI-MAESANO I. The relationships between air pollutants, and childhood asthma and eczema are modified by emotion and conduct problems. Annals of Epidemiology. 2013 September; 23(12):778-83.
- 3 ANNESI-MAESANO I, **ZHOU C**, BAIZ N, BANERJEE S, CHARPIN D, CAILLAUD D, BLAY F, RAHERISON C, LAVAUD F. Externalizing and internalizing behavioral problems related to asthma in school children. Allergy. 2013 July; 68(11):1471-4.

Articles soumis ou à soumettre (et insérés dans le manuscrit)

ZHOU C, BAIZ N, BANERJEE S, ANNESI-MAESANO I; EDEN Mother-Child Cohort Study Group. Maternal depression during pregnancy according to CES-D related to allergic rhinoconjunctivitis in the first 5 year of life in children of the EDEN mother-child cohort study. Epidemiology. (Soumis)

Communications Scientifiques

1. **ZHOU C**, BAIZ N, BANERJEE S, CHARPIN D, CAILLAUD D, BLAY F, RAHERISON C, LAVAUD F, ANNESI-MAESANO I. Emotions and conducts problems as modifiers of the relationship between air pollutants and childhood asthma. Les Journées de l'Ecole. Paris, France. October 2012. (Communication Poster).
2. **ZHOU C**, BAIZ N, ZHANG T, BANERJEE S, ANNESI-MAESANO I; EDEN Mother-Child Cohort Study Group. Modifiable environmental exposures related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. Le 5ème Journée des Docs et Post-docs de Saint-Antoine. Paris, France. May 2012. (Communication Orale).
3. **ZHOU C**, BAIZ N, ZHANG T, BANERJEE S, ANNESI-MAESANO I; EDEN Mother-Child Cohort Study Group. Environmental exposures and asthma-related outcomes in the first year of life in children: the EDEN mother-child cohort study. Journées des maladies respiratoires (J2R). Toulouse, France. October 2011. (Communication Poster).

Abbreviations

ADRB2	Beta-2 adrenergic receptor
aOR	Adjusted Odds Ratio
aPAR	Adjusted Population Attributable Risk
API	Asthma Predictive Index
BaP	Benzo(a)pyrene
BMI	Body Mass Index
CALINE4	California LINE Source Dispersion Model, version 4
CBCL	Child Behavior Checklist
CCEI	Crown-Crisp Experiential Index
CCPPRB	<i>Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biomédicales</i>
CDI	Child Depression Index
CES-D	Centre for Epidemiological Studies-Depression scale
CHCE	Composite Household Chemical Exposure
CI	Confidence Interval
CNIL	<i>Commission Nationale de l'Informatique et des Libertés</i>
CO	Carbon Monoxide
ECBI	The Eyberg Child Behavior Inventory
ECPs	Emotion and Conduct Problems
EPSs	Extracellular Polysaccharides
ETS	Environmental Tobacco Smoke
EU	European Union
EWAS	Environment-wide Associations Study
GEE	Generalized Estimating Equation (Equations estimées généralisées)
GINA	Global Initiative for Asthma
GIS	Geographic Information System
HR	Hazard Ratio
HPA	Hypothalamo-Pituitary-Adrenal
IFN-γ	Interferon gamma
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-8	Interleukin 8
IL-13	Interleukin 13
IL-23	Interleukin 23
INSERM	<i>Institut National de la Santé Et de la Recherche Médicale</i>
IPV	Intimate Partner Violence
IQR	Interquartile Range
ISAAC	International Study of Asthma and Allergies in Childhood
LR	Likelihood Ratio

MOSSS	Medical Outcome Study Social Support Survey
NH₃	Ammonia
NMVOCs	Non-Methane Volatile Organic Compounds
NO₂	Nitrogen Dioxide
NO_x	Nitrogen Oxide
O₃	Ozone
OR	Odds Ratio
Pb	Lead
POPs	Persistent Organic Pollutants
PPB	Parts-per-billion
PM_{2.5}	Particulate Matter with an Aerodynamic Diameter Below 2.5µm
PM₁₀	Particulate Matter with an Aerodynamic Diameter Below 10 µm
PSS	Perceived Stress Scale
PSS4	The 4-item Perceived Stress Scale
QIC	Quasilikelihood under the Independent Model Criteria
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SLEP	Stressful Life Events during Pregnancy
SO₂	Sulfur Dioxide
SO_x	Sulfur Oxide
SPT	Skin Prick Test
STAIC	The State-trait Anxiety Inventory for Children
STAT6	Signal Transducer and Activator of Transcription 6
Th1	T Helper Type 1
Th2	T Helper Type 2
Total PAH	Polycyclic aromatic hydrocarbon
VOCs	Volatile Organic Compounds
WA	Weeks of Amenorrhea

Contents

RÉSUMÉ LONG.....	4
RÉSUMÉ	15
ABSTRACT	17
Valorisation des travaux de thèse	19
Abbreviations	21
Contents	23
1. Introduction.....	25
1.1 Air pollution and childhood asthma	27
1.2 Psychological features and childhood asthma	40
1.3 Interactions between air pollutants and psychological features in relation to childhood asthma	44
1.4 Rationale and hypotheses of the thesis	45
1.5 Conceptual framework of the thesis	46
1.6 Objective of the thesis.....	47
2. Study population and methods	48
2.1 Introduction of the study protocols	48
2.2 Study population	51
2.3 Assessment of air pollutants	52
2.4 Assessment of psychological features.....	53
2.5 Assessment of health outcomes	55
2.6 Statistical analysis.....	57
3. Air pollutants and childhood asthma	61
3.1 Evidence from the French 6 Cities study	62
3.2 Evidence from the EDEN mother-child cohort study	63
4. Psychological features and childhood asthma	81
4.1 Evidence from French 6 cities study.....	81
4.2 Evidence from the EDEN mother-child cohort study	87
5. Interaction between air pollutants and psychological features in relation to childhood asthma	
100	

5.1 Evidence from French 6 cities study.....	100
5.2 Evidence from EDEN mother-child cohort study.....	111
6. Discussion	114
6.1 The measurement of air pollutants.....	114
6.2 Identification of health outcomes	116
6.3 Relationships between air pollutants and childhood asthma	117
6.4 Relationships between psychological features and childhood asthma	119
6.5 Interactions between air pollutants and psychological features in relation to childhood asthma	122
6.6 Potential mechanisms for the impacts of environmental and psychological factors on childhood	124
6.7 Conclusion	127
7. Strengths and limitations	128
7.1 Strengths	128
7.2 Limitations	129
8. Perspectives.....	130
References.....	132

1. Introduction

Asthma is defined as “a chronic inflammatory disorder of the airway in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment”¹. Childhood has been considered as a critical period for the development of asthma as the lung, the respiratory system and the immune system are developing. In the past decades, the prevalence of childhood asthma has increased constantly in western developed countries and only now has reached a plateau in some countries²⁻⁷. However, the increase of childhood asthma has still to be explained. In addition, asthma is a complex disease presenting various phenotypes caused by a variety of risk factors (Fig. 1)⁸⁻⁹, namely a genetic susceptibility in the presence of certain environmental stressors and conditions (see Fig. 2).

Air pollution (physical environment) and psychological features (social environment) that have known important variations during childhood asthma prevalence increase¹⁰⁻¹⁸ have been considered as important factors to be taken into account in order to explain the complex etiology of childhood asthma and thus its evolution. Nevertheless, although the impact of air pollution on asthma and allergies has been largely investigated with more evidence for asthma than for other allergies, the effects of psychological factors on these affections have rarely studied at the population level. In addition, few studies have investigated the interactions between air pollution and psychological features and the combined effects on childhood asthma of concurrent exposures to multiple risk factors. Yet, promising results have shown the existence of an interaction between air pollution and

some psychological factors with an increased impact of air pollution in individuals presenting psychological troubles¹⁷.

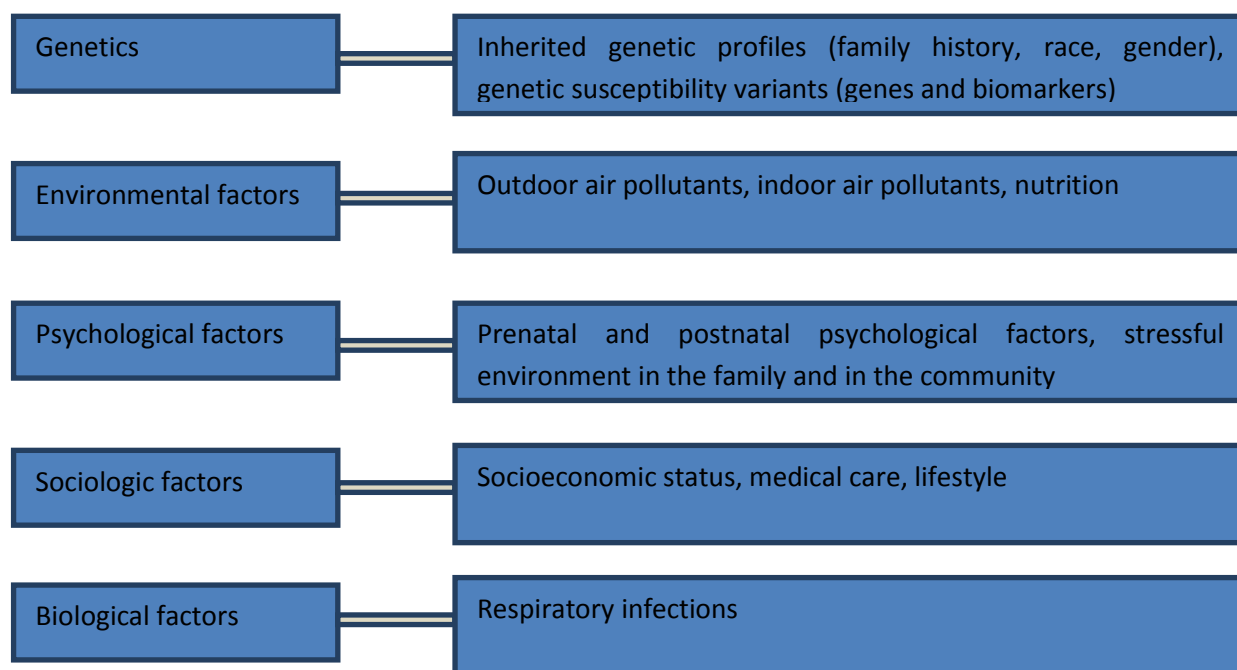


Fig. 1: Risk factors for childhood asthma

1.1 Air pollution and childhood asthma

Although policies have been implemented to reduce the air pollution in European countries, traffic, power plants, industry, household and agricultural activities continue to emit significant amount of air pollution¹⁹. Data from European Environment Agency (<http://www.eea.europa.eu/highlights/eu-meets-most-international-air>) showed that since 1990, emission of the main air pollutants of lead (Pb), sulfur oxide (SO_x), Carbon Monoxide (CO), non-methane volatile organic compounds (NMVOCs), polycyclic aromatic hydrocarbon (total PAH), nitrogen oxide (NO_x), benzo(a)pyrene (BaP) and ammonia (NH₃) decreased by 89 %, 82 %, 64 %, 59 %, 58 %, 48 %, 45 % and 28 % respectively, and emission continued to reduce between 2010 and 2011. However, emissions of ozone (O₃), particulate matter (PM), and persistent organic pollutants (POPs) have not decreased substantially. Table 1 presents the proportion of the European Union (EU) urban population exposed to pollutant concentration levels above the limit and target values set in EU legislation and the World Health Organization (WHO) air quality guidelines between 2009 and 2011¹⁹.

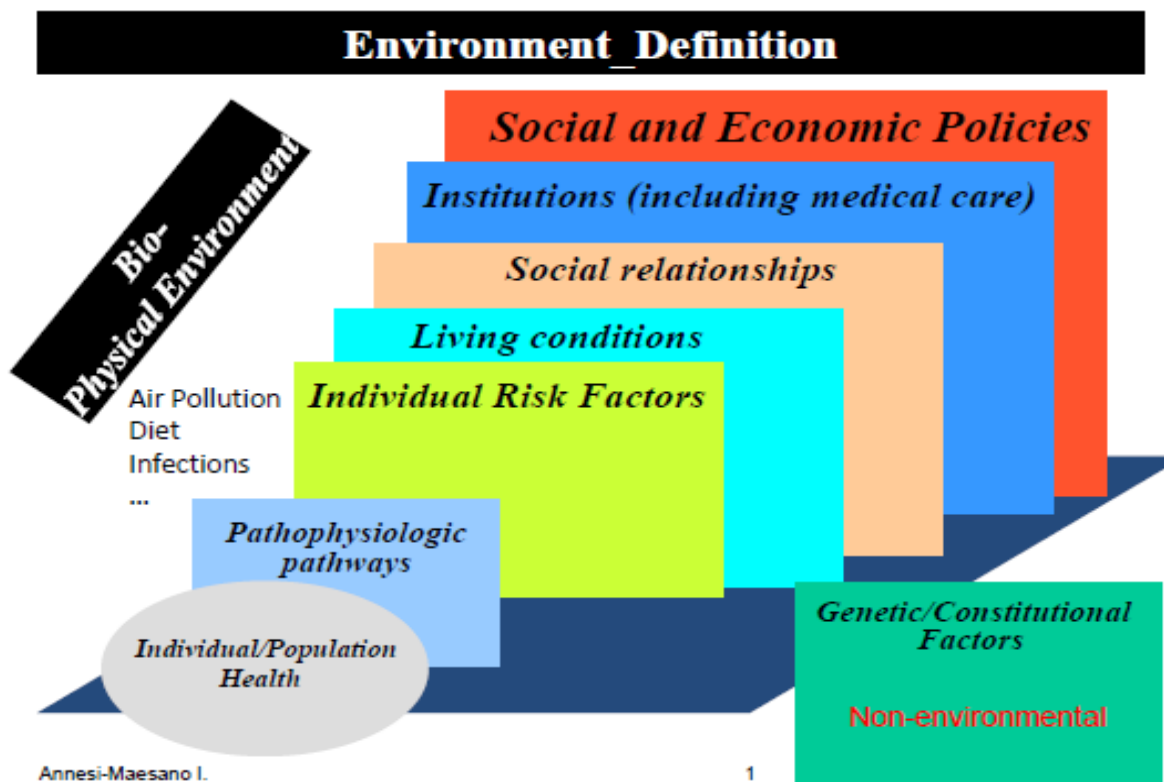


Fig. 2: Environmental and non-environmental factors for childhood asthma (by Annesi-Maesano I.)

In addition, air pollution as one of the environmental factors that influences the diseases²⁰⁻²¹ and the gene expression²², plays an important role in mediating the phenotypic expression of the respiratory system in ways that predisposes children to the development of respiratory and allergic diseases including asthma later in the life²¹.

Table 1— Percentage of the urban population in the EU exposed to air pollutant concentrations above the EU and WHO reference levels (2009-2011)

Pollutant	EU reference value	Exposure estimate (%)	WHO AQG	Exposure estimate (%)
PM _{2.5}	Year (20)	20-31	Year (10)	91-96
PM ₁₀	Day (50)	22-33	Year (20)	85-88
O ₃	8-hour (120)	14-18	8-hour (100)	97-98
NO ₂	Year (40)	5-13	Year (40)	5-13
BaP	Year (1)	22-31	Year (0.12)	76-94
SO ₂	Day (125)	< 1	Day (20)	46-54
CO	8-hour (10)	< 2	8-hour (10)	< 2
Pb	Year (0.5)	< 1	Year (0.5)	< 1
Benzene	Year (5)	< 1	Year (1.7)	12-13
Colour coding:	< 5 %	5-50 %	50-75 %	> 75 %

WHO AQG, WHO air quality guideline; PM_{2.5}, Particulate Matter with an Aerodynamic Diameter Below 2.5µm; PM₁₀, Particulate Matter with an Aerodynamic Diameter Below 10µm; NO₂, nitrogen dioxide; SO₂, sulfur dioxide.

1.1.1 Related sources of outdoor and indoor air pollutants and the methods of assessment

1.1.1.1 Related sources of air pollution

Table 2 presented the main sources of outdoor and indoor air pollutants in relation to childhood exposures. Outdoor air pollutants included traffic-related air pollution, allergen, particulate matter, NO_x, CO, Volatile Organic Compounds (VOCs), SO₂, O₃ and benzene that essentially from the combustion of coal and other fuels in industrial plants and emission of motor vehicles²³.

Indoor air pollution could be from the environment of dwelling, workplace, school, day care centers, bars, et al. Indoor air pollution consists of environmental tobacco smoke (ETS), NO_x, NO₂, VOCs, PM_{2.5}, dampness and molds in the house, and allergen (see table 2). The major sources are related to tobacco smoke, moisture in the home or school, domestic heating and cooking, paints, and contact with pets²³⁻²⁴. Of note, outdoor air pollutants correlate with indoor air pollutants²⁵. Habre R and coworkers²⁵ recently explored the sources of indoor air pollutants in New York city residences of asthmatic children. Results showed that outdoor sources account for 28 % of indoor PM_{2.5} mass.

Table 2— Sources of major outdoor and indoor air pollutants in relation to childhood exposures

Pollutants	Related sources
<u>Outdoor air pollutants</u>	
Traffic-related air pollution	Fuel combustion in vehicles
Allergens	Pollen
Particulate matter	Wild fire; Coal combustion in industrial plants; Fuel combustion in vehicles
NO _x	Mainly from fuel combustion in vehicles and industrial plants
CO	Coal combustion in industrial plants and fuel combustion in vehicles
VOCs	Mainly from fuel combustion in vehicles and industrial plants
SO ₂	Mainly from the emissions of fuel combustion at power plants and sulfuric acid manufacture
O ₃	Production of sunlight acting on NO _x and VOCs that emitted mainly from fuel combustion in vehicles and industrial plants
Benzene	Fuel combustion in vehicles and tobacco smoking
<u>Indoor air pollutants</u>	
Traffic-related air pollution	Mainly from fuel combustion in vehicles passed by the house by opening the windows
Environmental tobacco smoke	Tobacco smoking in the home, school...
Allergen	House dust mites excretion; Pollen; Pets; Molds
Molds	Moisture in the home or school
Particulate matter	Mainly from domestic heating or cooking and tobacco smoke
NO _x	Mainly from domestic fuel heating or cooking
CO	Mainly from domestic heating or cooking; Tobacco smoke
VOCs	New carpet; Glues and adhesives; Paints; Furniture and wood products; Cleaning agents and disinfectants

1.1.1.2 Air pollution assessment

Table 3 presented the methods of assessment of outdoor and indoor air pollutants in relation to childhood exposures²⁶⁻²⁸. The methods of measuring exposures to outdoor air pollutants include standard questionnaires, regional monitoring, proximity modeling, dispersion models, land-use regression, and individually active sampling and passive sampling. The methods of investigating exposures to indoor air pollutants consist of standard questionnaires and individual measurement using active and passive samplers.

Table 3—Methods of assessing exposures to outdoor and indoor air pollutants

Exposures to air pollutants	Methods
<u>Outdoor air pollutants</u>	
<i>Subjectively measured</i>	Standard questionnaire (such as ISAAC questionnaire)
<i>Objectively measured</i>	
Background exposures	Central site/regional monitoring conducted usually by local authority. Eventually coupled with GIS to better estimate air pollution exposure
Proximity exposures	Monitoring exposure to air pollutants at locations near to an emission source; Geographic information system (GIS) based estimating Dispersion models (incorporating background exposures and meteorological data);
Community-based exposures	Land-use regression (combining background exposures with spatially varying characteristics, typically for traffic-related air pollution); Dispersion models (incorporating background exposures and meteorological data);
Personal exposures	Active (pumped) sampling (including badges, tube, radical designs) ; Passive (diffusive) sampling (including badges, tube, radical designs)
<u>Indoor air pollutants</u>	
<i>Subjectively measured</i>	Standard questionnaire (such as ISAAC questionnaire)
<i>Objectively measured</i>	
Personal exposures	Active (pumped) sampling (including badges, tube, radical designs); Passive (diffusive) sampling (including badges, tube, radical designs)
<u>Both indoors and outdoors</u>	
Personal exposures	Active (pumped) sampling (including bages, tube, radical designs) ; Passive (diffusive) sampling (including bages, tube, radical designs)

1.1.2 Relationships between outdoor air pollution and childhood asthma

1.1.2.1 Relationships between short-term exposure to outdoor air pollution and childhood asthma

Evidence has consistently showed that short-term exposure to outdoor air pollution is related to increased asthma attacks and exacerbation, hospitalizations and asthma medication use²⁹⁻³³. O'Connor GT et al²⁹ found that higher daily NO₂ concentration (average of hourly measurements) obtained from the US Environmental Protection Agency Aerometric Information Retrieval System database was associated with more frequent asthma symptoms and asthma-related school absences in children of 7 urban US communities. Yamazaki S and coworkers³⁰ indicated that 24-hour mean concentration of ozone measured by monitoring stations of local authority was related to nighttime primary care visits for asthma attacks in warmer months in children in metropolitan Tokyo. In Greece, a study have showed that mean daily PM₁₀ (Particulate Matter with an Aerodynamic Diameter Below 10 µm) concentration recorded by the air pollution-monitoring network is related to asthma exacerbation among 5-14 year-old children³¹. In addition, short-term exposure to outdoor air pollution could trigger hospitalizations and increase medical use. Iskandar A et al³² have found that short-term exposures to NO_x, NO₂, PM₁₀ and PM_{2.5} were related to increased risk of hospital admissions for asthma in children aged 0-18 years. Slaughter JC³³ and coworkers found that short-term exposure to outdoor air pollution of PM₁₀ and PM_{2.5} was associated to increased risk of more severe asthma attacks and medication use in children with asthma.

1.1.2.2 Relationships between long-term exposure to outdoor air pollution and childhood asthma

Mounting evidence has showed that long-term outdoor air pollution is related to increased childhood asthma prevalence and incidence and hospital admissions^{13, 34-40}. Pénard-Morand C et al¹³

had found that long-term exposure to benzene, SO₂, PM₁₀, NO_x and CO measured by dispersion models was related to childhood asthma in the population-based French 6 Cities study. Erbas B et al³⁵ found that persistent outdoor pollen concentration in infancy (cumulative exposure up to 4-6 months) increases the risk of asthma in children aged 6-7 years. Lin S et al³⁹ indicated that chronic exposure to ambient ozone may increase the risk of hospital admissions among children aged 1-6 years.

As the main sources of air pollution in developed countries, where industrial pollution is decreasing continuously, traffic-related air pollution had been recognized particularly as an important factor for explaining the origins of childhood asthma in these countries^{21, 34, 36, 41-47}. Data of a Swedish birth cohort study showed that exposure to traffic-related air pollution in the first year of life is associated with development of asthma for preschool children⁴¹. In an American cohort study, results implicated that traffic-related air pollution at school and homes may both contribute the development of childhood asthma⁴³. In the past 5 years, the main birth cohort studies investigating the relationship between long-term exposure to traffic-related air pollution and childhood asthma are showed in Table 4. Of all selected cohort studies, 10 cohort studies showed that there was statistically significant causal relationship between traffic-related air pollution and childhood asthma, while only 2 cohort studies indicated no association.

Table 4 — Cohort studies on the relationships between long-term exposure to traffic-related air pollution and childhood asthma

study	Study population	Exposure	Asthma-related outcomes	Odds ratio or Relative risk
Morgenstern V et al ⁴⁷ , 2008	2860 children were followed up from birth to the age of 4 years and 3061 children were followed up until the age of 6 years in Munich metropolitan area, Germany	the distance to the nearest main road, a surrogate for traffic-related air pollution	Doctor-diagnosed and Parent-reported asthmatic bronchitis or asthma	Relationship for traffic-related air pollution and doctor-diagnosed asthma: 1.66 (1.01-2.59); Relationship for traffic-related air pollution and parent-reported asthma: 1.24 (1.01-1.52)
Jerrett M et al ⁴⁸ , 2008	217 children followed up 8 years until the age of 10-18 years in Southern California, US	Personal exposure to NO ₂ measured by passive (diffusion) sampling	Doctor-diagnosed asthma onset	A within-community interquartile range increase in annual residential NO ₂ : 1.28 (1.05-1.57)
Nording E et al ⁴¹ , 2008	4089 children from 4 Swedish municipalities were followed up from birth to 4 years-old age	NO _x and PM ₁₀ from traffic were assessed with a dispersion model	Parent-reported Wheezing	NO _x : 1.60 (1.09-2.36)
Krämer U et al ⁴⁹ , 2009	3390 newborns from small-town areas of Germany followed up until 6 years old age	Distance of the home address to the next major road and land-use regression model based concentration of NO ₂ and soot	Doctor-diagnosed asthmatic bronchitis or asthma	No association; Distance from major road: 0.86 (0.66-1.14); NO ₂ : 1.17 (0.86-1.58); Soot: 1.16 (0.87-1.54)
Oftedal B et al ⁵⁰ , 2009	2871 children followed up from birth to age of 9-10 years in Oslo, Norway	A dispersion model based concentration of NO ₂ and distance to the major road	Parent-reported doctor-diagnosed asthma onset	No association; An interquartile range increase of NO ₂ : 0.82 (0.67-1.02); Distance to major road: 0.99 (0.90-1.08)
Ryan PH et al ⁵¹ , 2009	762 children were enrolled at age 1 year and followed up until the age of 3 years in Cincinnati, US	Land-use regression model based concentration of traffic-related particles	Parent-reported recurrent wheezing and persistent wheezing at 36 months	Relationship between traffic-related particles and persistent wheezing: 1.75 (1.07-2.87)

Gehring, U et al ⁴² , 2010	3863 Netherland children were followed up from birth to 8 years-old age	Individual exposures to NO ₂ and PM _{2.5} at birth address were estimated by land-use regression model	Annual prevalence and incidence of asthma and related symptoms assessed by questionnaires	PM _{2.5} : 1.28 (1.10-1.49) for incidence of asthma; 1.20 (1.04-1.51) for prevalence of asthma and 1.15 (1.02-1.28) for asthma symptoms
McConnell R et al ⁴³ , 2010	2497 kindergarten and first-grade children were followed up for 3 years in South California, America	Traffic-related air pollution were measured annually by a line source dispersion model at school and homes address	New-onset asthma reported on a yearly questionnaire	Near homes: 1.51 (1.25-1.82). Near schools: 1.45 (1.06-1.98)
Clark NA et al ⁵² , 2010	37401 children followed up from birth to the age of 3-4 years in British Columbia, Canada	Land-use regression model based concentration of NO, NO ₂ , black carbon and PM _{2.5}	Doctor-diagnosed asthma identified from physician billing records and from hospital discharge records	10µg/m ³ increase of NO: 1.08 (1.04–1.12); 10µg/m ³ increase in NO ₂ : 1.12 (1.07–1.17); 100µg/m ³ increase in CO: 1.10 (1.06–1.13)
Carlsten C et al ⁵³ , 2011	184 children were followed up from birth to the age of 7 years in Vancouver, Canada	Land-use regression model based concentration of birth year exposures to NO, NO ₂ , black carbon and PM _{2.5}	Doctor-diagnosed asthma	An interquartile range increase of PM _{2.5} : 3.1 (1.3-7.4)
Patel MM et al ⁵⁴ , 2011	593 children followed up from birth to the age of 5 years in New York, US	GIS based residential proximity and density of traffic	Doctor-diagnosed asthma and wheezing reported by parents	Relationship between traffic density and wheezing: 1.25 (1.09-1.42)
Gruzieva O et al ⁴⁶ , 2013	4089 children from 4 Swedish municipalities were followed up from birth to 12 years-old age	NO _x and PM ₁₀ from traffic were assessed with a dispersion model	Parent-reported Wheezing and asthma	PM ₁₀ : 2.0 (1.1-3.5) for the association between exposure during the first year of life and asthma in 12 years-old children

1.1.3 Relationship between indoor air pollution and childhood asthma

Compared with outdoor air pollution, the exposure to indoor air pollution is more frequent than that of outdoor air pollution because people spend 90% of their time indoor globally. In European countries, because of the economic crisis and the decreased availability of oil and other combustion products, people insulated their homes which decreased the air exchange, and more recently used wood heating that reduced the indoor air quality. Considering that infants spend more time in house than adults for too young to walk out by themselves, it is important to assess the influence of indoor air pollution on the health of the children. In addition, pregnant mothers spent most of their time at home, indoor air pollution may also be critical for the pre-natal health of children. According to the WHO report, indoor smoke of solid fuel is the third important factor that contributes to the global burden of disease for 0-4 years' old children⁵⁵.

1.1.3.1 Relationships between short-term exposure to indoor air pollution and childhood asthma

Studies showed that short-term exposure to indoor air pollution was related to increased childhood asthma attacks, prevalence and asthma exacerbation⁵⁶⁻⁵⁸. Zhao Z et al⁵⁶ have found that a 7-day mean concentration of indoor exposure to SO₂ assessed by passive (diffusion) sampling was related to wheezing attacks in Chinese pupils. In France, Annesi-Maesano I et al⁵⁷ indicated that 5-day mean concentration of high level exposures to PM_{2.5}, acrolein and NO₂ measured by passive diffusion samplers were related to increased prevalence of past year asthma in schoolchildren. Hulin M et al⁵⁸ indicated that papers published up to the year 2011 in the peer-reviewed journals consistently support the short-term effect of indoor air pollutants measured quantitatively on asthma exacerbation.

1.1.3.2 Relationships between long-term exposure to indoor air pollution and childhood asthma

In literature, the association between long-term indoor air pollution and the development of childhood asthma is heterogeneous^{12, 58}. The most consistent results are for relationships between environmental tobacco smoke, residential proximity to busy road and household dampness or visible molds¹². Evidence is also reliable for indoor exposure to NO₂ and particles and childhood asthma⁵⁸.

In the past 5 years, the main cohort studies that have investigated the relationships between long-term exposure to indoor air pollutants and childhood asthma are showed in table 5^{12, 51, 59-72}. The evidence for the association between development of childhood asthma and environmental tobacco smoke is quite consistent^{12, 51, 62, 70, 72}. Dampness and molds, as for another important indoor air exposure, is found to have negative effects on childhood asthma^{12, 51, 62-63, 69, 73}. Of note, the evidence on the negative effect of visible molds determined by home inspection and childhood asthma is reliable^{51, 62-63}, but the effect of the microbial components measured by dust sampling is contradictory^{67, 69}. A recent meta-analysis on eight European birth cohorts data showed that exposure to molds in early life is associated with an increased risk of asthma particularly in young children⁷³. Exposures to dampness and molds could also interact with some genes (e.g. signal transducer and activator of transcription 6 (STAT6), interleukin13 (IL13) and beta-2 adrenergic receptor (ADRB2)) to increase the risk of asthma⁷⁴. Results on the relationships between childhood asthma and indoor long-term exposure to NO₂^{59, 65}, particles^{65-66, 68}, VOCs^{12, 61, 65}, pets^{12, 64, 71} and endotoxins^{51, 67} are heterogeneous.

Table 5 — Cohort studies investigated the relationships between long-term exposure to indoor air pollutants and childhood asthma

Studies	Study population	Exposures	Outcomes	Odds ratio/ Relative risk
Hansel NN et al ⁵⁹ , 2008	150 children aged 2-6 years with doctor-diagnosed asthma were followed up for 6 months in	3-day indoor NO ₂ measured by passive bage sampler at baseline, 3 months and 6 months,	Caregiver-reported asthma symptoms	Relationship between nocturnal awakenings due to cough, wheeze, shortness of breath or chest tightness and per 20-ppb (parts-per-billion) increase of NO ₂ : 1.12

	Mayland, US	respectively		(1.04-1.19)
Henderso -n J et al ⁶⁰ , 2008	13988 children were followed up from birth to 7 years of age in Avon, UK	Maternal reported composite household chemical exposure (CHCE) during pregnancy	Parent-reported wheezing	In nonatopic children: per z-score of CHCE for early-onset (<18 months) wheezing, intermediate-onset (18-30 months) persistent wheezing and late-onset (<30 months) wheezing were 1.41 (1.13-1.76), 1.43 (1.02-2.13) and 1.69 (1.19-2.41)
Ryan PH et al ⁵¹ , 2009	762 children were enrolled at age 1 year and followed up until the age of 3 years in Cincinnati, US	Environmental tobacco smoke and visible molds reported by parents, and endotoxins determined by dust sampling	Parent-reported persistent wheezing, recurrent wheezing and asthma predictive index (API)*	Relationships between environmental tobacco smoke, visible molds and endotoxins and API were 2.31 (1.26-4.21), 1.77 (1.04-3.03) and 1.67 (0.95-2.92)
Krauss- Etschman -n S et al ⁶¹ , 2009	176 mother-child pairs were followed up from the birth to 4 years old	Parent-reported room disinfectants	Parent-reported asthma	No associations; Relationship between Room disinfectants and asthma ever: 1.1 (0.4-2.8)
Iossifova YY et al ⁶² , 2009	483 children were followed up from birth to the age of 3 years in Cincinnati, US	Visible molds evaluated by means of home inspection and maternal smoking	Parent-reported asthma predictive index (API)*	Visible molds: 7.1 (2.2-12.6); Maternal smoking: 4.4 (1.7-11.6)
Karvonen AM et al ⁶³ , 2009	396 children followed up from birth to the age of 18 month	Moisture damage and visible molds evaluated by home inspection	Doctor-diagnosed wheezing reported by parents	Moisture damage in the kitchen: 3.85 (1.16-12.76); Visible molds in children's bedroom: 3.86 (1.28-11.69)
Kerkhof M et al ⁶⁴ , 2009	2951 children followed up from birth to the age of 8 years in Netherlands	Parent-reported pet keeping (children with a cat or dog at home)	Parent-reported childhood asthma	No association was found between exposure to pets at any age and childhood asthma
Raaschou -Nielsen, O. et al ⁶⁵ , 2010	411 Danish infants were followed up from birth to 18 months old	Long-term exposure to NO _x , NO ₂ , formaldehyde, PM _{2.5} and black smoke were measured	Parent-reported wheezing	No association was found between wheezing and long-term exposure to indoor air pollution
McCorma -ck MC et al ⁶⁶ , 2011	150 children aged 2-6 years with doctor-diagnosed asthma were followed up for 6	3-day indoor PM _{2.5} and PM _{2.5-10} measured by passive badge sampler at baseline,	Caregiver-reported asthma symptoms	Relationship between nocturnal awakenings due to cough, wheeze, shortness of breath or chest tightness and per 10 µg/m ³ increase

	months in Mayland, US	3 months and 6 months		of PM _{2.5} : 1.09 (1.03-1.14)
Tischer C et al ⁶⁷ , 2011	678 children were followed up from birth to the age of 6 years in 3 European cohort studies	Mold components of (1,3)-β-D-glucan and extracellular polysaccharides (EPSs) and endotoxins	Parent-reported asthma	In Germany children: ORs for EPSs and endotoxins are 0.60 (0.39-0.92) and 0.55 (0.31-0.97), respectively, but no association was observed among Dutch children
Jung, KH et al ⁶⁸ , 2012	408 children at 5-6 years old in New York city were followed up to 6 or 7 years old	PM _{2.5} and black carbon were measured objectively in residential places	Parent-reported Wheezing	PM _{2.5} :1.51(1.05,2.16) per interquartile range; Black carbon: 1.40(0.96, 2.05) per interquartile range;
Reponen T et al ⁶⁹ , 2012	289 children were followed up from birth to the age of 7 years in Cincinnati, US	36 molds measured by dust sampling	Parent-reported asthma	Relationship between summation of 3 mold species, <i>Aspergillusochraceus</i> , <i>Aspergillus unguis</i> , and <i>Penicilliumvariable</i> and asthma: 2.2 (1.8-2.7)
Neuman Å et al ⁷⁰ , 2012	21600 children followed up from birth to the age of 5 years in 8 birth cohort studies in European countries	Parent-reported maternal smoking during pregnancy and maternal smoking during the first year of life	wheeze and asthma at 4 to 6 years of age reported by parents	Adjusted ORs for the relationships between maternal smoking during pregnancy and wheeze and asthma were 1.39 (1.08-1.77) and 1.65 (1.18-2.31), respectively
LødrupCarlsen KC et al ⁷¹ , 2012	11489 children followed up from birth to the age of 6-10 years in Europe	Parent-reported pet keeping in the first 2 years of life of children	Parent-reported allergic asthma	No association between furry and feathered pet keeping early in life and asthma in school age
Bunyavanich S et al ⁷² , 2013	624 twin infants were followed up from birth to 3 years old	Environmental tobacco smoke reported by parents	Doctor-diagnosed asthma reported by parents	Environmental tobacco smoke contribute to variance in susceptibility to doctor-diagnosed asthma in the first year of life

*API was defined as having recurrent wheezing (2 or more wheezing episodes in the previous 12 months) at the age of 3 years and met at least 1 of 3 major criteria (parental history of asthma, allergic sensitization to ≥1 aeroallergens, and eczema (defined as either physician-diagnosed eczema on physical examination or parental report of frequent skin scratching for more than 6 months accompanied by red spots, raised bumps, or rough, dry, scaly skin)) or 2 or 3 minor criteria (wheezing without a cold, physician-diagnosed allergic rhinitis, and allergic sensitization to milk or egg).

1.2 Psychological features and childhood asthma

Several investigations, overall clinical studies, showed that psychological features were related to childhood asthma⁷⁵⁻⁸². Psychological features are well-known trigger of asthma attacks and exacerbations⁷⁹. Studies also showed an increased prevalence of asthma in children experiencing psychological disorders⁸⁰⁻⁸¹. Annesi-Maesano I. has indicated that psychological factors (including social relationships, individual risk factors (psychological)) are important risk factors for developing childhood asthma (see Fig. 2). In addition, Wright RJ has presented an ecological approach for understanding the relationships between stress and asthma in view of epidemiology⁸² (see Fig. 3), showing that the interplay between genetic factors, individual stress, stress related characteristics of family and community *in utero* life and during life course contribute to the development of asthma.

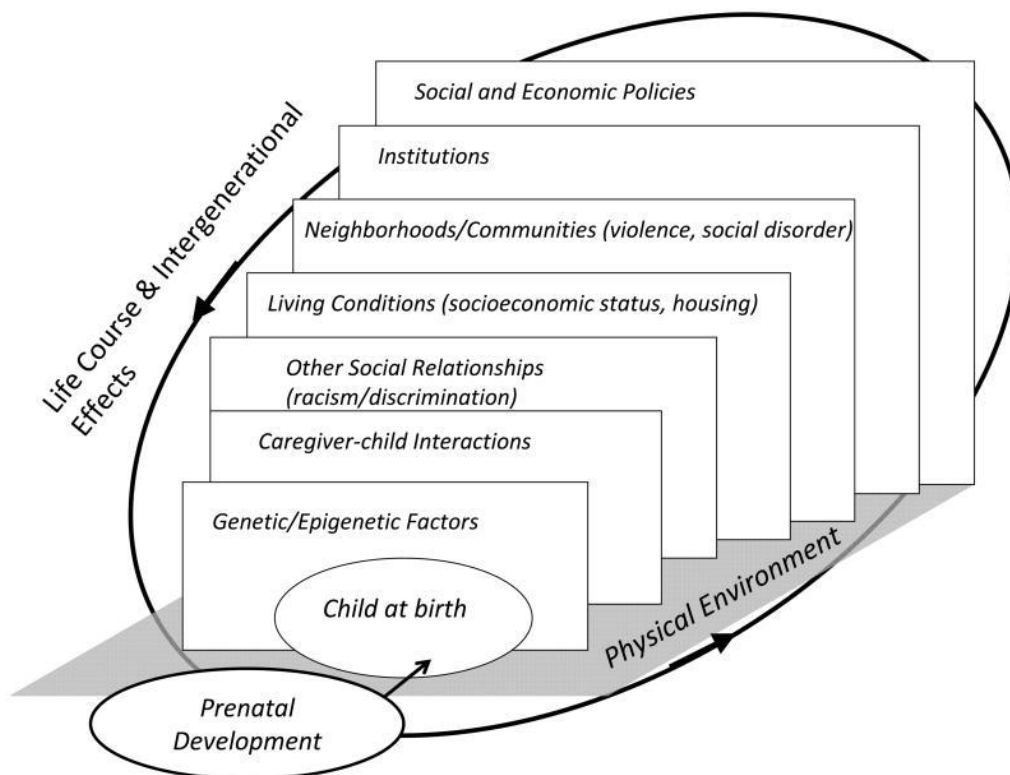


Fig. 3: Stress and asthma in view of epidemiology⁸²

1.2.1 Psychological factors and assessment tools in relation to asthma

Psychological disorders included micro- or individual, meso- and macro- levels⁸³. The micro- or individual level of psychological determinants included both prenatal (maternal disorders during pregnancy) and postnatal factors (disorders reported by parents/caregivers). Meso-level psychological factors included concepts of social network and support, work control, home control, effort/reward balance, security and autonomy that related to social formations, such as family, daycare centers and schools for the children and religious institution, the firm and the club for the parents or caregivers⁸³. In the previous studies, family structure and violence in the community are used as index of meso-level psychological factors. The macro-level psychological determinants are associated with social structure⁸³. We do not list the measurement of macro-level psychological determinants for no related epidemiological or clinical studies were found. We presented in table 6 the main psychological factors in relation to childhood asthma and their assessment in epidemiological studies.

Table 6 — Psychological factors and assessment tools in relation to childhood asthma

Psychological factors	Assessment tools
Micro-level (Individual level)	
Perceived Stress	Perceived stress scale (PSS): a total score of all 10 items is used to assess the degree to which children perceive situations in their lives as stressful ⁸⁴⁻⁸⁵ ; The 4-item Perceived stress scale (PSS4): a total score of all 4 items is calculated to assess the degree to which children perceive their lives were unpredictable, uncontrollable, and overwhelming in the preceding month ⁸⁶ .
Depression	Child depression index (CDI): a total score of all 27 items (cutoff score=13) is used to describe depressive symptoms ^{85, 87} ; Beck depression inventory short form: a total score of all 13 items (cutoff=5) to assess the symptoms of depression ⁸⁸⁻⁸⁹ ; The center for epidemiological studies-depression scale (CES-D): a total score of all 20 items (cutoff=16) to assess the depressive symptoms, demoralization, or general distress ⁹⁰ .
Anxiety	The state-trait anxiety inventory for children (STAIC): a total score of all 40 items (cutoff score=34) is used to measure

	anxiety symptoms ^{85, 89, 91} ; The anxiety subscale of crown-crisp experiential index (CCEI): a total score of 8 items is used to measure anxiety symptoms ⁹²⁻⁹³ .
Life events	A list of major stressful life events that might have occurred in the life of the subject or those of others close to the subject during the past 12 months with a total score indicating the number of events that the subject reported ^{75, 86, 92, 94} ; Whether have lost a close relative (mother, father or a sibling) ⁷⁹ .
Behavioral problems	Child behavior checklist (CBCL)-parent report form: including internalizing, externalizing and total problems ^{85, 95} ; The Eyberg child behavior inventory (ECBI): a total score of all 36 items (cutoff score=131) is calculated to measure child behavior problem ⁷⁶ .
Meso-level	
Stress in the family	Parental stress measured by 4-item perceived stress scale ⁹⁶ .
Violence in the family	Maternal intimate partner violence (IPV): a yes answer to question “how often does he (baby’s father) hit or slap you when he is angry?” ⁸¹ .
Violence in the community	The following events occurred in their neighborhoods during the past 6 months: 1) a fight in which a weapon was used, 2) a violent argument between neighbors, 3) a gang fight, 4) a sexual assault or rape, 5) a robbery or mugging ^{86, 90} ; crime rates in the community ⁹⁷ .
Social support	The medical outcome study social support survey (MOSSS): a total score of all 19 items on a 5-point Likert scale (the total score ranges from 0 to 100 with higher score indicating more support) is calculated to describe social support ⁹⁰ ; Perceived instrumental support: whether the family of the subject could count on someone during the next year for the loan, emergency babysitting or child care, place to live, consigner for bank loan ⁹⁸ .

1.2.2 Psychological factor related to childhood asthma

At individual level, both prenatal (e.g. during pregnancy) and postnatal psychological disorders are showed to be associated with the risk of childhood asthma^{75-76, 89, 92}. De Marco et al⁷⁵ have found that foetal exposures to stressful life events during pregnancy was positively associated with wheezing (odds ration=1.41, 95% confidence interval: 1.03-1.94), asthma (odds ratio=1.71, 95% confidence interval: 1.02-2.89). Calam et al⁷⁶ have investigated psychological factors at age 3 and subsequent development of wheeze by age 5, results showed that children with behavioural problems (assessed by the Eyberg Child Behavior Inventory, ECBI) were more likely to develop wheeze. For family-level

psychological features, Marin et al⁹⁹ have found that there was interaction between chronic family stress and individual stress to the production of asthma-related cytokines, thus increase the risk of childhood asthma. Considering the impact of meso-level psychological factors, results showed that stress in the family⁹⁶, violence in the family⁸¹, violence in the community^{86, 90, 97} and social support^{90, 98} related to childhood asthma.

One potential biological mechanism may be that psychological features could alter immune responses of children, thus increasing the risk of asthma^{82, 100}. Psychological features may also increase the release of inflammatory mediators and the subsequent cascade of inflammatory events, thus increasing the susceptibility to asthma¹⁰¹.

1.3 Interactions between air pollutants and psychological features in relation to childhood asthma

In previous study, evidence had consistently showed that air pollution may interact with psychological features to affect childhood asthma¹⁰²⁻¹⁰⁵. Clougherty et al¹⁰² found that there were synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology in American children. Recently, data further suggested an interaction between air pollution and prenatal community violence in relation to wheezing in children followed from birth to the age of 2 years¹⁰³. Chen et al¹⁰⁴ investigated the interaction between traffic-related air pollution and family stress in relation to childhood asthma. Results showed that traffic-related air pollution and family stress interacted in predicting both biologic and clinical outcomes in children with asthma. Peters JL et al¹⁰⁵ have found an interaction between prenatal negative life events and exposure to dust mite allergen in relation to elevated cord blood Immunoglobulin E (IgE), an altered immune system response for the development of asthma.

The potential mechanisms may be that both stress and air pollution may increase the risk of asthma through lung structure and lung function changes¹⁰⁶⁻¹⁰⁹, and altered immune system responses¹⁰⁵.

1.4 Rationale and hypotheses of the thesis

As a whole, there are few data on the interactions between asthma, air pollution and psychological factors. In our thesis, we used both cross-sectional and longitudinal data to examine the relationships between childhood asthma and air pollutants on one hand and psychological features on the other that could act on the structure and function of respiratory system in children possibly through overlapping biological mechanisms¹¹⁰. We also examined whether the relationships might be enhanced through the interaction between air pollution and psychological disorder which is scarcely documented in the literature.

The purposes of this thesis are to examine the hypothesis according to which psychological features constitute a modifier of the relation between air pollution and childhood asthma.

1.5 Conceptual framework of the thesis

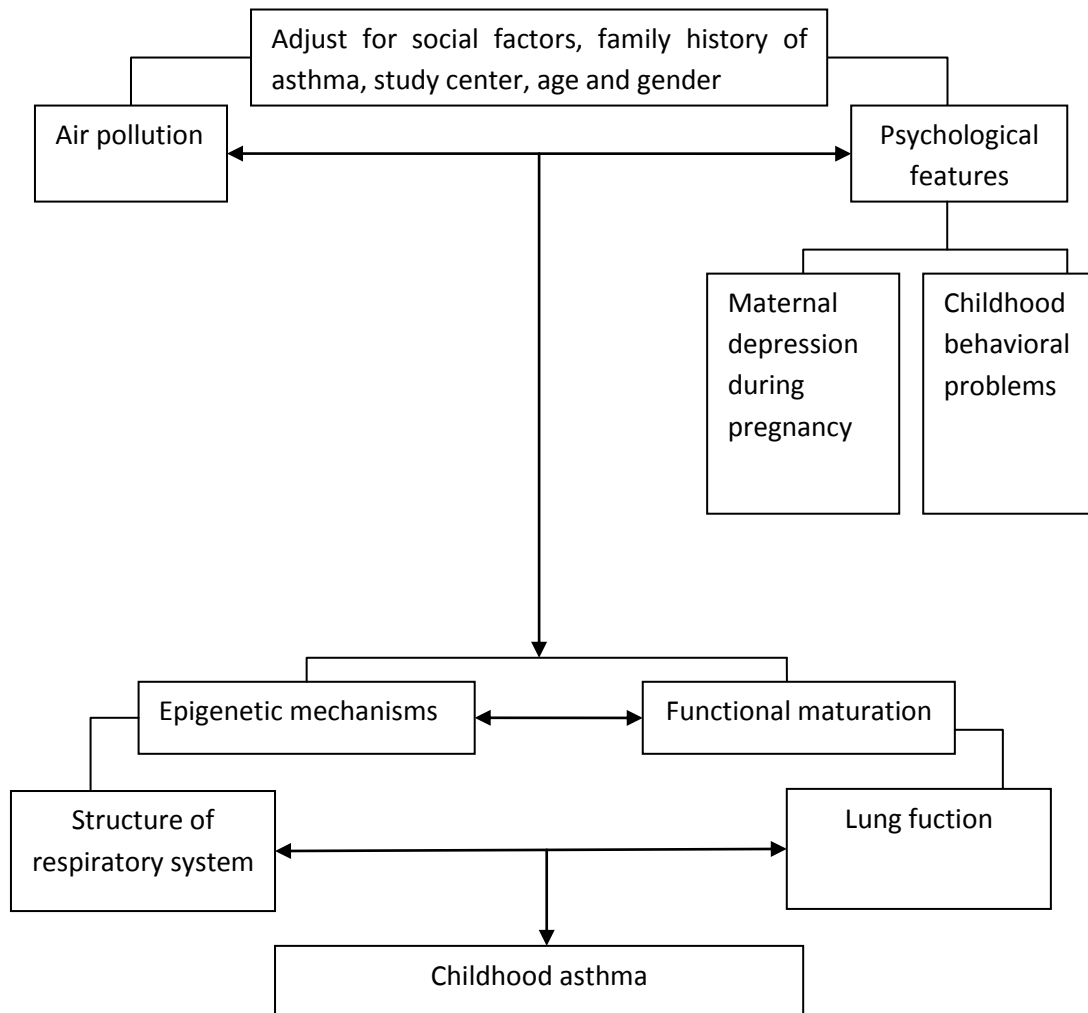


Fig. 4: Presents the conceptual framework underlying this thesis

We considered air pollution and psychological features since *in utero* life. Of note, we took into account the interrelationships among the two aforementioned factors and childhood asthma, as well as potential confounders of social factors, family history of asthma, study center, age and gender.

1.6 Objective of the thesis

This thesis aimed at:

- 1) Exploring the relationships between air pollutants and asthma in prenatal and early life;
- 2) Examining the relationships between psychological features and childhood asthma;
- 3) Showing whether there are interactions between air pollutants and psychological disorders in relation to childhood asthma.

To this extent, we used cross-sectional and longitudinal population based data of children living in France.

2. Study population and methods

We used the dataset from French 6 Cities study and EDEN mother-child cohort study (Study of pre- and post-natal determinants of children's growth and development) to examine the hypotheses of the thesis.

2.1 Introduction of the study protocols

2.1.1 French 6 cities study

The French 6 cities study is the phase II of International Study of Asthma and Allergies in Childhood (ISAAC) conducted in France between March 1999 and October 2000.

2.1.1.1 Objectives

The objectives of French 6 cities study included: 1) to study the risk factors of childhood allergic and respiratory diseases; 2) to explore whether the change of risk factors could explain the differences in diseases prevalences between phase I and phase II.

2.1.1.2 Study protocol

This study recruited 9615 children with an average age of 10 years in 6 cities (Creteil, Reims, Marseille, Strasbourg, Clermont-Ferrand, and Bordeaux) of France¹¹¹. The children were from 108 randomly selected schools from the 6 cities.

Standard core questionnaires on demographics, current and previous (including first year of life) risk factors, such as living conditions, birth weight, gestational age, place of birth, socioeconomic status, breastfeeding, family size, family history of atopic diseases, infections, vaccinations, crowding, pets, environment tobacco smoke, cooking fuels, damp housing, type of windows, type of bedding, area of residence, physical activity and nutritional factors, were completed by parents of the children¹¹². Data on clinical examination and skin prick test (SPT) for atopy were also collected by trained field workers¹¹².

The study protocol was approved by French National Ethics Board (*Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biomédicales, CCPPRB*, approval number: 01/07, Marseille, France).

2.1.2 EDEN mother-child cohort study

2.1.2.1 Objectives

The objectives of the EDEN mother-child cohort study are to examine the relationships between maternal exposures to risk factors and maternal health during pregnancy, the early life exposures to risk factors of children, and the health and (or) the development of diseases of children.

2.1.2.2 Study protocol

The EDEN mother-child cohort study is an ongoing study which recruited 2002 pregnant women (<24 weeks of amenorrhea (WA)) in Nancy and Poitiers in 2003 (<https://eden.vjf.inserm.fr>). The criteria for non-inclusion were: 1) twin pregnancy; 2) knowing diabetes before pregnancy; 3) planned to move outside of the region in the next 3 years; 4) not being able to speak or read French. We

conducted the first questionnaire investigation when women were at 24-28 WA. We then followed up the mother-child pairs when children were at birth, 4 months 8 months, 12 months, 2 years, 3 years, 4 years and 5 years. Most of the families are continued to be followed up right now. The data were collected mainly by questionnaires which were completed by the parents of the children.

The questionnaires including the health condition of the pregnant women, pre- and post-natal environmental exposures (domestic or professional exposures, contact with allergens), nutritional factors, socioeconomic factors, psychological factors and the health and (or) diseases conditions of the children were completed by the parents of the children. Data on clinical examination were also collected by physicians.

This study was approved by the ethical committee (*Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, CCPPRB*) of Kremlin Bicêtre and by the Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés, CNIL*).

2.2 Study population

2.2.1 French 6 cities study

In our study, we included only those children aged 10-12 years that resided at their current address for more than 3 years and without missing data on emotion and conduct problems (total sample of 4209).

2.2.2 EDEN mother-child cohort study

The total number of mother-child pairs followed up at ages of 1, 2, 3, 4, and 5 years of children was 1765, 1436, 1313, 1228, and 1139, respectively. In the thesis, we included children not moving outside of the region in the first year of life and without missing data on *in utero* and first year of life exposures to outdoor air pollutants, and maternal depression during pregnancy (total sample of 1222 in the first 3 years, and 722 in the first 5 years).

2.3 Assessment of air pollutants

2.3.1 French 6 Cities study

Concentrations of benzene, CO, NO₂, NO_x, PM₁₀, VOCs at 108 school addresses were estimated by a dispersion model through the STREET® 5 software, using data of the 3-years average (from 1998 to 2000). The STREET dispersion model has been validated in France (Pénard-Morand Atmospheric Environment 2008). Because in urban France almost all children live within 500 meters of their elementary schools, the exposure to outdoor air pollutants estimated in school addresses was considered as a satisfactory assessment of proximity to exposure to outdoor air pollutants in residential addresses.

2.3.2 EDEN mother-child cohort study

Early life exposures to parental smoking, traffic-related air pollution, dampness, molds, bleaching agents, house dust mites, pets and domestic heating were assessed by questionnaires completed by the parents of the children.

In utero and first year of life Concentrations of benzene, CO, NO₂, SO₂, PM₁₀, and VOCs at residential addresses were estimated by a dispersion model through the STREET® 5 software, taking into account of data from background air pollution, traffic characteristics, and condition of topographical and meteorological dispersion of air pollutants.

2.4 Assessment of psychological features

2.4.1 French 6 cities study

We used 2 scales (each scale has 5 items) of Strength and Difficulty Questionnaire (SDQ)¹¹³, which is emotional symptoms (internalizing disorder) and conduct problems (externalizing disorder), to measure the psychological disorders of the school children. We scored each items using a three-point Likert scale: 0 for “not true”, 1 for “somewhat true” or 2 for “very true”. The score of each item added up to a total score of emotion and conduct problems (ECPs), ranging from 0 to 20. There were 2 methods for classification of psychological variables in the thesis. In article 2, we used normative banding method for classifying the total SDQ scores¹¹⁴, children were classified into “normal”, “borderline” or “abnormal” using the following cut-off points: 0-3, 4, and 5-10 respectively for emotional (internalizing) problems; and 0-2, 3, 4-10 respectively for conduct (externalizing) problems. In article 3, however, we defined the psychological disorders as binary variables for statistical stratification the study population into 2 groups to show the interactions between outdoor air pollutants and psychological features. Both emotional symptoms and conducts problems children with highest 10 % scores (cut-off = 4) were defined as having difficulties. The total scores between 0 and 8 were defined as “emotion and conduct problems (ECPs)”, while the score range for “no emotion and conduct problems (No ECPs)” was 9-20.

2.4.2 EDEN mother-child cohort study

Maternal depression during pregnancy was assessed using the Centre for Epidemiological Studies-Depression scale (CES-D)¹¹⁵, which was translated and validated in French population¹¹⁶. This self-administered questionnaire included 20 items that assessed the depressive symptoms of depressive mood, feeling of guilty, worthlessness and helplessness, psychomotor retardation, loss of appetite,

and sleep difficulties over the past 7 days, and was completed by the mothers between 24 and 28 WA. Each item was scored from 0 (never) to 3 for (all the time). The score of each item was then added up into a total score, ranging from 0 to 60. The total scores between 0-2 were excluded from the analysis because these extremely low scores are thought to be related to denial of depressive symptoms¹¹⁷. According to the previous studies¹¹⁸⁻¹²⁰, maternal depression was defined as a binary variable: maternal depression (the total score ≥ 16) and no maternal depression (the total score < 16).

2.5 Assessment of health outcomes

2.5.1 French 6 Cities study

Current wheezing was defined by a “yes” response to question “In the last 12 months, had your child had wheezing in the chest?”¹²¹. Current doctor-diagnosed asthma was defined by: (i) a “yes” response to question “Has the asthma of your child been diagnosed by a physician”; (ii) parent-reported wheezing attacks in the last 12 months and (or) asthma medication use in the last 12 months¹²². We also included current eczema, a disorder sharing genetic and environmental risk factors with asthma and having a causal link with asthma¹²³. Current eczema was defined as itchy rash in flexural areas in the last 12 months¹²¹.

2.5.2 EDEN mother-child cohort study

Ever wheezing was defined by a “yes” response to question of “Did your child ever have wheezing or whistling in the chest?”. Ever doctor-diagnosed asthma was defined by a “yes” response to question of “Did your child have a diagnosed asthma by a physician during 0-4 months, or 4-8 months, or 8-12 months, or 1-2 years, or 2-3 years, or 3-4 years, or 4-5 years?”. Doctor-diagnosed eczema was identified by “yes” responses to all of the questions of “Did you child ever have a doctor-diagnosed eczema by a physician during 0-4 months, or 4-8 months, or 8-12 months, or 1-2 years, or 2-3 years, or 3-4 years, or 4-5 years?”, “Did you child ever have an itchy skin rash (red patches, buttons...) that you want to scratch, which was coming and going intermittently during 0-4 months, or 4-8 months, or 8-12 months, or 1-2 years, or 2-3 years, or 3-4 years, or 4-5 years?”, and “Did this itchy rash any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?”. Allergic rhinoconjunctivitis was identified by positive answers to the following questions of “Did your child have a problem with

sneezing, or a runny or blocked nose when she/he did not have a respiratory infection (without a cold, or nasopharyngitis, or a flu)?". All the health outcomes were assessed in the survey waves conducted when children were at ages of 4 months, 8 months, 12 months, 2 years, 3 years, 4 years, 5 years. In each survey waves, both lifetime incidences and prevalences of the health outcomes were calculated.

2.6 Statistical analysis

1.6.1 Descriptive analysis

2.6.1.1 Characteristics of study population

The population characteristics were presented by means and standard deviation when the variables are continuous, and described by counts and percentages when the variables are categorical. According to the type of variables, *t*-test and chi-square test were implemented to analyze the differences of the characteristics between boys and girls or different exposure levels.

2.6.1.2 Exposure to air pollutants

The exposures to air pollutants through sources measured by standard ISAAC questionnaires were described by counts and percentages. Chi-square test was used to analyze the differences of exposures to these air pollutants between different characteristics.

Concentrations of air pollutants measured objectively by dispersion models were presented as means and standard deviation. The differences of exposures to these air pollutants between boys and girls or other characteristics were examined by *t*-test.

2.6.1.3 Exposure to psychological features

The Exposures to psychological features were described by counts and percentages. Chi-square test was used to analyze the differences of exposures to psychological disorders between different characteristics.

2.6.1.4 Health outcomes

The health outcomes were presented by counts and percentages. Chi-square test was used to analyze differences of health outcomes between different characteristics. Morbidity associated with health outcomes was defined in terms of prevalence (number of cases/number of children at risk at

the considered period) and incidence (number of new cases/number of children at risk at the considered period after having excluded those that developed the same health outcome in the previous periods).

1.6.2 Analytical analysis

2.6.2.1 Multivariable logistic regression

Multivariable logistic regression was used to analyze the relationships between exposures to air pollutants or psychological features and the health outcomes when exposure assessed simultaneously with the health outcomes, adjusting potential confounders. Adjusted odds ratios (aORs) and 95 % confidence interval (CI) were used to estimate the relationships between exposures to air pollutants or psychological disorders and the health outcomes.

There are 3 steps for the analysis using multivariable logistic models:

1) To examine whether the covariates are confounders. Confounders had been identified when the addition of a covariate to the model with only exposures and intercept changed the odds ratio (OR) by 10%, without considering statistical significance.

2) To test the statistical significance of interaction terms of gender and exposures, and family history of asthma, eczema, allergic rhinitis or food allergy and exposures, adjusting for confounders. As the interaction terms were not significant ($P\text{-value} > 0.20$) in all the models, they were consequently dropped. If the interaction terms were statistical significant ($P\text{-value} < 0.20$) as tested in Wald chi-square test in the logistic model, they were kept in the final models.

3) To choose the best-fitted models using the method of likelihood ratio (LR) chi-square test. For each outcome, we included firstly the exposures, and then interaction terms, and finally the confounders in the models. When the model added a new term, it was compared with the model without the new added term using the LR chi-square statistic which was calculated by $-2 \log L$ (the

model without the added term) - 2 Log L(fitted model with the added term). The best-fitted model was found when the model added one more item and the LR chi-square statistic was not significant.

2.6.2.2 Marginal models

Marginal models were applied for taking into account of the non-independence of data of children measured repeatedly in different survey waves for the longitudinal dataset, or children living in the same community¹²⁴⁻¹²⁵. The marginal models were estimated by the Generalized Estimating Equation (GEE) approach, using exchangeable working correlation matrices. Adjusted odds ratios (aORs) and 95 % confidence interval (CI) were used to estimate the relationships between exposures to air pollutants or psychological disorders and the health outcomes.

There are 3 steps for the analysis using GEE models:

1) To examine whether the covariates are confounders. Confounders had been identified when the addition of a covariate to the model with only exposures and intercept changed the odds ratio (OR) by 10%, without considering statistical significance.

2) To test the statistical significance of interaction terms of time and exposures, gender and exposures and family history of asthma, eczema, allergic rhinitis or food allergy and exposures, adjusting for confounders. As the interaction terms were not significant (P -value>0.20) in all the models, they were consequently dropped. If the interaction terms were statistical significant (P -value<0.20) as tested in Wald chi-square test in the GEE models, they were kept in the final models.

3) To choose the best-fitted models. For each outcome, we included firstly the exposures, and then interaction terms, and finally the confounders in the models. When the model added a new term, it was compared with the model without the new added term. The best-fitted model had a smallest value of QIC (Quasilikelihood under the Independent model Criteria) compared with other models.

1.6.3 Adjusted population attributable risk

The impact of each exposure on health outcomes was estimated by the adjusted Population Attributable Risk (aPAR), the fraction of the total disease experienced in the population that would not have occurred if the effect associated with the risk factor of interest was absent¹²⁶. The estimates of aPAR were calculated based on multivariable logistic regression or GEE model-based odds ratio, using the formula provided by Bruzzi¹²⁶:

$$aPAR = 1 - \sum (\rho_j / RR_j)$$

ρ_j is the proportion of all disease cases within the stratum j . The model-based odds ratios were used to estimate the relative risk for stratum j compared with the baseline stratum (RR_j). When the model-based odds ratio was less than 1.0, the aPAR estimate was negative, representing a potentially protective effect. The lower and upper 95% confidence interval (95% CI) of odds ratios for each stratum was used to estimate the lower and upper bounds of aPAR. We present in the thesis significant aPAR.

All statistical tests were performed using SAS® statistical software version 9.2 (SAS® Institute Inc, Cary, North Carolina). All P-values were two-tailed. $P < 0.05$ was considered statistically significant, except for considering the significance of the interaction term ($P\text{-value} < 0.20$).

3. Air pollutants and childhood asthma

In this part, we show the results on the relationships between air pollutants and childhood asthma and allergies, using both cross-sectional (French 6 Cities study) and longitudinal data (EDEN mother-child cohort study). Several articles were published on the relationships in the French 6 Cities study. We also add some new results on the relationships, using the dataset for the thesis. For the EDEN mother-child cohort study, we published 1 article in BMC public health. We present in the thesis the detail of this article.

3.1 Evidence from the French 6 Cities study

In French 6 Cities study, we have already published several articles, which consistently showed that air pollutants were related to school children's asthma and allergies^{13, 111, 127}. We found that allergic sensitization related to residential proximity (*in situ* assessment) fine particles¹²⁷, asthma (lifetime and past year) related to benzene, SO₂, PM₁₀, NO_x and CO (dispersion model based assessment)¹³, eczema (lifetime and past year) was significantly positively associated with benzene, PM₁₀, NO₂, NO_x and CO (dispersion model based assessment) and lifetime allergic rhinitis was significantly associated with PM₁₀ (dispersion model based assessment) in primary school children¹³.

3.2 Evidence from the EDEN mother-child cohort study

3.2.1 Presentation of article 1

In article 1, we studied the impacts of various air pollutants on the development of asthma phenotypes in the first year of life. We assessed both *in utero* and first year of life exposures to air pollutants of passive smoking and traffic-related air pollution, and the first year of life exposures to air pollutants of dampness, visible moulds, bleaching agents, house dust mites, contact with cats, contact with dogs, domestic gas heating, domestic petroleum heating, and domestic wood heating. For the health outcomes, we took into account both single asthma phenotypes (Ever bronchiolitis, ever wheezing and ever doctor-diagnosed asthma) and multi-dimensional asthma phenotypes (bronchiolitis and wheezing, doctor-diagnosed asthma with a history of bronchiolitis, doctor-diagnosed asthma with wheezing, doctor-diagnosed asthma with wheezing and a history of bronchiolitis). Results showed that both single and multi-dimensional asthma phenotypes were positively related to the first year of life exposures to passive smoking, traffic related air pollution and dampness, but negatively associated with contact with cats and domestic wood heating. Results persisted for *in utero* exposures to passive smoking and traffic-related air pollution. For comparing the impacts of different air pollutants on health outcomes by measuring adjusted population attributable risk, traffic-related air pollution *in utero* life and in the first year of life had a greater impact than other pollutants on the health outcomes.

3.2.2 Article 1. Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study

RESEARCH ARTICLE

Open Access

Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study

Cailiang Zhou^{1,2,3*}, Nour Baiz^{1,2}, Tuohong Zhang³, Soutrik Banerjee^{1,2}, Isabella Annesi-Maesano^{1,2} and The EDEN Mother-Child Cohort Study Group

Abstract

Background: Studies have shown diverse strength of evidence for the associations between air pollutants and childhood asthma, but these associations have scarcely been documented in the early life. The purpose of this study was to evaluate the impacts of various air pollutants on the development of asthma phenotypes in the first year of life.

Methods: Adjusted odds ratios were estimated to assess the relationships between exposures to air pollutants and single and multi dimensional asthma phenotypes in the first year of life in children of the EDEN mother child cohort study (n = 1,765 mother child pairs). The Generalized Estimating Equation (GEE) model was used to determine the associations between prenatal maternal smoking and *in utero* exposure to traffic related air pollution and asthma phenotypes (data were collected when children were at birth, and at 4, 8 and 12 months of age). Adjusted Population Attributable Risk (aPAR) was estimated to measure the impacts of air pollutants on health outcomes.

Results: In the first year of life, both single and multi dimensional asthma phenotypes were positively related to heavy parental smoking, traffic related air pollution and dampness, but negatively associated with contact with cats and domestic wood heating. Adjusted odds ratios (aORs) for traffic related air pollution were the highest [1.71 (95% Confidence Interval (CI): 1.08-2.72) for ever doctor diagnosed asthma, 1.44 (95% CI: 1.05-1.99) for bronchitis with wheezing, 2.01 (95% CI: 1.23-3.30) for doctor diagnosed asthma with a history of bronchitis]. The aPARs based on these aORs were 13.52%, 9.39%, and 17.78%, respectively. Results persisted for prenatal maternal smoking and *in utero* exposure to traffic related air pollution, although statistically significant associations were observed only with the asthma phenotype of ever bronchitis.

Conclusions: After adjusting for potential confounders, traffic related air pollution *in utero* life and in the first year of life, had a greater impact on the development of asthma phenotypes compared to other factors.

Keywords: Environment, Traffic related air pollution, Environmental Tobacco Smoke (ETS), Pets, Moulds, Asthma, Children

Background

The prevalence of asthma has increased constantly in recent decades [1-3] and different factors have been implicated in its aetiology. Although genetic factors are important determinants of asthma [4], exposures to certain environmental factors play an essential role in the

phenotypic expression of this condition [5,6] thus contributing substantially to the risk of its development [7].

The strength of evidence for the associations between exposures to various air pollutants and the development of childhood asthma is diverse [8]. Robust data casually related asthma to allergens including aero-allergens such as house dust mite [9]. Studies consistently demonstrated that Environmental Tobacco Smoke (ETS) increases the risk of asthma in children [10-12]. Other investigations showed an independent effect of dampness and moulds on the development of childhood asthma [13,14], although

* Correspondence: zhoucailiang707jussieu.fr

¹Université Pierre et Marie Curie, Paris 6, Sorbonne Universités, UMR S 707: EPAR (Epidémiologie des maladies allergiques et respiratoires), Medical School Saint-Antoine, Paris, France

²INSERM U 707: EPAR, Paris, France

Full list of author information is available at the end of the article



some investigations argued that the relationship may be partly explained by reporting bias [15]. Conversely, a protective effect was suggested for early life exposure to pets [16,17], exposure to domestic wood heating and rural living [18]. In contrast with initial findings [19], recent investigations, including birth cohort studies, have indicated a link between exposure to outdoor air pollution and subsequent asthma development [20-22]. Indoor air pollutants have also been related to asthma [23], but there is a lack of longitudinal data in this respect.

The aim of our study is to investigate the impacts of exposures to passive smoking, traffic-related air pollution, dampness, visible moulds, bleaching agents, house dust mites, pets and domestic heating on the development of asthma in the first year of life, which is a period of life when the lung is still developing. For passive smoking and traffic-related air pollution, *in utero* exposures were taken into account to better understand the development of childhood asthma. The health outcomes we considered in this study included both single and multi-dimensional asthma phenotypes at 0-4 months, 4-8 months, and 8-12 months respectively as well as their evolution during the first year of life. To this extent, we used data from a birth cohort to study the impacts of the *in utero* and first year of life exposures on asthma phenotypes in the first year of life.

Methods

Study population

The EDEN mother-child cohort study (Study of pre- and post-natal determinants of children's growth and development) is an on-going investigation in two study centres, Nancy and Poitiers, in France. This study enrolled 2,002 women during pregnancy and was described in more detail previously [24]. This study was approved by the ethical committee (*Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale*, CCPPRB) of Kremlin Bicêtre and by the Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*, CNIL). Two hundred and thirty-seven children failed to be followed-up at 1 year of age.

Data collection

Data were collected when children were at birth, and at 4, 8 and 12 months of age respectively, by standardised questionnaires that allowed the investigation of socio-demographic characteristics, *in utero* and first year of life environmental exposures and respiratory health of the children throughout the first year of life. At birth and 12 months of age, the questionnaires were completed by mothers with the assistance of the midwives in the hospitals. When children were at 4 and 8 months of age, the questionnaires sent by mail were completed and returned back by the parents within 1 month after the

distribution. If needed, parents could ask for assistance to complete the questionnaire by telephoning the midwives. The response rate of our study was 90%. At the age of 12 months, the children were offered a clinical examination.

Assessment of exposures to air pollutants

Table 1 describes *in utero* and first year of life exposures to air pollutants assessed by standardised questionnaires and their temporal sequence with asthma phenotypes, namely, prenatal maternal smoking and *in utero* exposure to traffic-related air pollution and exposures to heavy parental smoking, traffic-related air pollution, dampness, visible moulds, bleaching agents, house dust mites, pets and domestic heating in the first year of life.

Assessment of asthma phenotypes

An enriched version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to define asthma phenotypes. In order to cover the spectrum of asthma outcomes fully in the first year of life, both single and multi-dimensional asthma phenotypes (as defined in Table 2) were assessed.

Statistical analysis

This included 3 steps: 1) classical descriptive analysis; 2) analytical analysis for the estimation of the adjusted odds ratios between exposures and asthma phenotypes; 3) the estimation of the adjusted population attributable risk for exposures having statistically significant relationships with the prevalences of asthma phenotypes.

Descriptive analysis

The population characteristics were presented by means and percentages. Chi-square test was used to analyze differences of proportion of exposures and asthma phenotypes between boys and girls. Morbidity associated with asthma phenotypes was defined in terms of prevalence (number of cases/number of children at risk at the considered period) and incidence (number of new cases/number of children at risk at the considered period after having excluded those that developed the same asthma phenotype in the previous periods).

Analytical analysis

The investigation of the relationships between exposures and asthma phenotypes was conducted using two different models according to whether exposure was assessed simultaneously with health outcome or whether it preceded the health outcome.

- 1) Exposure assessed simultaneously with asthma
Multivariable logistic regression was implemented to estimate odds ratios (OR) of the relationships

Table 1 *In utero* and first year of life exposures to air pollutants sources and their temporal sequence with asthma phenotypes in children of the EDEN mother-child cohort study

Period of life/Air pollutant and related sources	Corresponding questions	Temporal sequence of asthma phenotypes in relation to exposure	
		Exposure assessed in the first of life (at the period of the outcome)	<i>In utero</i> exposure (preceding the outcome)
<i>In utero</i> life			
Prenatal maternal smoking	1. Did you smoke during the first trimester of pregnancy?		
	2. Did you smoke during the second trimester of pregnancy?	No	Yes
	3. Did you smoke during the third trimester of pregnancy?		
Traffic-related air pollution	1. Does your house located near a bus stop or a passageway of trucks?	No	Yes
	2. Does the cars often or continuously pass by your house?		
First year of life			
Heavy parental smoking in the last 12 months	1. Did you smoke at present?		
	2. An answer of "more than 20" to the question "How many cigarettes do you smoke every day?"	Yes	No
Traffic-related air pollution in the last 12 months	1. Do you live less than 200 meters away from a road with heavy traffic?		
	2. Notably, Google Earth was used to check the validity of maternal reporting by taking into account a 200 m circular buffer and more than 10,000 vehicles per day (traffic volumes were provided by local authorities) using the home address as reference..	Yes	No
Dampness in the last 12 months	Are there any problems of dampness, moisture or condensation that have often, or permanently, existed in the house since the birth of the child?	Yes	No
Visible moulds in the past 12 months	Are there any visible moulds that have often, or permanently, existed in the house of the child since the birth of the child?	Yes	No
Bleaching agents in the past 12 months	Do you often clean with or use the bleaching agents in the presence of the child?	Yes	No
House dust mites in the past 12 months	Has your child frequently been in contact with carpets, or glazing, or curtains?	Yes	No
Contact with cats in the past 12 months	1. Was there a new cat in your house and (or) did you let the cat enter the sleeping room of the child?	Yes	No
	2. Did your child contact with cats outside your house at least once per week?		
Contact with dogs in the past 12 months	1. Was there a new dog in your house and (or) did you let the dog enter the sleeping room of the child?	Yes	No
	2. Did your child contact with dogs outside your house at least once per week?		
Type of domestic heating in the past 12 months	Which is your main type of heating in the house: gas, petroleum, wood or others?	Yes	No

between all exposure variables together and the prevalence of each asthma phenotype during the first year of life after adjusting for confounders. Potential confounders included study centre, maternal occupation, maternal age at recruitment, maternal pre-pregnancy body mass index (BMI) as

estimated by weight in kilograms divided by the square of the height (kg/m^2), child's birth weight, cesarean delivery, preterm birth, breastfeeding, siblings, gender and family history of asthma, eczema, allergic rhinitis or food allergy.

2) Exposure assessed before asthma development

Table 2 Asthma phenotypes in the first year of life in the children of the EDEN mother-child cohort study

Asthma phenotypes	Corresponding questions	Periods
Single phenotypes		
Ever bronchiolitis	Question 1: Did your child suffer from bronchiolitis during the last 4 months?	0-4 months, 4-8 months and 8-12 months
Ever wheezing	Question 2: Did your child ever have wheezing or whistling in the chest after the birth? Question 3: Did your child ever have wheezing or whistling in the chest during the last 4 months?	0-8 months, 8-12 months
Ever doctor-diagnosed asthma	Question 4: Did your child have a diagnosed asthma during the last 4 months?	0-4 months, 4-8 months and 8-12 months
Multi-dimensional phenotypes		
Bronchiolitis and wheezing	Questions 1, 2, 3	0-8 months, 8-12 months
Doctor-diagnosed asthma with a history of bronchiolitis	Questions 1, 4	0-4 months, 4-8 months and 8-12 months
Doctor-diagnosed asthma with wheezing	Questions 2, 3, 4	0-8 months, 8-12 months
Doctor-diagnosed asthma with wheezing and a history of bronchiolitis	Questions 1, 2, 3, 4	0-8 months, 8-12 months

The marginal model [25] was used to analyze the associations of prenatal maternal smoking and *in utero* exposure to traffic-related air pollution together with the prevalence of each asthma phenotype at 3 survey time points (at 4, 8 and 12 months of age) after adjustment for confounders. The parameters of the marginal models were estimated by the Generalized Estimating Equation (GEE) approach, using exchangeable working correlation matrices. In order to study the relationships between the exposures, i.e., prenatal maternal smoking and *in utero* exposure to traffic-related air pollution, and each health outcome in the GEE model, we introduced a variable of time and tested the statistical significance of the presence of interactions between this time variable (-1 if at the age of 4 months, -2 if at the age of 8 months, -3 if at the age of 12 months) and each exposure, adjusting for confounders. As the interaction terms were not significant (P -value > 0.05) in the models, they were consequently dropped. In the next step, we studied the associations of all exposures together with each health outcome, including the time variable and confounders. This enabled to estimate the impact of time on the associations between the exposures and each health outcome.

Adjusted population attributable risk

The impact of each exposure on asthma phenotypes was estimated by the adjusted Population Attributable Risk (aPAR), the fraction of the total disease experienced in the population that would not have occurred if the effect associated with the risk factor of interest was absent

[26]. The aPARs were calculated with the formula provided by Bruzzi [26]:

$$aPAR = 1 - \sum (p_j / RR_j)$$

p_j is the proportion of an asthma phenotype within the stratum j . The multivariable logistic regression or GEE model-based odds ratios were used to estimate the relative risk for stratum j compared with the baseline stratum (RR_j). When the model-based odds ratio was less than 1.0, the aPAR estimate was negative, representing a potentially protective effect. The lower and upper 95% confidence interval (95% CI) of odds ratios for each stratum was used to estimate the lower and upper bounds of aPAR.

Confounders had been identified when the addition of a covariate to the model changed the odds ratio (OR) by 10%, without considering statistical significance. Effect modifiers had been identified when a covariate had a statistically significant interaction (P -value < 0.05) with the exposure as tested with the logistic model or the statistic of Wald chi-square in the case of the GEE model.

All statistical tests were performed using SAS® statistical software version 9.2 (SAS® Institute Inc, Cary, North Carolina). All P -values were two-tailed. P < 0.05 was considered statistically significant.

Results

Characteristics of study population

The characteristics of the study population and the potential confounders are described in Table 3. The number of children was equally distributed between two study centres and according to gender. There were no differences for the characteristics between boys and girls

($P > 0.05$), except for study centre, cesarean delivery and birth weight.

Exposures to air pollutants

Table 4 describes the frequency of the exposures to air pollutants in the study population. During *in utero* life, 25% of the children had been exposed to maternal smoking and 28% of their mothers had lived close to a road with heavy traffic. Similar figures were found for

exposure to traffic-related air pollution in the first year of life (21%), but not for passive smoking (13% exposed to heavy parental smoking). Exposures did not differ between boys and girls ($P > 0.05$).

Asthma phenotypes in the first year of life

The prevalences and incidences of each asthma phenotype at the 3 survey time points (at ages of 4, 8 and 12 months, respectively) are presented in Table 5. In terms of single

Table 3 Characteristics of the study population according to gender in the children of the EDEN mother-child cohort study

Variables	All (N = 1765)	Boys (n = 918)	Girls (n = 847)	P^*
Study centre, n (%)				
Poitiers	866(49.07)	490(53.38)	376(44.39)	<0.01
Nancy	899(50.93)	428(46.62)	471(55.61)	
Family income (€/month), n (%)				
Low(≤ 1500)	262(14.84)	140(15.25)	122(14.40)	0.15
Middle(1501-3000)	1001(56.71)	534(58.17)	467(55.14)	
High(>3001)	492(27.88)	237(25.82)	255(30.11)	
Maternal education attainment, n (%)				
Less than high school	104(5.89)	55(5.99)	49(5.79)	0.97
High school	683(38.70)	352(38.34)	331(39.08)	
College/University or more	960(53.82)	492(53.59)	458(54.07)	
Maternal occupation, n (%)				
Blue-collar (laborers)	81(4.59)	49(5.34)	32(3.78)	0.24
White-collar (occupations of intermediate, administrative, sales and customers and personal services)	1339(75.86)	688(74.95)	651(76.86)	
Professional (professional occupations, managers and senior officials)	217(12.29)	108(11.76)	109(12.87)	
Maternal age at recruitment (years), (Mean \pm SD[†])	30.64 \pm 4.81	30.70 \pm 4.81	30.58 \pm 4.81	0.61
Maternal pre-pregnancy body mass index, n (%)				
Underweight (<18.50 kg/m ²)	136(7.71)	74(8.06)	62(7.32)	0.80
Normal (18.50-24.99 kg/m ²)	1139(64.53)	597(65.03)	542(63.99)	
Overweight (25.00-29.99 kg/m ²)	305(17.28)	156(16.99)	149(17.59)	
Obese (≥ 30.00 kg/m ²)	149(8.44)	73(7.95)	76(8.97)	
Cesarean delivery, n (%)	278(15.75)	162(17.65)	116(13.70)	0.02
Preterm birth[‡], n (%)	428(24.25)	231(25.16)	197(23.26)	0.35
Birth weight (grams), (Mean \pm SD)	3285.56 \pm 506.65	3350.52 \pm 529.41	3214.89 \pm 470.89	<0.01
Breastfeeding, n (%)				
Never	795(45.04)	436(47.49)	359(42.38)	0.07
≤ 4 months	550(31.16)	279(30.39)	271(32.00)	
> 4 months	420(23.80)	203(22.11)	217(25.62)	
Siblings, n (%)	962(54.50)	505(55.01)	457(53.96)	0.68
Family history of asthma, eczema, allergic rhinitis or food allergy, n (%)	912(51.67)	484(52.72)	428(50.53)	0.33

*P, the P value for t test or chi square test between boys and girls;

[†]SD, standard deviation;

[‡]Maternal gestational age < 37 weeks.

asthma phenotypes, ever bronchiolitis was the commonest condition at each survey, followed by ever wheezing and then ever doctor-diagnosed asthma. The most frequent multi-dimensional phenotype was constituted by bronchiolitis with wheezing. Almost 6% of children had suffered from all the 3 single phenotypes (ever bronchiolitis, ever wheezing and ever doctor-diagnosed asthma) in the first year of life.

Associations between exposures to air pollutants and asthma phenotypes

Exposure assessed simultaneously with asthma

Applying the multivariable logistic regression models yielded that various asthma phenotypes were positively associated with heavy parental smoking, traffic-related air pollution and dampness in the last 12 months and negatively associated with contact with cats and domestic wood heating in the last 12 months (see Additional file 1: Table S1). No statistically significant associations ($P > 0.05$) were found between asthma outcomes and visible moulds, bleaching agents, house dust mites, contact with dogs, domestic gas heating, or domestic petroleum heating in the last 12 months (data not showed). A statistically significant interaction between gender and traffic-related air pollution in the last 12 months was

found in the multivariable logistic model with ever wheezing as the dependent variable ($P < 0.01$).

Exposure preceding asthma development

The application of the marginal model, taking into account the evolution of asthma phenotypes, indicated that prenatal maternal smoking and *in utero* exposure to traffic-related air pollution were associated with ever bronchiolitis (aOR = 1.39 (95% CI: 1.10-1.76) for prenatal maternal smoking, aOR = 1.51 (95% CI: 1.18-1.92) for *in utero* exposure to traffic-related air pollution), but only a trend (with aOR > 1) was found between *in utero* exposures and other asthma phenotypes (data not shown). There was no statistical significance ($P > 0.05$) for the interaction term between exposure to the risk factors and time in the models. The aOR for time was 2.43 (95% CI: 2.28-2.60) for the model describing the relationships between *in utero* exposures and ever bronchiolitis.

Adjusted population attributable risk

aPARs varied from 17.78% for exposure to traffic air pollution in the last 12 months to -14.41% for contact with cats in the last 12 months, both in the case of doctor-diagnosed asthma with a history of bronchiolitis (see Additional file 1: Table S1). When considering *in utero* life, aPAR was 7.60%

Table 4 *In utero* and first year of life exposures to air pollutants sources in the children of the EDEN study population according to gender

Variables	All (N = 1765)		Boys (n = 918)		Girls (n = 847)		P ^a
	n	(%)	n	(%)	n	(%)	
<i>In utero</i> life							
Prenatal maternal smoking	450	25.50	228	24.84	222	26.21	0.48
Traffic-related air pollution	501	28.39	246	26.80	255	30.11	0.10
<i>First year</i> of life							
Heavy parental smoking in the last 12 months	227	12.86	113	12.31	114	13.46	0.75
Traffic-related air pollution in the last 12 months	372	21.08	201	21.90	171	20.19	0.61
Dampness in the last 12 months	86	4.87	46	5.01	40	4.72	0.90
Visible moulds in the last 12 months	76	4.31	41	4.47	35	4.13	0.84
Bleaching agents in the last 12 months	102	5.78	50	5.45	52	6.14	0.46
House dust mites in the last 12 months	209	11.84	117	12.75	92	10.86	0.29
Cats in the past 12 months	156	8.84	79	8.61	77	9.09	0.75
Dogs in the past 12 months	117	6.63	65	7.08	52	6.14	0.45
<i>Domestic heating</i> in the last 12 months							
Electricity	353	20.00	187	20.37	166	19.60	0.24
Gas	736	41.70	383	41.72	353	41.68	
Petroleum	314	17.79	160	17.43	154	18.18	
Wood	79	4.48	47	5.12	32	3.78	
Others	45	2.55	30	3.27	15	1.77	

* P , the P value for chi square test between boys and girls.

Table 5 Prevalence and incidence of asthma phenotypes in the children of the EDEN study population in the first year of life

Variables	4 months survey		8 months survey		12 months survey	
	Incidence (n,%)	Prevalence (n,%)	Incidence (n,%)	Prevalence (n,%)	Incidence (n,%)	Prevalence (n,%)
Single phenotypes						
Ever bronchiolitis	197(11.16)	197(11.16)	359(22.90)	556(31.50)	156(12.90)	712(40.34)
Ever wheezing				294(16.66)	91(6.19)	385(21.81)
Ever doctor-diagnosed asthma	17(0.96)	17(0.96)	101(5.72)	118(6.69)	17(1.03)	135(7.65)
Multi-dimensional phenotypes						
Bronchiolitis with wheezing				148(8.39)	44(2.49)	301(17.05)
Doctor-diagnosed asthma with a history of bronchiolitis	11(0.62)	11(0.62)	50(2.86)	61(3.46)	4(0.24)	112(6.35)
Doctor-diagnosed asthma with wheezing				92(5.22)	5(0.28)	118(6.69)
Doctor-diagnosed asthma with wheezing and a history of bronchiolitis				48(2.72)	3(0.17)	103(5.84)

for prenatal maternal smoking and 10.81% for *in utero* exposure to traffic-related air pollution, both in relation to the asthma phenotype of ever bronchiolitis.

Discussion

In our study, passive smoking and exposure to traffic-related air pollution, both *in utero* life and in the first year of life, and dampness were found to be risk factors for various asthma phenotypes in the first year of life, while contact with cats and domestic wood heating were found to be protective against asthma in the first year of life. Some studies had observed the effects of air pollutants and related sources that we considered in our study. Results of the SIDIRA-2 study (Italian Studies on Respiratory Disorders in Children and the Environment-2nd phase) had showed that passive smoking, high traffic and dampness were risk factors for asthma in children aged 6–7 years [27]. Our data further support the associations in the first year of life.

Evidence for the association between asthma and prenatal and postnatal parental smoking is fairly consistent [10,28–30]. Recently, a systematic review of prospective studies published between 1997 and February 2011 indicated that both prenatal maternal smoking and postnatal maternal smoking were associated with wheezing in the first 2 years of life (OR = 1.41 (95% CI: 1.19–1.67) and OR = 1.70 (95% CI: 1.24–2.35), respectively) [30]. In our study, prenatal maternal smoking had a greater impact on childhood asthma than postnatal heavy parental smoking. This could be explained by the fact that the proportion of prenatal maternal smoking (25%) is higher than that of heavy parental smoking in the last 12 months (13%) in our population. Notably, results of a recent French national prenatal survey showed that 24% of women smoked during pregnancy [31], which is in agreement with our data. Furthermore, compared to

postnatal passive smoking, prenatal maternal smoking is more likely to reduce respiratory function after birth [32], which would consequently have a greater impact on the development of asthma.

The association between asthma and traffic-related air pollution has been well documented in the literature [21,27,33–37], but few studies have investigated the association between traffic-related air pollution and asthma in the first year of life. In a previous case-control study in 5 French metropolitan areas, results indicated that traffic related pollutants might be associated with the incidence of asthma in children aged 0–3 years old [37]. In our study, results showed that there were robust associations between *in utero* and first year of life exposure to traffic-related air pollution and asthma phenotypes in the first year of life. Furthermore, the impact of traffic-related air pollution on asthma phenotypes in the first year of life was greater than that of other risk factors even after adjustment for potential confounders, which is consistent with the results of the SIDIRA-2 study previously described [27]. One asset of our study is that we used Google Earth® and traffic volume provided by local authorities at mothers' address to check the validity of the subjectively measured exposure to traffic and thus minimise the exposure misclassification. The subjectively measured variable of traffic-related air pollution showed high concordance with the Google Earth®-derived variable, with up to 92% of children were well classified. Only 5% of the children whose mother reported traffic-related air pollution were not exposed according to the Google Earth®-derived variable, whereas 3% of the children that did not declare to be exposed were exposed according to this objectively assessed variable. Some studies have compared the subjectively measured exposure to traffic with objectively assessed exposures, implying that both have their own advantages and no method

could be *per se* considered as the gold standard [38]. In the USA, Gauderman *et al.* reported that the simple and widely available indicator of the distance between living house and freeway was as strongly and precisely associated with childhood asthma as were more complex objective estimates based on dispersion models [34].

Interestingly, our data further confirmed the findings from previous studies having related bronchiolitis to passive smoking [39] and air pollution [40,41]. This is important in terms of public health because bronchiolitis is an important phenotype of asthma in early life [42].

More consistently, several investigations showed a positive association between dampness and asthma, although very few have considered it in the first year of life. In the DRIAS study (Respiratory Symptoms in children and the Environment in Sardegna, Italy), results showed that exposure to dampness during the first year of life was associated with increased prevalence of current wheeze for primary school children (OR = 1.96; 95% CI: 1.34-2.88) [14]. Similarly, a more recent review implied that dampness was the risk factor for respiratory and allergic health in birth cohorts [43]. However, because of recall bias in the case of questionnaire investigation, the relationship between dampness in the last 12 months and asthma phenotypes in the first year of life needs to be further confirmed. Contrarily to other investigations [9], we did not find any relationship between exposure to house dust mite and the prevalences of asthma phenotypes, probably because the sources (carpets, or glazing, or curtains) we considered were not sufficient.

Our data showed that contact with cats in the last 12 months may be protective against asthma in the first year of life. This is in agreement with previous studies [17]. A potential mechanism was proposed by Platts-Mills *et al.* who indicated that contact with cats could induce IgG and IgG4 antibody responses, which is protective against the development of asthma [44].

In our study, domestic wood heating in the last 12 months was found to be negatively associated with asthma phenotypes in the first year of life. Among other authors, Kilpeläinen *et al.* investigated the association between early life exposure to wood stove heating and subsequent asthma development, results showed that a farm environment was the main confounding factor for the association between wood stove heating and asthma [45]. However, in the present study, the associations between domestic wood heating and asthma phenotypes were not confounded by the rural environment. This is in agreement with the fact that in France wood begins to be widely used for heating even in the urban and peri-urban settings because of its low cost. In addition, it is publicly supported in terms of tax reductions.

The major limitation of our study is that exposures and health outcomes were assessed by questionnaires, without

objective assessments. However, our data collection was prospective and the mothers replied for well-standardised questionnaires that were previously validated. In addition, our findings are consistent with those of other studies conducted in other Western European countries and based on questionnaire investigation [14,36,37]. Another limitation of our study is that the exposure to risk factors was assessed simultaneously with asthma outcomes except for prenatal maternal smoking and *in utero* exposure to traffic-related air pollution. Therefore, the causal link implied by our study should be interpreted with caution. Lastly, the questions for assessing *in utero* and first year of life exposure to traffic-related air pollution were different (as showed in Table 1). This is because, after the survey time point of at birth, in order to take results from recent studies into account [46,47], we modified the questionnaire and assessed distances of the dwellings to major road, and in particular the 200 m circular buffer with which a risk of asthma had been associated. As a consequence, responses for *in utero* and first year of life exposure to traffic were not exactly comparable. In addition, the response rates varied from one survey to the other. Indeed, for some mothers, it was difficult to figure out the exact circular buffer and there were more missing values for the variable of first year of life exposure to traffic-related air pollution than for the variable of *in utero* exposure to traffic-related air pollution. Notably, some mother-child pairs changed their residences after the birth of the child. However, in spite of these differences, the associations between asthma phenotypes and the exposure to traffic-related air pollution *in utero* life and in the first year of life are consistent.

The strength of our investigation lies in the fact that the sample is large and drawn from the general population and that we use standardised instruments for the assessment of both exposure and asthma phenotypes. The fact that our investigation focuses on the first year of life which is crucial for the development of asthma using the data of a birth cohort constitutes an added value. In addition, we used different models to analyse the relationships between asthma outcomes and *in utero* and first year of life exposures respectively, taking into account the temporal sequence in relation to asthma outcomes. We also considered the potential confounders and effect modifiers in the models to show the independent effects of exposures *in utero* life and in the first year of life. Lastly, several asthma phenotypes covering a large spectrum of asthma outcomes in early childhood were included thus reducing misclassification of asthmatic cases.

Conclusions

In our study, asthma outcomes in the first year of life were found to be positively related to maternal smoking, traffic-related air pollution and dampness, but negatively

associated with contact with cats and domestic wood heating. Furthermore, *in utero* exposures to passive smoking and traffic-related air pollution were both related to the development of asthma phenotypes in the first year of life. After adjusting for potential confounders, traffic-related air pollution had a greater impact on the development of asthma phenotypes compared to other factors. Interventional studies need to be implemented to evaluate the consequences of the avoidance or the promotion of these factors.

Consent

Written informed consent was obtained from all participating women for publication of this report and any accompanying images.

Additional file

Additional file 1: Table S1. Association between exposures to air pollutants sources and asthma phenotypes in the first year of life in children of the EDEN mother child cohort study.

Abbreviations

OR: Odds ratio; aOR: Adjusted odds ratio; aPAR: Adjusted Population Attributable Risk; BMI: Body mass index; SD: Standard deviation; NO₂: Nitrogen dioxide; PM₁₀: Particulate matter with an aerodynamic diameter below 10 µm.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IAIM conceived the study. NB and IAIM participated in the data collection. CZ performed statistical analysis and data interpretation with the assistance of NB and SB. CZ wrote the manuscript with the co-supervision of IAIM and TZ. All authors read and approved the final manuscript.

Acknowledgements

We are indebted to the children and the families that participated in this study and to the midwife research assistants (L. Douhaud, S. Bedel, B. Lortholary, S. Gabriel, M. Rogeon, and M. Malinbaum) for data collection, and P. Lavoine, J. Sahuquillo and G. Debotte for data check, coding, and entry. Many thanks to Milica Milivojevic (Imperial College London, United Kingdom) for the help of editing the written English. We acknowledge all the funding sources of the EDEN study: Fondation pour la Recherche Médicale (FRM); French Ministry of Research: IFR program; INSERM Nutrition Research Program; French Ministry of Health Perinatal program; French Agency for Environmental Security (AFFSET); French National Institute for Population Health Surveillance (INVS); Paris sud University; French National Institute for Health Education (INPES); Nestlé, Mutuelle Générale de l'Éducation Nationale (MGEN); French Speaking Association for the Study of Diabetes and Metabolism (ALFEDIAM); National Agency for Research (ANR) and the fellowship of Erasmus Mundus External Cooperation Window (EM ECW) for China, lot 14 coordinated by Lund University. The EDEN Mother Child Cohort Study Group: M. A. Charles, M. de Agostini, A. Forhan, B. Heude, P. Ducimetière, M. Kaminski, M. J. Saurel Cubizolles, P. Dargent, X. Fritel, B. Larroque, N. Lelong, L. Marchand, C. Nabet, I. Annesi Maesano, R. Slama, V. Goua, G. Magnin, R. Hankard, O. Thiebaugeorges, M. Schweitzer, B. Folguet, and N. Job Spira.

Author details

¹Université Pierre et Marie Curie, Paris 6, Sorbonne Universités, UMR S 707: EPAR (Epidémiologie des maladies allergiques et respiratoires), Medical School Saint Antoine, Paris, France. ²INSERM U 707: EPAR, Paris, France. ³School of Public Health, Peking University, Beijing, China.

Received: 6 November 2012 Accepted: 21 May 2013
Published: 24 May 2013

References

1. Anthracopoulos MB, Antonogeorgos G, Liolios E, Triga M, Panagiotopoulou E, Piftis KN: Increase in chronic or recurrent rhinitis, rhinoconjunctivitis and eczema among schoolchildren in Greece: three surveys during 1991–2003. *Pediatr Allergy Immunol* 2009, **20**:180–186.
2. Eder W, Ege MJ, von Mutius E: The asthma epidemic. *N Engl J Med* 2006, **355**:2226–2235.
3. Russell G: The childhood asthma epidemic. *Thorax* 2006, **61**:276–278.
4. March ME, Sleiman PM, Hakonarson H: The genetics of asthma and allergic disorders. *Discov Med* 2011, **11**:35–45.
5. Renz H, Conrad M, Brand S, Teich R, Garn H, Pfefferle PI: Allergic diseases, gene-environment interactions. *Allergy* 2011, **66**(Suppl 95):10–12.
6. Annesi Maesano I: Epidemiology of asthma in the world and in France. *Rev Prat* 2011, **61**:329–335.
7. Sly PD: The early origins of asthma: who is really at risk? *Curr Opin Allergy Clin Immunol* 2011, **11**:24–28.
8. Heinrich J: Influence of indoor factors in dwellings on the development of childhood asthma. *Int J Hyg Environ Health* 2011, **214**:1–25.
9. Gaffin JM, Phipatanakul W: The role of indoor allergens in the development of asthma. *Curr Opin Allergy Clin Immunol* 2009, **9**:128–135.
10. Vork KL, Broadwin RL, Blaisdell RJ: Developing asthma in childhood from exposure to secondhand tobacco smoke: insights from a meta-regression. *Environ Health Perspect* 2007, **115**:1394–1400.
11. Tsai CH, Huang JH, Hwang BF, Lee YL: Household environmental tobacco smoke and risks of asthma, wheeze and bronchitic symptoms among children in Taiwan. *Respir Res* 2010, **11**:11.
12. Hugg TT, Jaakkola MS, Ruotsalainen RO, Pushkarev VI, Jaakkola JJ: Parental smoking sensitization and effects of tobacco smoke on children's health in Finland and Russia. *Eur J Public Health* 2008, **18**:55–62.
13. Jaakkola JJ, Hwang BF, Jaakkola N: Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect* 2005, **113**:357–361.
14. Pirastu R, Bellu C, Greco P, Pelosi U, Pistelli R, Accetta G, Biglieri A: Indoor exposure to environmental tobacco smoke and dampness: respiratory symptoms in Sardinian children. DRIAS study. *Environ Res* 2009, **109**:59–65.
15. Larsson M, Hägerhed Engman L, Moniruzzaman S, Janson S, Sundell J, Bornehag CG: Can we trust cross-sectional studies when studying the risk of moisture-related problems indoors for asthma in children? *Int J Environ Health Res* 2011, **21**:237–247.
16. Pohlmann H, Jacobs S, Böhm J: Exposure to pets and the risk of allergic symptoms during the first 2 years of life. *J Invest Allergol Clin Immunol* 2007, **17**:302–308.
17. Dharmage SC, Lodge CL, Matheson MC, Campbell B, Lowe AJ: Exposure to cats: update on risks for sensitization and allergic diseases. *Curr Allergy Asthma Rep* 2012, **12**:413–423.
18. von Mutius E, Illi S, Nicolai T, Martinez FD: Relation of indoor heating with asthma, allergic sensitization, and bronchial responsiveness: survey of children in south Bavaria. *BMJ* 1996, **312**:1448–1450.
19. Binková B, Bobak M, Chatterjee A, Chauhan A, Dejmeck J, Dockery DW, Everard M, Forastiere F, Gilliland F, Holgate S, Johnston S, Maynard R, Raaschou-Nielsen O, Samet J, Skerrett PJ, Šram RJ, Walters D, Weiland S, Winneke G, Krzyzanowski M, Kuna Dibbert B: *Effects of air pollution on children's health and development: a review of the evidence*. Geneva: World Health Organization; 2005.
20. Tzivian L: Outdoor air pollution and asthma in children. *J Asthma* 2011, **48**:470–481.
21. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, Oldenwening M, Smit HA, Brunekreef B: Traffic related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010, **181**:596–603.
22. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Krämer U, Behrendt H, Herbarth O, von Berg A, Bauer CP, Wichmann HE, Heinrich J, GINI Study Group, LISA Study Group: Atopic diseases, allergic sensitization, and exposure to traffic related air pollution in children. *Am J Respir Crit Care Med* 2008, **177**:1331–1337.
23. Hulin M, Simoni M, Viegi G, Annesi Maesano I: Respiratory health and indoor air pollutants based on quantitative exposure assessments. *Eur Respir J* 2012, **40**:1033–1045.

24. Drouillet P, Kaminski M, De Lauzon Guillaumin B, Forhan A, Ducimetière P, Schweitzer M, Magnin G, Goua V, Thiébauges O, Charles MA: Association between maternal seafood consumption before pregnancy and fetal growth: evidence for an association in overweight women. The EDEN mother-child cohort. *Paediatr Perinat Epidemiol* 2009, **23**:76-86.
25. Omar RZ, Wright EM, Turner RM, Thompson SG: Analysing repeated measurements data: a practical comparison of methods. *Stat Med* 1999, **18**:1587-1603.
26. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C: Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985, **122**:904-914.
27. Forastiere F, Galassi C, Biglieri A, Richiardi L, Baussano I, Simoni M, Viegi G, Gruppo Collaborativo SIDRIA 2: The proportion of respiratory disorders in childhood attributable to preventable and not preventable risk factors. *Epidemiol Prev* 2005, **29**(Suppl 2):67-69.
28. Wu H, Romieu I, Sierra Monge JJ, del Rio Navarro BE, Anderson DM, Dunn BW, Steiner LL, Lara Sanchez Idel C, London SJ: Parental smoking modifies the relation between genetic variation in tumor necrosis factor alpha (TNF) and childhood asthma. *Environ Health Perspect* 2007, **115**:616-622.
29. Blizzard L, Ponsonby AL, Dwyer T, Venn A, Cochrane JA: Parental smoking and infant respiratory infection: how important is not smoking in the same room with the baby? *Am J Public Health* 2003, **93**:482-488.
30. Burke H, Leonardi Bee J, Hashim A, Pine Abata H, Chen Y, Cook DG, Britton JR, McKeever TM: Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012, **129**:735-744.
31. Blondel B, Kermarrec M: *Perinatal Situation in France in 2010: First Results of the National Perinatal Survey*. Paris: DREES; 2010:2011.
32. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëff PN: Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996, **348**:1060-1064.
33. Annesi Maesano I, Moreau D, Caillaud D, Lavaud F, Le Moullec Y, Taytard A, Pauli G, Charpin D: Residential proximity fine particles related to allergic sensitization and asthma in primary school children. *Respir Med* 2007, **101**:1721-1729.
34. Gauderman WJ, Avol E, Lurmann F, Kuenzli N, Gilliland F, Peters J, McConnell R: Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 2005, **16**:737-743.
35. Nordling E, Berglund N, Melén E, Emenius G, Hallberg J, Nyberg F, Pershagen G, Svartengren M, Wickman M, Bellander T: Traffic related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 2008, **19**:401-408.
36. Pénaud Morand C, Raherison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, Annesi Maesano I: Long term exposure to close proximity air pollution and asthma and allergies in urban children. *Eur Respir J* 2010, **36**:33-40.
37. Zmirou D, Gauvin S, Pin I, Mornas I, Sahraoui F, Just J, Le Moullec Y, Biémont F, Cassadou S, Reungoat P, Albertini M, Lauveigne N, Chion M, Labbé A, Vesta Investigators: Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. *J Epidemiol Community Health* 2004, **58**:18-23.
38. Forastiere F, Galassi C: Self report and GIS based modelling as indicators of air pollution exposure: is there a gold standard? *Occup Environ Med* 2005, **62**:508-509.
39. Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi Bee J: Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. *Respir Res* 2011, **12**:5.
40. Karr CJ, Demers PA, Koehoorn MM, Lencar CC, Tamburic L, Brauer M: Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. *Am J Respir Crit Care Med* 2009, **180**:995-1001.
41. Clark NA, Demers PA, Karr CJ, Koehoorn MM, Lencar C, Tamburic L, Brauer M: Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010, **118**:284-290.
42. Smyth RL, Openshaw PJ: Bronchiolitis. *Lancet* 2006, **368**:312-322.
43. Mendell MJ, Miler AG, Cheung K, Tong M, Douwes J: Respiratory and allergic health effects of dampness, mold, and dampness related agents: a review of the epidemiologic evidence. *Environ Health Perspect* 2011, **119**:748-756.
44. Platts Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R: Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population based cross sectional study. *Lancet* 2001, **357**:752-756.
45. Kilpeläinen M, Koskenvuo M, Helenius H, Terho E: Wood stove heating, asthma and allergies. *Respir Med* 2001, **95**:911-916.
46. Gilbert NL, Woodhouse S, Stieb DM, Brook JR: Ambient nitrogen dioxide and distance from a major highway. *Sci Total Environ* 2003, **312**:43-46.
47. Cesaroni G, Badaloni C, Porta D, Forastiere F, Perucci CA: Comparison between various indices of exposure to traffic related air pollution and their impact on respiratory health in adults. *Occup Environ Med* 2008, **65**:683-690.

doi:10.1186/1471-2458-13-506

Cite this article as: Zhou et al.: Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. *BMC Public Health* 2013 **13**:506.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit



Additional file 1 – Association between exposures to air pollutants sources and asthma phenotypes in the first year of life in children of the EDEN study

	aOR [†] (95% CI)	aPAR(%) [‡] (95%CI)
Single phenotypes		
Ever bronchiolitis		
Heavy parental smoking in the last 12 months	1.65(1.16,2.33)	6.50(2.29,9.48)
Traffic-related air pollution in the last 12 months	1.18(0.90,1.55)	—
Dampness in the past 12 months	1.32(0.80,2.18)	—
Contact with cats in the past 12 months	0.69(0.47,1.03)	—
Domestic wood heating in the past 12 months	0.63(0.38,1.06)	—
Ever wheezing		
Heavy parental smoking in the past 12 months	1.53(1.06,2.19)	6.56(1.13,10.35)
Traffic-related air pollution in the past 12 months [§]	1.47(1.09,1.97)	9.67(2.50,14.89)
Boys	2.01(1.16,3.48)	13.05(3.58,18.51)
Girls	0.56(0.28,1.15)	—
Dampness in the past 12 months	2.12(1.30,3.46)	4.84(2.13,6.50)
Contact with cats in the past 12 months	0.94(0.61,1.46)	—
Domestic wood heating in the past 12 months	0.53(0.27,1.03)	—
Ever doctor-diagnosed asthma		
Heavy parental smoking in the last 12 months	1.25(0.68,2.29)	—
Traffic-related air pollution in the last 12 months	1.71(1.08,2.72)	13.52(2.38,20.53)
Dampness in the past 12 months	2.19(1.06,4.53)	5.26(0.56,7.54)
Contact with cats in the past 12 months	0.27(0.08,0.86)	-11.50(-46.65,-0.67)
Domestic wood heating in the past 12 months	0.97(0.37,2.50)	—
Multi-dimensional phenotypes		
Bronchiolitis with wheezing		
Heavy parental smoking in the last 12 months	1.48(0.99,2.21)	—
Traffic-related air pollution in the last 12 months	1.44(1.05,1.99)	9.39(1.32,15.25)
Dampness in the past 12 months	1.88(1.09,3.24)	4.00(0.72,5.90)
Contact with cats in the past 12 months	0.80(0.48,1.33)	—
Domestic wood heating in the past 12 months	0.31(0.12,0.79)	-4.70(-15.14,-0.57)
Doctor-diagnosed asthma with a history of bronchiolitis		
Heavy parental smoking in the last 12 months	1.24(0.63,2.43)	—
Traffic-related air pollution in the last 12 months	2.01(1.23,3.30)	17.78(6.54,24.63)
Dampness in the past 12 months	1.77(0.76,4.09)	—
Contact with cats in the past 12 months	0.22(0.05,0.91)	-14.41(-72.19,-0.39)
Domestic wood heating in the past 12 months	0.46(0.11,1.93)	—
Doctor-diagnosed asthma with wheezing		
Heavy parental smoking in the last 12 months	1.40(0.76,2.58)	—
Traffic-related air pollution in the last 12 months	1.71(1.05,2.77)	13.27(1.59,20.50)
Dampness in the past 12 months	2.21(1.04,4.71)	5.52(0.35,7.95)
Contact with cats in the past 12 months	0.31(0.09,0.99)	-10.55(-45.04,-0.01)
Domestic wood heating in the past 12 months	0.85(0.30,2.42)	—

Doctor-diagnosed asthma with wheezing and a history of bronchiolitis

Heavy parental smoking in the last 12 months	1.31(0.67,2.59)	—
Traffic-related air pollution in the last 12 months	1.90(1.14,3.15)	15.92(4.11,23.01)
Dampness in the past 12 months	1.90(0.82,4.43)	—
Contact with cats in the past 12 months	0.23(0.06,0.97)	-14.16(-78.77,-0.13)
Domestic wood heating in the past 12 months	0.23(0.03,1.68)	—

[†]aOR: odds ratio adjusted by potential confounders of study center, maternal occupation, maternal age at recruitment, maternal pre-pregnancy body mass index (BMI), birth weight, cesarean delivery, preterm birth, breastfeeding, siblings, gender and family history of asthma, eczema, allergic rhinitis or food allergy, according to the multivariable logistic regression models.

[‡]aPAR: adjusted population attributable risk based on multivariable logistic regression models;

[§]Interaction between gender and traffic-related air pollution in the last 12 months.

3.2.3 Complementary results from the EDEN mother-child cohort study

3.2.3.1 Relationships between *in utero* exposures to air pollutants sources and health outcomes in the first 5 years of life.

In order to confirm the relationships between *in utero* exposures to air pollutants sources and the development of asthma in the first year of life in our study population, we used GEE model to examine the relationships between maternal smoking during pregnancy and *in utero* exposure to traffic-related air pollution, and health outcomes in the first 5 years of life in children of the EDEN mother-child cohort study (results were described in table 7).

Results showed that maternal smoking during pregnancy was related to the development of wheezing in the first 5 years of life, while *in utero* exposure to traffic-related air pollution was related to the development of wheezing and allergic rhinoconjunctivitis in the first 5 years of life. Compared to maternal smoking during pregnancy, *in utero* exposure to traffic-related air pollution had greater impacts on the development of respiratory health outcomes according to the values of aPARs. This confirms previous results and suggests that maternal smoking and *in utero* exposure to traffic-related air pollution could contribute to the causality chain in asthma development.

Table 7 – Association between *in utero* exposures to air pollutants sources and health outcomes in the first 5 years of life in children of the EDEN mother-child cohort study (n=722)

Health outcomes	aOR [†] (95% CI)	aPAR(%) [‡] (95%CI)
Ever wheezing		
Maternal smoking during pregnancy	1.24(1.01,1.52)	4.54(0.23,8.03)
<i>In utero</i> exposure to traffic-related air pollution	1.23(1.01,1.50)	5.38(0.28,9.29)
Ever doctor-diagnosed asthma		

Maternal smoking during pregnancy	0.93(0.60,1.43)	—
In <i>utero</i> exposure to traffic-related air pollution	1.19(0.79,1.79)	—
Ever doctor-diagnosed eczema		
Maternal smoking during pregnancy	1.27(0.92,1.77)	—
In <i>utero</i> exposure to traffic-related air pollution	1.19(0.89,1.61)	—
Ever allergic rhinoconjunctivitis		
Maternal smoking during pregnancy	1.11(0.71,1.71)	—
In <i>utero</i> exposure to traffic-related air pollution	1.71(1.16,2.51)	13.72(4.56,19.88)

aOR, adjusted odds ratio; CI, confidence interval;

[†]aOR:odds ratio adjusted by potential confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

[‡]aPAR: adjusted population attributable risk based on GEE models

3.2.3.2 Relationships between objectively measured outdoor air pollutants in *utero* life and health outcomes in the first 5 years of life

In order to further examine the relationships between *in utero* exposures to objectively measured air pollutants *in utero* life and the development of asthma in early life in our study population, we used GEE model to explore the relationships between an interquartile increase of *in utero* exposures to outdoor air pollutants and health outcomes in the first 3 years and the first 5 years of life (table 8) in children of the EDEN mother-child cohort study, respectively.

No significant relationships were found between objectively measured outdoor air pollutants *in utero* life and the development of asthma both in the first 3 years of life and in the first 5 years of life. However, a trend existed between ever wheezing and rhinoconjunctivitis and benzene, between ever wheezing and doctor-diagnosed eczema and CO, and between ever wheezing and VOCs. The similar results was indicated in the recently published data of ESCAPE project, which showed that no significant associations between air pollution exposure at birth address (assessed by land-use regression models) and lung function in children aged 6-8 years¹²⁸.

Table 8 – Association between an interquartile increase of *in utero* exposures to outdoor air pollutants and health outcomes in early life in children of the EDEN mother-child cohort study

Health outcomes	The first 3 years of life (n=1222)		The first 5 years of life (n=722)	
	IQR ($\mu\text{g}/\text{m}^3$)	aOR [†] (95 % CI)	IQR ($\mu\text{g}/\text{m}^3$)	aOR [†] (95 % CI)
Ever wheezing				
Benzene	2.09-2.21	1.03 (0.98-1.09)	2.10-2.21	1.02 (0.97-1.07)
CO	489.19-568.23	1.15 (0.99-1.34)	494.07-580.88	1.03 (0.88-1.19)
NO ₂	18.09-28.28	1.03 (0.86-1.23)	17.84-24.04	1.03 (0.95-1.12)
PM ₁₀	18.00-21.89	0.98 (0.83-1.16)	17.78-21.67	0.98 (0.85-1.13)
SO ₂	2.61-3.33	1.02 (0.91-1.16)	2.67-3.31	0.98 (0.89-1.08)
VOCs	4.07-6.83	1.04 (0.96-1.12)	4.02-6.08	1.03 (0.99-1.07)
Ever doctor-diagnosed asthma				
Benzene	2.09-2.21	0.95 (0.84-1.08)	2.10-2.21	0.89 (0.77-1.03)
CO	489.19-568.23	1.00 (0.73-1.36)	494.07-580.88	0.93 (0.70-1.23)
NO ₂	18.09-28.28	0.94 (0.68-1.32)	17.84-24.04	1.11 (0.94-1.31)
PM ₁₀	18.00-21.89	0.93 (0.68-1.27)	17.78-21.67	0.94 (0.69-1.27)
SO ₂	2.61-3.33	0.97 (0.75-1.24)	2.67-3.31	1.10 (0.91-1.32)
VOCs	4.07-6.83	0.93 (0.80-1.09)	4.02-6.08	0.99 (0.91-1.08)
Ever doctor-diagnosed eczema				
Benzene	2.09-2.21	0.96 (0.88-1.05)	2.10-2.21	1.02 (0.94-1.11)
CO	489.19-568.23	1.13 (0.95-1.35)	494.07-580.88	1.11 (0.86-1.44)
NO ₂	18.09-28.28	0.93 (0.74-1.17)	17.84-24.04	0.95 (0.83-1.09)
PM ₁₀	18.00-21.89	1.05 (0.87-1.28)	17.78-21.67	0.99 (0.81-1.20)
SO ₂	2.61-3.33	1.07 (0.93-1.23)	2.67-3.31	0.99 (0.92-1.06)
VOCs	4.07-6.83	1.02 (0.94-1.10)	4.02-6.08	0.98 (0.87-1.11)
Ever allergic rhinoconjunctivitis				
Benzene	2.09-2.21	1.10 (0.97-1.26)	2.10-2.21	1.01 (0.94-1.09)
CO	489.19-568.23	1.10 (0.85-1.42)	494.07-580.88	0.84 (0.64-1.11)
NO ₂	18.09-28.28	1.00 (0.76-1.33)	17.84-24.04	1.01 (0.86-1.18)
PM ₁₀	18.00-21.89	0.93 (0.72-1.20)	17.78-21.67	0.89 (0.69-1.14)
SO ₂	2.61-3.33	1.03 (0.86-1.23)	2.67-3.31	0.95 (0.81-1.10)

VOCs	4.07-6.83	1.01 (0.91-1.12)	4.02-6.08	1.00 (0.93-1.07)
------	-----------	------------------	-----------	------------------

aOR: adjusted prevalence odds ratio; CI, confidence interval; IQR, interquartile range for the concentrations of outdoor air pollutants.

[†]aOR: odds ratio adjusted by potential confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

4. Psychological features and childhood asthma

4.1 Evidence from French 6 cities study

4.1.1 *Presentation of article 2*

In article 2, we explored the relationships between psychological features and asthma severity and early onset in school children. The psychological disorders, namely behavioural problems, were assessed by the SDQ questionnaire. Asthma outcomes were assessed by the ISAAC questionnaire. Asthma severity was classified as intermittent, mild persistent, moderate persistent (in our study, no child had severe persistent asthma), while early-onset asthma was defined as an asthma having started in the first 4 years of life. Results showed that children with abnormal or borderline emotional or conduct problems were found to be more asthmatic. Compared to being normal, abnormal or borderline emotional or conduct problems were found to be related to mild to moderate persistent asthma and to an asthma having started before the age of 4 years. No relationship was found between behavioural problems and asthma management and treatment adherence.

4.1.2 Article 2. Externalizing and internalizing behavioural problems related to asthma in school children

BRIEF COMMUNICATION

Externalizing and internalizing behavioural problems related to asthma in school children

I. Annesi-Maesano^{1,2}, C. Zhou^{1,2}, N. Baiz^{1,2}, S. Banerjee^{1,2}, D. André Charpin³, D. Caillaud⁴, F. de Blay⁵, C. Raherison^{6,7} & F. Lavaud⁸

¹EPAR, INSERM, Paris; ²EPAR, Université Pierre et Marie Curie, Paris; ³Hôpital Nord, Marseille; ⁴Hôpital Gabriel Montpied, Clermont Ferrand; ⁵Hôpital Civils, Strasbourg; ⁶Hôpital du Haut Lévêque, Bordeaux; ⁷ISPED Université, Bordeaux; ⁸Hôpital Maison Blanche, Reims, France

To cite this article: Annesi-Maesano I, Zhou C, Baiz N, Banerjee S, André Charpin D, Caillaud D, de Blay F, Raherison C, Lavaud F. Externalizing and internalizing behavioural problems related to asthma in school children. *Allergy* 2013; 68: 1471–1474.

Keywords

asthma; behavioural problems; onset; severity; Strengths and Difficulties Questionnaire.

Correspondence

Isabella Annesi Maesano, Epidemiology of Allergic and Respiratory Department, UMR S 707, INSERM and UPMC Paris 6, Medical School Pierre et Marie Curie, Site Saint Antoine, 27 rue Chaligny, 75571 Paris Cedex 12, France.
Tel.: +33 144 73 84 37
Fax: +33 144 73 84 54
E-mail: isabella.annesi-maesano@inserm.fr

Accepted for publication 20 July 2013

DOI:10.1111/all.12241

Edited by: Stephan Weidinger

Abstract

We investigated the relationships of behavioural problems as assessed using the standardized Strengths and Difficulties Questionnaire (SDQ) to asthma in view of improving asthma management. Six thousand eight hundred and eighty children (mean age 10.4 years, male: 49%) were recruited in the French 6 Cities Study. Children with abnormal or borderline emotional symptoms (internalizing problems) or conduct problems (externalizing problems) were more asthmatic than others ($P < 0.01$). Compared to being normal, abnormal emotional symptoms or conduct problems were found to be related to mild-to-moderate persistent asthma (logistic model adjusted odds ratio = 1.55 (95% CI = 1.26–1.90) and 1.42 (95% CI = 1.17–1.71), respectively) and to early-onset asthma (Cox's model Adjusted Hazard Risk = 1.60 (95% CI = 1.27–2.01) and 1.34 (95% CI = 1.05–1.70). Borderline conduct problems were found to be negatively related to parents' knowledge on how to prevent asthma attacks, compared to normal conduct problems (adjusted OR = 0.51 (95% CI = 0.31–0.85)). Further data are needed to better understand the involvement of behavioural problems in childhood asthma according to phenotypes.

Asthma is a common chronic disease (1) caused by a variety of factors (2). Recently, asthma has also been associated with stress and other psychological factors (3–5), although whether these precede or follow asthma is still controversial (Table 1). Among them, few investigations have investigated whether the association is modulated by asthma phenotypes, which could be useful for improving asthma management (3, 4, 6–8). All these studies used small populations.

The aim of this study was to investigate, in a large population-based sample of children and using internationally referenced instruments, the relationships between behavioural problems and current asthma considering its severity and age of onset, management and treatment adherence.

Methods

Participants

Nine thousand six hundred and fifteen children recruited in relevant primary school classes (CM1 and CM2 in France) in schools randomly selected in the frame of the French 6 City study (6C Study) (9) participated.

Behavioural problems

Emotional symptoms (internalizing problems) and conduct problems (externalizing problems) were assessed through the French validated version of the SDQ (Strengths and Difficulties Questionnaire) questionnaire scales. In each scale, all five items were scored based on a three-point Likert scale: 0 for 'not true', 1 for 'somewhat true' or 2 for 'very true' and summed up into a total score ranging from 0 to 10. According to the normative banding method for parent-reported SDQ scores in France (10), children were classified into 'normal', 'borderline' or 'abnormal' using the following cut-off points: 0–3, 4 and 5–10, respectively, for emotional (internalizing) problems; and 0–2, 3–4 and 10, respectively, for conduct (externalizing) problems.

Asthma outcomes

The International Study of Asthma and Allergies in Childhood (ISAAC) Questionnaire filled by parents was used to assess current asthma (defined by wheezing or whistling in the chest in the past year and having ever had asthma) and

Table 1 Comparison of our study with prospective studies having investigated relationships between behavioural problems and childhood asthma

Studies	Differences					
	Age of samples	Behaviours/ instruments	Outcomes	Adjusted odds ratios/hazard risk, and other results	Confounders	Comments
Sandberg et al. (3) Acute and chronic stress and asthma attack	Recruited age: 6–13, followed up for 18 months (<i>n</i> = 90)	Life events/ PACE	New asthma attacks	Asthma attacks in subsequent 2–4 weeks: 1.71 (1.04–2.82); Asthma attacks in subsequent 4–6 weeks: 2.17 (1.32–3.57)	Age, sex, social class, parental smoking, season and asthma history	Not differentiating internalizing and externalizing problems, and small study population
Stevenson et al. (6) Relation between behavioural and asthma	Recruited age: 1–2, followed up for 18 months (<i>n</i> = 265)	Behavioural problems/BSQ	Asthma onset at age of 35–53 months	1.15 (1.02–1.29)	Treatment, IgE level for house dust mite, IgE level for grass pollen	
Calam et al. (7) Behavioural Problems antecede wheeze	Recruited prenatally, reviewed at ages of 3 and 5 (<i>n</i> = 771)	Behavioural problems/ECBI	Development of wheezing (parent report)	3.5 (1.2–9.9)	Gender, maternal smoking, socioeconomic status	
Martin et al. (8) Acute stress and chronic family stress and immune change	Recruited age: 9–18, followed up for 2 years (<i>n</i> = 147)	Acute and chronic stress/ UCLALSI CV	Production of cytokine interleukin (IL 4, IL 5, IL 13, and IFN γ) and asthma symptoms	Increased production of IL 4, IL 5, IFN γ and increased asthma symptoms	Medication, asthma severity and socioeconomic status	
6 Cities Study	Recruited age: 8–13, cross sectional study (<i>n</i> = 6 880)	Internalizing and externalizing disorders/SDQ	Asthma severity and morbidity	1.55 (1.26–1.90) for internalizing problems and 1.42 (1.17–1.71) for externalizing problems	Child age, Gender, family history of asthma, passive smoking, mother age at delivery, parental educational level, parental socioeconomic status, family background and the number of children	The study could differentiate internalizing and externalizing problems, and large study population

PACE, The Psychosocial Assessment of Childhood Experiences; BSQ, Behavior Screening Questionnaire; ECBI, The Eyberg Child Behavior Inventory; UCLALSI CV, University of California Los Angeles Life Stress Interview Child Version; SDQ, Strengths and Difficulties Questionnaire.

asthma management and treatment adherence. Asthma severity at the period of the survey was classified as intermittent, mild persistent, moderate persistent and severe persistent using the 2004 Global Initiative for Asthma (GINA) guidelines (11). Early-onset asthma was defined as an asthma having started in the first 4 years of life according to the 'Carnet de Santé', which is compulsory in France, filled by the physician.

Statistical analysis

Classical statistical analysis was used to describe the sample and investigating missing data. Logistic proportional odds model for ordinal responses (12) was used to obtain odds ratios (OR) between behavioural problems and asthma outcomes after adjustment for potential confounders. The Cox's proportional hazard model was used to compute hazard ratio

of the relationship between behavioural problems and asthma onset.

Version 9.3 of sas system (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Ethics

This study was approved by the French national Ethics Board (C.C.P.P.R.B., approval number: 01/07, Marseille AP, France). Parents signed a formal consent after having been informed about the study.

Results

Characteristic of study population

The 6880 children (72%) included in the analyses from 401 classrooms of 108 schools were aged 10.4 years in mean and in majority women (51%). They did not differ in characteristics and asthma outcomes from children with missing data ($P > 0.05$).

Behavioural problems and asthma outcomes

Emotional symptoms were abnormal in 15% of the children and borderline in 10%, whereas conduct problems were abnormal in 14% and borderline in 14%.

Children with behavioural problems, either emotional symptoms or conduct problems, had higher asthma prevalence rates ($P < 0.05$), and the relationships persisted after adjustment for confounders (Fig. 1). Emotional symptoms and conduct problems were related to an early asthma onset (50%) [HR = 1.60 (95% CI = 1.27–2.01) and 1.34 (95% CI = 1.05–1.70), respectively]. Borderline conduct problems were found to be negatively related to parents' knowledge on how to prevent asthma attack, compared to normal conduct problems [adjusted OR = 0.51 (95% CI = 0.31–0.85)].

Discussion

In our large population-based sample of children, internalizing and externalizing behavioural problems were related to mild to persistent asthma.

The evidence indicating the association between asthma and behavioural problems is increasing (3–8). Recently, Kohlboeck et al. (5) reported the association between asthma and emotional symptoms overall in nonatopic children, which contrasts with our results with a stronger link in atopic children. Several hypotheses have been proposed to explain why behavioural problems are related to asthma. Child's behavioural difficulties may result in part from disturbed family functioning or family structure also related to child's asthma (13). This could also depend on maternal depression associated with child's behaviour and lower self-efficacy in ability to care for their children with asthma. Lastly, behaviour could be at the origin of increasing symptoms frequency and asthma severity through poor asthma management (14). However, our findings did not support this explanation, as asthma management and treatment

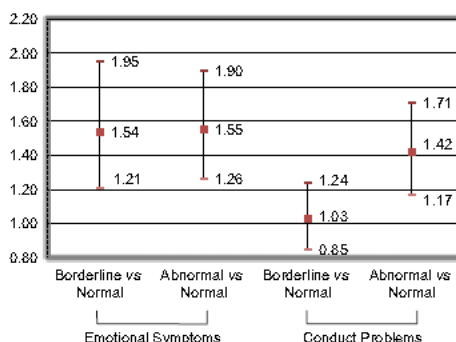


Figure 1 Relationships between asthma severity according to GINA and behavioural problems in the French 6 Cities study ($n = 6880$). Asthma prevalence: 16.7%, 16.0% and 11.1%, in abnormal, borderline and normal emotional symptoms respectively and 17.3%, 14.2% and 11.4%, in abnormal, borderline and normal conduct problems respectively. Squares are odds ratios (assessed by an adjusted logistic proportional odds model); bars are 95% Confidence Intervals. Confounders include: age, gender, family history of asthma and allergic diseases, passive smoking, mother age at delivery, parental educational level, parental socioeconomic status, family background (intact family, one parent family or other), and the number of children in the household. Asthma severity was classified as intermittent, mild persistent, moderate persistent (in our study, no child had severe persistent asthma, based on the combined assessments of asthma symptoms (frequency of diurnal and night attacks), peak expiratory flow and daily medication regimen for asthmatics already on treatment).

adherence were not associated with behavioural problems in our sample, except for parents' knowledge on how to prevent asthma attack relating to conduct problems. The potential physiological explanation for the relationships between behavioural problems and childhood asthma could be that children with externalizing and internalizing behavioural problems show high autonomic nervous system reactivity principally in the parasympathetic branch (15). Behavioural problems could also impact on the central nervous system to release hormones affecting the immune system, leading to increase Th2 (T helper-2 type) immune response to increase the risk of asthma (16). In our study, we found that both emotional (internalizing) and conduct (externalizing) problems were related to atopic asthma, which supports the hypothesis of an intervention of stress in allergic response. We also observed a link between behavioural problems and early-onset asthma that deserves to be further explained. To sum up, a complex picture of the behavioural difficulties associated with paediatric asthma has to be retained (17) to explain the link between behaviour and asthma in children.

Our results must be taken with caution because parents were the informant about both asthma and behavioural symptoms in our study. The cross-sectional study design

could also limit our results as it did not allow us exploring the possible causal relationships between behavioural problems and childhood asthma. Another limitation lies in the fact that we assessed asthma management and treatment adherence by a small set of screening questions with unknown psychometric properties, thus the results may not show the potential relationships between behavioural problems and asthma management and treatment adherence in our study population.

The strength of our study lies in the fact that we use data drawn from the general population and that a large sample is included in the study. In addition, we could differentiate internalizing and externalizing problems.

In conclusion, in our large sample drawn from the general population, emotional and conduct problems were positively associated with mild-to-moderate persistent asthma, thus suggesting the involvement of behavioural difficulties in childhood asthma. Whether behaviour adjustment has to be taken into account in the management of asthma needs further *ad hoc* investigations.

Acknowledgments

We are particularly indebted to the pupils and their parents without whom the study would not have been possible. We thank David Moreau (EPAR, UMR-S 707) who initially contributed to the manuscript, created the data set and contributed to the statistical analysis.

Author contributions

Isabella Annesi-Maesano: Prof. Annesi-Maesano conceptualized and designed the study, drafted the initial manuscript,

and approved the final manuscript as submitted. Caihang Zhou: Mr. Zhou engaged in the data set preparation, carried out the data analysis with Nour Baiz, Soutrik Banerjee and Prof. Annesi-Maesano, assisted in the drafting of the initial manuscript, and approved the final manuscript as submitted. Nour Baiz: Dr. Baiz engaged in the data set preparation, assisted in the data analysis, reviewed the manuscript and approved the final manuscript as submitted. Soutrik Banerjee: Dr. Banerjee assisted in the data analysis, reviewed the manuscript and approved the final manuscript as submitted. Denis André Charpin: Prof. Charpin participated in designing the data collection instruments, coordinated and supervised data collection in Marseille, reviewed the manuscript and approved the final manuscript as submitted. Denis Caillaud: Prof. Caillaud participated in designing the data collection instruments, coordinated and supervised data collection in Clermont-Ferrand, reviewed the manuscript and approved the final manuscript as submitted. Frédéric de Blay: Prof. de Blay reviewed the manuscript and approved the final manuscript as submitted. Chantal Raherison: Prof. Raherison participated in designing the data collection instruments, coordinated and supervised data collection in Bordeaux, reviewed the manuscript and approved the final manuscript as submitted. François Lavaud: Prof. Lavaud participated in designing the data collection instruments, coordinated and supervised data collection in Reims, reviewed the manuscript and approved the final manuscript as submitted.

Conflicts of interest

Dr. Annesi-Maesano, Mr. Zhou, Dr. Baiz, Dr. Banerjee, Dr. Charpin, Dr. Caillaud, Dr. Blay, Dr. Raherison and Dr. Lavaud have no competing interests to disclose.

References

1. Brannan SS. The global burden of asthma. *Chest* 2006;130:4–12.
2. Baiz N, Annesi-Maesano I. Is the asthma epidemic still ascending? *Clin Chest Med* 2012;33:419–429.
3. Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356:982–987.
4. Tibboch MM, Verhaak CM, Merkus PJ. Psychological characteristics associated with the onset and course of asthma in children and adolescents: a systematic review of longitudinal effects. *Patient Educ Couns* 2011;82:11–19.
5. Kohlböck G, Koletzko S, Bauer CP, von Berg A, Berdel D, Krämer U et al. Association of atopic and non-atopic asthma with emotional symptoms in school children. *Pediatr Allergy Immunol* 2013;24:230–236.
6. Stevenson J. ETA-C Study Group. Relationship between behaviour and asthma in children with atopic dermatitis. *Psychosom Med* 2003;65:971–975.
7. Calam R, Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems antecede the development of wheeze in childhood: a birth cohort study. *Am J Respir Crit Care Med* 2005;171:323–327.
8. Marin TJ, Chen E, Munch JA, Miller GE. Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. *Psychosom Med* 2009;71:378–384.
9. Annesi-Maesano I, Moreau D, Caillaud D, Lavaud F, Le Moullec Y, Tayard A et al. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respir Med* 2007;101:1721–1729.
10. Shojaei T, Wazana A, Pitrou I, Kovess V. The strengths and difficulties questionnaire: validation study in French school-aged children and cross-cultural comparisons. *Soc Psychiatry Psychiatr Epidemiol* 2009;44:740–747.
11. Von Mutius E. Presentation of new GINA guidelines for paediatrics. The Global Initiative on Asthma. *Clin Exp Allergy* 2000;30:6–10.
12. Ananth CV. Regression models for ordinal responses: a review of methods and applications. *Int J Epidemiol* 1997;26:1323–1333.
13. Victorino OC, Gauthier AH. The social determinants of child health: variations across health outcomes—a population-based cross-sectional analysis. *BMC Pediatr* 2009;17:9–53.
14. Barton C, Clarke D, Sulaiman N, Abramson M. Coping as a mediator of psychosocial impediments to optimal management and control of asthma. *Respir Med* 2003;97:747–761.
15. Boyce WT, Quas J, Alkan A, Smider NA, Essex MJ, Kupfer DJ et al. Autonomic reactivity and psychopathology in middle childhood. *Br J Psychiatry* 2001;179:144–150.
16. Trueba AF, Ritz T. Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology. *Brain Behav Immun* 2013;29:11–27.
17. Klimert MD, McQuaid EL, McCormick D, Adinoff A, Bryant NE. A multimethod assessment of behavioral and emotional adjustment in children with asthma. *J Pediatr Psychol* 2000;25:35–46.

4.2 Evidence from the EDEN mother-child cohort study

4.2.1 *Presentation of article 3*

In article 3, we tested the hypothesis that maternal depression during pregnancy related to the development of childhood asthma and allergies in early life. Maternal depression was assessed by the Centre for Epidemiological Studies-Depression scale (CES-D). The health outcomes included wheezing, doctor-diagnosed asthma, doctor-diagnosed eczema and allergic rhinoconjunctivitis in the first 5 years of life. Results showed that there were significant relationships between maternal depression during pregnancy and the development of allergic rhinoconjunctivitis in the first 5 years of life of the children in EDEN mother-child cohort study, while no significant relationships were found between maternal depression during pregnancy and the development of wheezing, doctor-diagnosed asthma and doctor-diagnosed eczema.

4.2.2 Article 3. Maternal depression during pregnancy according to the CES-D scale related to allergic rhinoconjunctivitis in the first 5 years of life in children of the EDEN mother-child cohort study

Maternal depression during pregnancy according to the CES-D scale related to allergic rhinoconjunctivitis in the first 5 years of life in children of the EDEN mother-child cohort study (submitted to Epidemiology)

Cailiang Zhou^{1,2,3}, Ibanez Gladys^{1,4}, Tuohong Zhang³, Nour Baiz^{1,2}, Soutrik Banerjee^{1,2}, Julie Chastang^{1,2}, Isabella Annesi-Maesano^{1,2*}, The EDEN Mother-Child Cohort Study Group[§]

¹Sorbonne Universités, UPMC Univ Paris 06, UMR S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, Paris, France

²INSERM, UMR S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, Paris, France

³School of Public Health, Peking University, Beijing, China;

⁴INSERM, UMR S 953, Epidemiological Research Unit on Perinatal Health and Women's and Children's Health, Hôpital Tenon, Paris, France.

*Corresponding to: Isabella Annesi-Maesano, Epidemiology of allergic and respiratory department, UMR-S 707, INSERM and UPMC Paris 6, Medical School Pierre et Marie Curie, Site Saint-Antoine, 27 rue Chaligny, 75571 Paris CEDEX 12 (France)

Tel. +33 144 73 84 37, Fax +33 144 73 84 54,

E-mail: isabella.annesi-maesano@inserm.fr

[§]The EDEN Mother-Child Cohort Study Group: M. A. Charles, M. de Agostini, A. Forhan, B. Heude, P. Ducimetière; M. Kaminski, M. J. Saurel-Cubizolles, P. Dargent, X. Fritel, B. Larroque, N. Lelong, L. Marchand, C. Nabert; I. Annesi-Maesano, R. Slama; V. Goua, G. Magnin, R. Hankard; O. Thiebaugeorges, M. Schweitzer, B. Foliguet, and N. Job-Spira

Abstract

BACKGROUND

Evidence on relationship between maternal depression and the development of childhood asthma and allergies in early life is still scarce. We aim to examine this relationship using data set of EDEN mother-child cohort study.

METHODS

One thousand one hundred and thirty-nine children were followed-up until the age of 5 years. Maternal depression was self-reported through the Centre for Epidemiological Studies-Depression scale (CES-D) questionnaire. Maternal depression was classified into binary variable (maternal depression: CES-D scores ≥ 16 , and no maternal depression: CES-D scores < 16). Asthma and allergies in the first 5 years of life were assessed using the questionnaire of International Study of Asthma and Allergies in Childhood. Adjusted odds ratio (aOR) was estimated for the relationship between maternal depression and early-life asthma and allergies by marginal models through the method of generalized estimating equation (GEE), adjusting for the confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

RESULTS

In our study population, 13.67 % of the mothers had clinical significant depression (the total scores for CES-D ≥ 16) during pregnancy. For children at ages of 5 years, the prevalences of wheezing, doctor-diagnosed asthma, doctor-diagnosed eczema and allergic rhinoconjunctivitis were 46.78 %, 20.99 %, 29.17 %, and 22.54 %, respectively. Maternal depression during pregnancy was associated with ever ever allergic rhinoconjunctivitis (aOR = 1.87 (95% CI=1.33-2.62)). No significant relationships were found between maternal depression during pregnancy and wheezing, doctor-

diagnosed asthma and doctor-diagnosed eczema (aOR = 1.12 (95% CI=0.91-1.39), 1.23 (95% CI=0.81-1.85) and 1.17 (95% CI=0.86-1.61, respectively).

CONCLUSIONS

Maternal depression during pregnancy is related to ever allergic rhinoconjunctivitis in the first 5 years of life in children of EDEN mother-child cohort study.

Keywords: asthma, allergies, maternal depression, CES-D, early life, children

Introduction

In utero life is an important period for the development of immune system, which is crucial for the development of asthma and allergies^{100, 129}. In previous studies, *in utero* life stressors have well been identified as critical factors that impact on asthma and allergies of children in early life^{75, 92, 100, 130-131}. Peter JL et al¹³⁰ has summarized findings on prenatal environmental factors influencing atopy and early asthma. Results support the influence of maternal exposures to environmental pollutants, such as allergens, traffic-related air pollution, tobacco smoke, and organochlorine and social factors on asthma and allergies. However, few studies examined the relationships between maternal psychological disorders during pregnancy and the development of asthma and allergies. Recently, de Marco R et al⁷⁵ has reported the impact of foetal exposure to maternal stressful life events during pregnancy (SLEP) on asthma and atopic diseases, results showed that children of mothers who had experienced SLEP had moderate risk of developing wheezing, asthma, eczema and allergic rhinitis during their childhood. Cookson H et al⁹² have found that maternal anxiety during pregnancy (measured by anxiety scale of the Crown-Crisp Experiential Index (CCEI)) was related to asthma in children aged 7 ½ years.

The purpose of our study is to explore the potential relationship between maternal depression during pregnancy (assessed by Centre for Epidemiological Studies-Depression scale (CES-D) questionnaire) and the risk of developing asthma and allergies in the first 5 years of life.

Methods

Study population and data collection

In EDEN (Study of pre- and post-natal determinants of children's growth and development) mother-child cohort study, we recruited 2002 pregnant women (<24 weeks of amenorrhea (WA)) in

Nancy and Poitiers in 2003. One thousand one hundred and thirty-nine mother-child pairs were followed-up until the age of 5 years (the sample size of our study).

Measurement of maternal depression

To measure maternal depression, we used the self-reported CES-D questionnaire which was completed by mothers between 24 and 28 WA. This self-administered questionnaire included 20 items, of which each was scored from 0 (never) to 3 for (all the time). The score of each item was then added up into a total score, ranging from 0 to 60. In the statistical models, maternal depression was classified into binary variable according to the total scores (maternal depression: CES-D scores \geq 16 and no maternal depression: CES-D scores $<$ 16).

Measurement of health outcomes

Health outcomes were assessed by ISAAC questionnaires filled by the parents for the period: 0-4 months, 4-8 months, 8-12 months, between 1 and 2 years, between 2 and 3 years, between 3 and 4 years, between 4 and 5 years. For the analyses, the following health outcomes were considered: wheezing, doctor-diagnosed asthma, doctor-diagnosed eczema and allergic rhinoconjunctivitis at 1 year, 2 years, 3 years, 4 years and 5 years. One health outcome was considered as present in the first year of life if it was reported at least once at one of the 4 questionnaire distributed in the first year of life.

At each period of follow-up, detailed questions were as follows: wheezing was defined by a “yes” response to question of “Did your child ever have wheezing or whistling in the chest?”. Ever doctor-diagnosed asthma was defined by a “yes” response to question of “Did your child have a diagnosed asthma by a physician?”. Doctor-diagnosed eczema was identified by “yes” responses to all of the questions of “Did you child ever have a doctor-diagnosed eczema by a physician. Allergic rhinoconjunctivitis was identified by positive answers to the following questions of “Did your child

have a problem with sneezing, or a runny or blocked nose when she/he did not have a respiratory infection (without a cold, or nasopharyngitis, or a flu)?”.

Statistical analysis

The population characteristics were presented by means and percentages. Morbidity associated with asthma phenotypes was defined in terms of prevalence and incidence. Marginal models were used to measure the relationships between maternal depression during pregnancy and childhood asthma, adjusting for the covariates of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy. The marginal model was estimated by the Generalized Estimating Equation (GEE) approach, using exchangeable working correlation matrices.

All statistical tests were performed using SAS® statistical software version 9.2 (SAS® Institute Inc, Cary, North Carolina). All *P*-values were two-tailed. *P*<0.05 was considered statistically significant.

Results

Characteristics of the study population

The characteristics of all recruited sample at the beginning of the study and the sample used in our study were described in table 9. We followed up 607 (53.29 %) boys and 532 (46.71 %) girls until the age of 5 years. Among 21.81 % of these children's mother smoked during pregnancy and 13.67 % of these children's mothers had clinical significant depression (the total scores for CES-D ≥ 16) during pregnancy. Compared to the characteristics of all recruited sample, children followed up to ages of 5 years (the study sample of our study) had significant different characteristics of study center, maternal education attainment, maternal smoking during pregnancy and maternal depression during

pregnancy ($P<0.01$), except for the characteristics of maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender and family history of asthma, eczema, allergic rhinitis or food allergy.

Table 9 — Characteristics of all recruited sample and sample of our study

Variables	All recruited Sample (N=2002)	Sample of our study (n=1139)	P^*
Study center, n (%)			
Poitiers	968 (48.35)	630 (55.31)	<0.01
Nancy	1034 (51.65)	509 (44.69)	
Total	2002 (100.00)	1139 (100.00)	
Maternal education attainment, n (%)			
Less than high school	143 (7.56)	51 (4.54)	<0.01
High school	745 (39.38)	397 (35.35)	
College/University or more	1004 (53.07)	675 (60.11)	
Total	1892 (100.00)	1123 (100.00)	
Maternal smoking during pregnancy, n (%)			
Smoking	520 (27.62)	246 (21.81)	<0.01
No smoking	1363 (72.38)	882 (78.19)	
Total	1883 (100.00)	1128 (100.00)	
Maternal age at recruitment (years), (Mean\pmSD[†])	30.98 \pm 4.90	31.13 \pm 4.70	0.42
Maternal pre-pregnancy body mass index, n (%)			
Underweight (<18.50kg/m ²)	154 (8.17)	85 (7.59)	0.90
Normal (18.50-24.99kg/m ²)	1228 (65.18)	740 (66.07)	
Overweight (25.00-29.99 kg/m ²)	334 (17.73)	192 (17.14)	
Obese (\geq 30.00 kg/m ²)	168 (8.92)	103 (9.20)	
Total	1884 (100.00)	1120 (100.00)	
Siblings, n (%)			
No siblings	848 (44.56)	534 (46.97)	0.20
With siblings	1055 (55.44)	603 (53.03)	
Total	1903 (100.00)	1137 (100.00)	
Gender of the newborn, n (%)			
Male	1000 (52.55)	607 (53.29)	0.69
Female	903 (47.45)	532 (46.71)	
Total	1903 (100.00)	1139 (100.00)	
Family history of asthma, eczema, allergic rhinitis or food allergy, n (%)			
No family history	918 (48.26)	533 (47.29)	0.61
With family history	984 (51.74)	594 (52.71)	
Total	1902 (100.00)	1127 (100.00)	
Maternal depression during pregnancy, n (%)			
No depression	1308 (81.75)	897 (86.33)	<0.01
Depression	292 (18.25)	142 (13.67)	

Total	1600 (100.00)	1039 (100.00)
-------	---------------	---------------

* *P*, *P*-value for t-test or chi-square test between all recruited sample and sample of the thesis;

[†] SD, standard deviation

Health outcomes in the first 5 years of life

The health outcomes in the first 5 years of life were presented in table 10. For children at ages of 5 years, the prevalences of wheezing, doctor-diagnosed asthma, doctor-diagnosed eczema and allergic rhinoconjunctivitis were 46.78 %, 20.99 %, 29.17 %, and 22.54 %, respectively.

Table 10— Incidences and prevalences of health outcomes in the first 5 years of life

Age of the children	Wheezing	Doctor-diagnosed asthma	Doctor-diagnosed eczema	Allergic rhinoconjunctivitis
1 year				
Incidence, n (%)	271 (25.88)	98 (9.96)	117 (10.69)	—
Prevalence, n (%)	271 (25.88)	98 (9.96)	117 (10.69)	—
2 years				
Incidence, n (%)	70 (6.70)	18 (1.76)	63 (5.68)	74 (7.28)
Prevalence, n (%)	341 (34.07)	116 (12.51)	180 (16.45)	74 (7.28)
3 years				
Incidence, n (%)	37 (3.57)	19 (1.89)	38 (3.73)	53 (5.25)
Prevalence, n (%)	378 (39.75)	135 (15.70)	218 (21.91)	127 (13.55)
4 years				
Incidence, n (%)	26 (2.54)	18 (1.83)	30 (3.04)	35 (3.62)
Prevalence, n (%)	404 (44.15)	153 (18.89)	248 (27.40)	162 (18.73)
5 years				
Incidence, n (%)	24 (2.13)	17 (1.52)	16 (1.42)	33 (2.94)
Prevalence, n (%)	428 (46.78)	170 (20.99)	264 (29.17)	195 (22.54)

Relationships between maternal depression during pregnancy and health outcomes

The relationships between maternal depression during pregnancy and health outcomes were showed in table 11. There were significant relationships between maternal depression during pregnancy and the development of allergic rhinoconjunctivitis in the first 5 years of life of the

children in EDEN mother-child cohort study, while no significant relationships were found between maternal depression during pregnancy and the development of wheezing, doctor-diagnosed asthma and doctor-diagnosed eczema.

Table 11— Relationships between maternal depression during pregnancy and health outcomes in the first 5 years of life

Health outcomes	aOR [†]	95 % CI [†]
Wheezing	1.12	0.91, 1.39
Doctor-diagnosed asthma	1.23	0.81, 1.85
Doctor-diagnosed eczema	1.17	0.86, 1.61
Allergic rhinoconjunctivitis	1.87	1.33, 2.62

aOR, adjusted odds ratio; CI, confidence interval;

[†]aOR:odds ratio adjusted by potential confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

Discussion

In our study population, 13.67 % of the mothers had clinical significant depression (the total scores for CES-D ≥ 16) during pregnancy and maternal depression during pregnancy was related to ever allergic rhinoconjunctivitis in the first 5 years of life.

Maternal depression during pregnancy is an important risk factor for the health of both mothers and infants, thus it has been considered as a major public health concern¹³². One study recruited 579 women (average age=29.37) in Bordeaux, France, indicated that 24 % of the women presented with a highly intense depressive symptoms during pregnancy (assessed by CES-D). Results of another French population-base study showed that the prevalence rate of maternal depression during pregnancy (assessed by the Edinburgh Postnatal Depression Scale, EPDS) was 18.3 %¹³³. Tandon SD et al have compared the sensitivity, specificity and positive predictive value of the 3 tools of measuring maternal depression during pregnancy, namely CES-D, EPDS and BDI-II (Beck Depression Inventory II).

Results showed that the 3 tools were accurate and reliable in detecting major and minor depression among low-income African American prenatal women¹³⁴. The prevalence rates of maternal depression during pregnancy are 18.25 % and 13.67 % in all recruited women and mothers whose children were followed up until the age of 5 years, respectively. This difference may be explained that mother-child pairs with higher maternal depression during pregnancy in our study sample have more dropouts in the 5-year follow-up.

In our study, we focus on the influence of maternal depression during pregnancy on the offspring's development of asthma and allergies, disorders with complex etiology. In the previous studies, data indicated that maternal depression was associated with the development of asthma and allergy in children of western countries^{89, 135}. Wood RA et al have found that maternal depression during pregnancy (assessed by Edinburgh Postnatal Depression Scale, EPDS) was positively associated with wheezing (two or more episodes) in children aged 12 months in URECA (Urban Environment and Childhood Asthma) birth cohort study¹³⁵. Lefevre F et al⁸⁹ have assessed the relationship between maternal depression (investigated by the questionnaire of the Beck Depression Inventory short form) in early life and wheezing in children aged ≤ 3 years, using a case-control study design. Results showed that there was a statistical link between maternal depression and infants' wheezing and its severity. In our study population, we found the maternal depression during pregnancy was the risk factor for ever allergic rhinoconjunctivitis in the first 5 years of children.

One potential explanation of the relationship between maternal depression and the development of allergic rhinoconjunctivitis could be that psychological factors may have influence on the immune system¹³⁶⁻¹³⁸, favoring the development of asthma and allergies. Another explanation could be that psychological factors may have detrimental effect on the lung structure and function¹³⁹. In addition, as presented in existing data, *in utero* life exposures were identified as important factors for the development of the structure and functions of immune system and respiratory system¹⁴⁰⁻¹⁴¹, favoring the further development of asthma and allergies. *In utero* life exposures to psychological disorders as important exposures that influence the development of asthma and allergies of the children have

been well documented in the literature^{75, 89, 142-143}. Recently, Khashan AS et al¹⁴² found that prenatal exposure to severe life events increases the risk of hospitalization for asthma in the offspring. “Fetal programming” theory, indicating that *in utero* life exposures may alter expression of the fetal genome and may have lifelong consequences, has been used to further explain potential mechanism of the risk of *in utero* life exposures to asthma and allergies. This theory also considers that *in utero* life is a critical period and may have permanent effects on structure, physiology and metabolism of the offspring¹⁴⁴⁻¹⁴⁶.

The strengths of our investigation consist in the facts that the sample was drawn from the general population and that our study is a longitudinal study which allows us to determine the potential causality between exposures and health outcomes. The limitation of our study lays in that both exposure and health outcomes are assessed by questionnaires and reporting bias may be existed in the investigation. Another limitation could be that our study sample has fewer mothers with depression during pregnancy than the general French Population. Therefore, the health effect of maternal depression on the development of childhood asthma and allergies may be underestimated.

5. Interaction between air pollutants and psychological features in relation to childhood asthma

5.1 Evidence from French 6 cities study

5.1.1 *Presentation of article 4*

In article 4, we explored the interaction between outdoor air pollutants and psychological disorders, namely emotion and conduct problems, in relation to childhood asthma and eczema. Outdoor air pollutants were assessed by a dispersion model through the STREET® 5 software, using data of the 3-years average (from 1998 to 2000). Psychological features were measured by 2 scales (emotional symptoms and conduct problems) of SDQ questionnaire. The health outcomes included current wheezing, current doctor-diagnosed asthma and current eczema. Results showed that there were interactions between outdoor air pollutants and emotion and conduct problems. Children with emotion and conduct problems had 1.17 to 1.51 times higher adjusted odds ratios for the associations between outdoor air pollutants, and asthma phenotypes and current eczema than children with emotion and conduct problems.

5.1.2 Article 4. Relationships between ambient air pollutants and childhood asthma and eczema were modified by emotion and conduct problems



Original article

The relationships between ambient air pollutants and childhood asthma and eczema are modified by emotion and conduct problems

Cailiang Zhou MS ^{a,b,*}, Nour Baïz PhD ^{a,b}, Soutrik Banerjee MD, PhD ^{a,b},
 Denis André Charpin MD ^c, Denis Caillaud MD ^d, Frédéric de Blay MD ^e,
 Chantal Raherison MD, PhD ^{f,g}, François Lavaud MD ^h,
 Isabella Annesi-Maesano MD, PhD, DSc ^{a,b}

^a Université Pierre et Marie Curie, Paris 6, Sorbonne Universités, UMR S 707: EPAR (Epidémiologie des maladies allergiques et respiratoires), Medical School Saint Antoine, Paris, France

^b INSERM, U 707: EPAR, Paris, France

^c Service de Pneumologie allergologie, Hôpital Nord, Marseille, France

^d Service de Pneumologie, Hôpital Gabriel Montpied, Clermont Ferrand, France

^e Service de Pneumologie, Hôpital Civils, Strasbourg, France

^f Service des Maladies Respiratoires, Hôpital du Haut Lévêque, Bordeaux, France

^g ISPED, Université Bordeaux Segalen, Bordeaux, France

^h Service de Pneumologie, Hôpital Maison Blanche, Reims, France

ARTICLE INFO

Article history:

Received 30 May 2013

Accepted 30 September 2013

Available online 5 October 2013

Keywords:

Air pollutants

Asthma

Eczema

Psychological factors

ABSTRACT

Purpose: This study examined the hypothesis that emotion and conduct problems (ECPs) may modify the relationships between ambient air pollutants and childhood asthma and eczema.

Methods: In the cross-sectional study, 4209 French schoolchildren (aged 10–12 years) were investigated between March 1999 and October 2000. Ambient air pollutants exposures were estimated with dispersion modeling. Health outcomes and ECPs were evaluated by validated questionnaires, completed by the parents. Marginal models were used to analyze the relationships of exposures to ambient air pollutants and/or ECPs to asthma phenotypes and current eczema, adjusting for potential confounders.

Results: In our population, interactions were found between ECPs and exposures to ambient air pollutants (benzene, carbon monoxide, nitrogen dioxide, nitrogen oxides, particulate matter with an aerodynamic diameter below 10 μm , volatile organic compounds) ($P < .20$). In addition, ECPs were related to current wheezing (adjusted prevalence odds ratio [aOR], 2.35; 95% confidence interval [CI], 1.59–3.47), current doctor-diagnosed asthma (aOR, 1.82; 95% CI, 1.25–2.66), and current eczema (aOR, 2.21; 95% CI, 1.61–3.02). Children with ECPs had 1.17–1.51 times higher aORs for the associations between ambient air pollutants and asthma phenotypes and current eczema than those without ECPs.

Conclusions: ECPs may modify the relationships between ambient air pollutants and childhood asthma and eczema.

© 2013 Elsevier Inc. All rights reserved.

Introduction

Increasing evidence has indicated that social environment could alter susceptibility to ambient air pollution in relation to health outcomes [1–4]. Psychological features as an important social environmental factor that impacts on the development of childhood asthma and eczema have been well documented in literature [5–9]. However, few studies have included ambient air pollutants

and psychological disorders together to gain a more comprehensive picture of how ambient air pollutants contribute to childhood asthma and eczema. Now a small but growing number of scientists are investigating whether chronic psychological stress interacts with pollutants to produce adverse health effects [10]. In North America, Chen et al. [2] found that there was an interaction between chronic stress (measured by the University of California Los Angeles Life Stress Interview) and chronic traffic-related air pollution in relation to asthma outcomes in 9- to 18-year-old Canadian children. Later, data investigating on the first grade schoolchildren (5–9 years) in 13 southern California communities of America indicated that the risk of asthma attributable to traffic-related air pollution was significantly higher for children with

* Corresponding author. Department of Epidemiology of Allergic and Respiratory Disease, UMR S 707, INSERM and Université Pierre et Marie Curie Paris 6, Medical School Pierre et Marie Curie, Site Saint Antoine, 27 rue Chaligny, 75571 Paris, cedex 12, France. Tel.: +33 144 73 86 57; fax: +33 144 73 84 54.

E-mail address: zhou@u707.jussieu.fr (C. Zhou).

higher parental stress than for children with lower stress [3]. However, these studies did not consider internalizing and externalizing disorders together.

In the present study, we hypothesize that both emotional symptoms (internalizing disorders) and conduct problems (externalizing disorders) interact with ambient air pollutants in relation to schoolchildren's asthma phenotypes (current wheezing and current doctor-diagnosed asthma) and current eczema. We used the data set of the French Six Cities Study to examine this hypothesis.

Methods

Study population

Between March 1999 and October 2000, 9615 children were recruited from 108 randomly selected elementary schools to participate in the French Six Cities Study (the six cities included Creteil, Reims, Marseille, Strasbourg, Clermont-Ferrand, and Bordeaux) [11]. Our study population included only those children aged 10–12 years that resided at their current address for more than 3 years and without missing data on emotion and conducts problems (ECPs) (total sample of 4209). Children's parents filled standard questionnaires to measure health outcomes and ECPs after having signed an informed consent for the survey. All the questionnaires were completed by the parents of the children between 1999 and 2000. The study protocol was approved by French National Ethics Board (Comité Consultatif de Protection des Personnes se prêtant à des Recherches Biomédicales, approval number: 01/07, Marseille, France).

Exposure and health data collection

Long-term exposures to ambient air pollutants were estimated by a dispersion model through the STREET 5 software (Kunz Technologie Transfer [KIT] Umweltberatung in cooperation with Targeting; Versailles, France), using data of the 3-year average (from 1998 to 2000) concentrations of benzene, carbon monoxide (CO), nitrogen dioxide (NO₂), nitrogen oxides (NO_x), particulate matter with an aerodynamic diameter below 10 µm (PM₁₀), (volatile organic compounds (VOCs) at 108 school addresses, and were described in more detail previously [12]. Because in urban France almost all children live within 500 m of their elementary schools, the exposure to ambient air pollutants estimated in school addresses was considered as a satisfactory assessment of proximity to exposure to ambient air pollutants in residential addresses. Data on asthma phenotypes, current eczema, and covariates were collected by an enriched version of the International Study of Asthma and Allergies in Children questionnaire [13]. ECPs were investigated by Strengths and Difficulties Questionnaire (SDQ) [14].

Assessment of asthma phenotypes and eczema

Current wheezing was defined by a "yes" response to question "In the last 12 months, had your child had wheezing in the chest?" [15]. Current doctor-diagnosed asthma was defined by (1) a "yes" response to question "Has the asthma of your child been diagnosed by a physician?" and (2) parent-reported wheezing attacks in the last 12 months and/or asthma medication use in the last 12 months [16]. We also included current eczema, a disorder sharing genetic and environmental risk factors with asthma and having a causal link with asthma [17]. Current eczema was defined as itchy rash in flexural areas in the last 12 months [15].

Assessment of ECPs

ECPs (internalizing and externalizing problems, respectively) were measured by two scales (emotional symptoms and conduct problems scales, with five items for each scale) of SDQ on children's behavior in the past 6 months. Each item was scored, using a three-point Likert scale: 0 for "not true," 1 for "somewhat true," or 2 for "very true." The score of each item added up to a total score of ECPs, ranging from 0 to 20. In our study, for both emotional symptoms and conducts problems, children with highest 10% scores (cut-off = 4) were defined as having difficulties [14,18]. The total scores between 0 and 8 were defined as "emotion and conduct problems (ECPs)", whereas the score range for "no emotion and conduct problems (No ECPs)" was 9–20.

Statistical analysis

The population characteristics were provided by percentages and means. Differences of air pollutant concentrations between children with ECPs and those without and among children in the six study centers were analyzed by *t*-test and analysis of variance, respectively. To take into account the potential nonindependence of data for children living in the same community [11], marginal models [19] were used to analyze the relationships of exposures to ambient air pollutants and/or ECPs to asthma phenotypes and current eczema, controlling for the potential confounders of gender, study center, ethnic origin, parental educational attainment, siblings, family history of asthma, prenatal parental smoking, dampness in the house during the first year of life, and contact with pets during the first year of life and age. The parameters of the marginal models were estimated by the generalized estimating equation approach [19], using exchangeable working correlation matrices. Confounders were identified when the addition of a covariate to the model changed the prevalence odds ratio by 10%, without considering statistical significance. Interactions were identified when the model with a statistically significant ($P < .20$) interaction term had a smaller value of quasi-likelihood under the independent model criteria compared with the model included all other covariates of the aforementioned model except for the interaction term. In the models, ambient air pollutants were entered as continuous variables. Adjusted prevalence odds ratios (aORs) for the relationships between ambient air pollutants and asthma phenotypes and current eczema were calculated based on an interquartile increase in exposures to ambient air pollutants. When interactions between ECPs and ambient air pollutants existed, aORs and 95% confidence interval for the relationships between ambient air pollutants and asthma phenotypes and current eczema were calculated according to ECPs.

All statistical tests were performed using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC). All values of *P* were two-tailed. A value of $P < .05$ was considered statistically significant, except for the values of *P* for interaction terms.

Results

Characteristics of study population

The characteristics of the study population were described in Table 1 and Supplementary Table S1, according to ECPs and study centers, respectively. There were 2097 (50%) boys in the study population. The mean age of the study population was 10.80 years. The prevalence of current eczema was highest (13%), followed by current wheezing (7%) and current doctor-diagnosed asthma (5%). There were significant differences for certain characteristics between children with ECPs and those without ($P < .05$), except for

Table 1
Characteristics of the study population according to ECPs

Characteristics	All (n = 4209)	No ECPs (n = 3735)	ECPs (n = 474)	P*
Gender, n (%)				.02
Male	2097 (50)	1837 (49)	260 (55)	
Female	2112 (50)	1898 (51)	214 (45)	
Total	4209 (100)	3735 (100)	474 (100)	
Study center, n (%)				.39
Creteil	841 (20)	730 (20)	111 (23)	
Reims	487 (12)	431 (12)	56 (12)	
Marseille	672 (16)	599 (16)	73 (15)	
Strasbourg	778 (18)	689 (18)	89 (19)	
Clermont Ferrand	720 (17)	649 (17)	71 (15)	
Bordeaux	711 (17)	637 (17)	74 (16)	
Total	4209 (100)	3735 (100)	474 (100)	
Ethnic origin, n (%)				.76
Metropolitan France	2618 (63)	2323 (63)	295 (64)	
French overseas departments and foreign countries	1515 (37)	1349 (37)	166 (36)	
Total	4133 (100)	3672 (100)	461 (100)	
Parental educational attainment†, n (%)				<.01
Low (primary or secondary)	1974 (50)	1721 (49)	253 (58)	
High (tertiary)	1957 (50)	1774 (51)	183 (42)	
Total	3931 (100)	3495 (100)	436 (100)	
Preterm birth‡, n (%)				.77
Yes	361 (9)	322 (9)	39 (8)	
No	3848 (91)	3413 (91)	435 (92)	
Total	4209 (100)	3735 (100)	474 (100)	
Siblings (>1), n (%)				.10
Yes	3140 (75)	2801 (75)	339 (72)	
No	1069 (25)	934 (25)	135 (28)	
Total	4209 (100)	3735 (100)	474 (100)	
Family history of asthma, n (%)				.08
Yes	890 (21)	775 (21)	115 (24)	
No	3319 (79)	2960 (79)	359 (76)	
Total	4209 (100)	3735 (100)	474 (100)	
Prenatal parental smoking, n (%)				<.01
Yes	1446 (34)	1255 (34)	191 (40)	
No	2763 (66)	2480 (66)	283 (60)	
Total	4209 (100)	3735 (100)	474 (100)	
Dampness in the house during the first year of life, n (%)				<.01
Yes	667 (18)	564 (17)	103 (24)	
No	3124 (82)	2799 (83)	325 (76)	
Total	3791 (100)	3363 (100)	428 (100)	
Contact with pets during the first year of life, n (%)				<.01
Yes	1222 (29)	1058 (28)	164 (35)	
No	2987 (71)	2677 (72)	310 (65)	
Total	4209 (100)	3735 (100)	474 (100)	
Current wheezing, n (%)				<.01
Yes	289 (7)	233 (6)	56 (12)	
No	3846 (93)	3439 (94)	407 (88)	
Total	4135 (100)	3672 (100)	463 (100)	
Current doctor diagnosed asthma, n (%)				<.01
Yes	196 (5)	160 (5)	36 (8)	
No	3709 (95)	3302 (95)	407 (92)	
Total	3905 (100)	3462 (100)	443 (100)	
Current eczema, n (%)				<.01
Yes	518 (13)	422 (12)	96 (21)	
No	3545 (87)	3182 (88)	363 (79)	
Total	4063 (100)	3604 (100)	459 (100)	
Maternal age at recruitment (y), mean (SD)	38.84 (4.98)	38.90 (4.99)	38.42 (4.95)	.05
Age (y), mean (SD)	10.80 (0.69)	10.79 (0.68)	10.86 (0.71)	.04
Birth weight (g), mean (SD)	3261 (517)	3262 (520)	3251 (489)	.67

SD = standard deviation.

* The value of P for t test or chi square test between children with ECPs and those without.

† The highest educational attainment of both fathers and mothers.

‡ Maternal gestational age <37 wk and low birth weight (<2500 g).

study center, ethnic origin, preterm birth, family history of asthma, and birth weight (Table 1). There were significant differences for various characteristics among children in the six study centers ($P < .05$), except for gender, family history of asthma, birth weight, emotional symptoms, conduct problems, ECPs and prevalences of current wheezing, current doctor-diagnosed asthma, and current eczema (Supplementary Table S1).

Exposure to ambient air pollutants

Exposures to ambient air pollutants were described in Table 2 and Supplementary Table S2, according to eECPs and study centers, respectively. The concentrations of air pollutants did not differ between children with ECPs and those without ($P > .05$; Table 2). However, there were significant differences for the concentrations

Table 2

Concentrations of ambient air pollutants in study population according to ECPs, mean (SD)

Air pollutants	All (n = 4209)	No ECPs (n = 3735)	ECPs (n = 474)	P*
Benzene (μg/m ³)	2.41 (0.87)	2.42 (0.87)	2.39 (0.84)	.51
CO (μg/m ³)	558.94 (153.16)	559.14 (153.53)	557.36 (150.34)	.81
NO ₂ (μg/m ³)	44.19 (10.85)	44.15 (10.84)	44.56 (10.99)	.43
NO _x (μg/m ³)	78.82 (32.04)	78.80 (32.05)	78.95 (31.97)	.92
PM ₁₀ (μg/m ³)	26.68 (6.57)	26.70 (6.59)	26.48 (6.46)	.49
VOCs (μg/m ³)	17.35 (18.27)	17.41 (18.31)	16.88 (17.96)	.55

SD = standard deviation.

* The value of P for the differences of air pollutants concentrations between children with ECPs and those without.

of air pollutants among children in the six study centers ($P < .01$; [Supplementary Table S2](#)).

ECPs, asthma phenotypes, and eczema

Both emotional symptoms and conduct problems were significantly related to current wheezing, current doctor-diagnosed asthma, and current eczema ([Table 3](#)).

Interactions between ECPs and ambient air pollutants

There were interactions between ECPs and ambient air pollutants in relation to current doctor-diagnosed asthma, current wheezing, and current eczema ($P < .20$). The aORs between ambient air pollutants and asthma phenotypes and current eczema were 1.17–1.51 times higher for children with ECPs than for those without. The prevalence odds ratio discrepancy attenuated to 1.15–1.43 times when comparing with the whole study population ([Table 4](#)). Both emotional symptoms and externalizing disorders conduct problems interacted with ambient air pollutants in relation to asthma phenotypes and eczema ($P < .20$; [Supplementary Figure S1A and B](#)).

An interquartile increase in exposures to benzene, NO_x, and VOCs were found to be related to current wheezing, whereas exposure to NO_x was related to current doctor-diagnosed asthma, among children with ECPs ([Table 4](#)). However, no relationships were found between ambient air pollutants and asthma phenotypes among children without ECPs. Current eczema was found to be associated with an interquartile increase in exposures to benzene, CO, NO₂, NO_x, PM₁₀, and VOCs among children with ECPs ([Table 4](#)). The relationships persisted among children without ECPs in cases of exposures to CO, NO₂, and PM₁₀.

Discussion

Our data showed that ECPs may modify the relationships between ambient air pollutants and schoolchildren's asthma and eczema.

Increasing evidence had implicated the associations between ambient air pollutants and asthma and eczema [20–23]. Most recently, results of a large birth cohort study in Sweden showed

that exposures to PM₁₀ and NO_x from traffic in the first year of life as measured by a dispersion model were positively associated with asthma in children up to 12 years of life [22]. In two German birth cohort studies (German Infant Nutritional Intervention [GINI] and Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in East and West Germany [LISA]), results showed that long-term exposure to NO₂ assessed at residential addresses by geographic information system based regression models and living near to the main road were related to childhood eczema [23]. In our study, there were significant relationships for benzene, NO_x, and VOCs exposures and current wheezing, and NO_x exposure and current doctor-diagnosed asthma, among children with ECPs. Current eczema was also found to be associated with exposures to benzene, CO, NO₂, NO_x, PM₁₀, and VOCs among children with ECPs. In addition, the relationships persisted among children without ECPs in cases of exposures to CO, NO₂, and PM₁₀.

Studies have also showed that psychological disorders may increase susceptibility to childhood asthma and eczema [5,7,9,24,25]. Among those psychological disorders, stress is a factor well documented in the literature [5]. In addition, stress has been observed to be related to ECPs [26,27], implicating that ECPs may be also an important psychological factor in the development of childhood asthma and eczema. The potential mechanism could be that prenatal stress is associated with fetal hypothalamic-pituitary-adrenocortical axis dysregulation, thus relating to ECPs in children [27]. Compelling evidence has indicated the association between behavior problems and childhood asthma. Calam et al. [25] have investigated behavior problems at the age of 3 years and subsequent development of wheezing by the age of 5 years; results showed that children with behavior problems (assessed by the Eyberg Child Behavior Inventory) were more likely to develop wheezing. As a disorder sharing genetic and environmental risk factors with asthma [17], eczema could be related to behavior problems through potentially overlapping mechanisms [28]. In our population, we found that both internalizing and externalizing behavior problems assessed by the SDQ were significantly related to asthma phenotypes and current eczema. However, prospective studies are needed to further examine those associations.

In our study, children with ECPs had higher prevalence odds ratios for associations between ambient air pollutants and asthma phenotypes and current eczema, compared with children without ECPs. The odds ratio differences were attenuated when compared with the whole study population. The explanation could be that ECPs play a role as social stressors and interact with air pollutants [29], one of the most important environmental stressors. ECPs as a modifier of the relationships between ambient air pollutants and asthma and eczema could also be interpreted using the conceptual framework of social determinants of health [30], indicating that the social environment is the upstream factor that determines different exposure patterns to contribute to health risk. However, the empirical evidence for psychological disorders as a modifier in the relationships between air pollutants and childhood asthma and eczema is limited. One study conducted in American implicated that parental stress interacted with traffic-related air pollution to predict childhood asthma [3]. Another study elucidated the

Table 3

The relationships between ECPs and the prevalences of asthma phenotypes and eczema

Health outcomes	Emotional symptoms (aOR, 95% CI)*	Conduct problems (aOR, 95% CI)*	All ECPs (aOR, 95% CI)*
Current wheezing	2.23 (1.51–3.30) [†]	1.66 (1.14–2.42) [†]	2.35 (1.59–3.47) [†]
Current doctor diagnosed asthma	1.78 (1.26–2.50) [†]	1.63 (1.06–2.52) [†]	1.82 (1.25–2.66) [†]
Current eczema	1.95 (1.47–2.60) [†]	1.39 (1.02–1.91) [†]	2.21 (1.61–3.02) [†]

* aORs were from the generalized estimating equation models and adjusted for potential confounders of gender, study center, ethnic origin, parental educational attainment, siblings, family history of asthma, prenatal parental smoking, dampness in the house during the first year of life, and contact with pets during the first year of life and age.

[†] Indicates $P < .05$.

Table 4

The relationships between an interquartile increase in exposures to ambient air pollutants and asthma phenotypes and eczema in models with and without interaction terms of ECPs and ambient air pollutants

Health outcomes	IQR ($\mu\text{g}/\text{m}^3$)	Models without interaction term (aOR, 95% CI)*	Models with interaction term (aOR, 95% CI)*		Interaction P†
			No ECPs	ECPs	
Current wheezing					
Benzene	1.73–2.92	0.99 (0.84–1.15)	0.95 (0.81–1.11)	1.22 (1.00–1.50)‡	<.01
CO	435.36–635.93	0.97 (0.85–1.10)	0.94 (0.83–1.07)	1.15 (0.97–1.36)	<.01
NO ₂	35.77–52.18	1.00 (0.83–1.46)	0.96 (0.80–1.17)	1.21 (0.95–1.55)	<.01
NO _x	49.49–100.15	1.00 (0.84–1.19)	0.95 (0.80–1.13)	1.35 (1.06–1.72)‡	<.01
PM ₁₀	22.00–31.00	1.00 (0.82–1.21)	0.97 (0.79–1.18)	1.21 (0.97–1.51)	<.01
VOCs	2.05–28.04	1.00 (0.87–1.15)	0.95 (0.82–1.09)	1.43 (1.03–2.00)‡	.02
Current doctor diagnosed asthma					
Benzene	1.73–2.92	0.97 (0.81–1.15)	0.94 (0.78–1.13)	1.18 (0.94–1.47)	.01
CO	435.36–635.93	0.98 (0.84–1.15)	0.96 (0.82–1.12)	1.15 (0.95–1.38)	<.01
NO ₂	35.77–52.18	1.00 (0.80–1.25)	0.97 (0.77–1.21)	1.17 (0.92–1.49)	<.01
NO _x	49.49–100.15	1.03 (0.86–1.25)	0.99 (0.82–1.21)	1.30 (1.01–1.67)‡	.02
PM ₁₀	22.00–31.00	1.02 (0.84–1.24)	1.00 (0.82–1.22)	1.17 (0.94–1.45)	.01
VOCs	2.05–28.04	0.98 (0.82–1.16)	0.94 (0.79–1.13)	1.24 (0.88–1.76)	.14
Current eczema					
Benzene	1.73–2.92	1.17 (1.03–1.33)‡	1.13 (0.99–1.29)	1.48 (1.24–1.75)‡	<.01
CO	435.36–635.93	1.19 (1.07–1.34)‡	1.16 (1.03–1.30)‡	1.42 (1.24–1.62)‡	<.01
NO ₂	35.77–52.18	1.28 (1.11–1.47)‡	1.24 (1.08–1.43)‡	1.52 (1.31–1.77)‡	<.01
NO _x	49.49–100.15	1.20 (1.04–1.39)‡	1.15 (0.99–1.34)	1.55 (1.30–1.85)‡	<.01
PM ₁₀	22.00–31.00	1.21 (1.07–1.38)‡	1.18 (1.04–1.34)‡	1.43 (1.24–1.66)‡	<.01
VOCs	2.05–28.04	1.17 (1.03–1.33)‡	1.12 (0.98–1.29)	1.54 (1.21–1.96)‡	.02

IQR = interquartile range for the concentrations of ambient air pollutants.

^a aORs were based on an interquartile increase in exposures to ambient air pollutants which entered as continuous variable in the generalized estimating equation models and adjusted for the potential confounders of gender, study center, ethnic origin, parental educational attainment, siblings, family history of asthma, prenatal parental smoking, dampness in the house during the first year of life, and contact with pets during the first year of life and age.

[†] The values of P from the statistics for testing the interactions between ECPs and ambient air pollutants in the generalized estimating equation models.

[‡] Indicates $P < .05$.

interaction in terms of epigenetic mechanisms, implicating that air pollution and psychological factors interacted to impact on DNA methylation [31], a biomarker of disease risk [32]. This could be denoted that air pollution and psychological features may have overlapping biological mechanisms in relation to the development of childhood asthma and eczema [31]. Overall, psychological features and air pollution may interact to affect the structure and function of respiratory system, as well as the immune system. It has been observed that both stress and air pollution may increase the risk of asthma and eczema through altered cytokine response [28,33–36]. Wright et al. [35] found that prenatal stress was associated with altered innate and adaptive cytokine responses thus impacting on the expression of asthma and allergic diseases in children. Nakamura et al. [36] examined potential biological mechanisms for the relationship between airway inflammation and cigarette smoking, an important indoor air pollutant. Results showed that increased T helper type 2 immune response may explain the relationship between airway inflammation and cigarette smoking. Furthermore, psychological features could modify the relationships between air pollution and schoolchildren's lung function [37], thus increasing the risk of asthma and eczema. In our study, we explored the interactions between internalizing psychological disorder and externalizing psychological disorders and ambient air pollutants in relation to health outcomes in France where schoolchildren have higher scores for both emotional symptoms and conduct problem than the representative sample of schoolchildren from United States [18], adding new evidence for considering children with ECPs as a susceptible population and taking into account air pollution and ECPs simultaneously into the paradigm of childhood asthma and eczema prevention. Interestingly, we found an association of psychological disorders as defined by internalizing and externalizing behavior problems with childhood asthma and eczema. The definition of psychological disorders used in previous studies was based on violence experimented by

the child. This violence could alter the normal course of both structure and function of key organ systems (e.g., immune, respiratory) more straightforward than behavior problems through adrenaline patterns [38].

The limitation of our study is its cross-sectional design, which could not explore the etiology of childhood asthma and eczema. Future longitudinal studies are needed to elucidate how ambient air pollutants and ECPs interact to predict childhood asthma and eczema. Another limitation of our investigation derives from taking into account the air pollution at schools instead of at home, where children spend most of their time. Even if children generally live within 500 m of their schools in urban areas in France and even if exposure at school represents an important component of children's exposure experience, exposure assessments errors might have occurred. However, exposure misclassification would err toward an underestimation of the potential link, but in no way to a bias.

Strengths of our study was that our data were based on a large sample drawn from general population and collected from six cities, which could gain an overall view of the possible joint impacts of ambient air pollutants and ECPs on childhood asthma and eczema in France.

In conclusion, results of our study show that relationships between exposures to benzene, CO, NO₂, NO_x, PM₁₀, and VOCs and schoolchildren's asthma phenotypes and current eczema had different patterns among children with ECPs and those without and that ECPs might modify the relationships between ambient air pollutants and health outcomes of current wheezing, current doctor-diagnosed asthma, and current eczema.

Acknowledgments

We are particularly indebted to the pupils and their parents without whom the study would not have been possible. We acknowledge all the funding sources of the French Six Cities Study

[National Institute for Health and Medical Research (INSERM) (Programme "Déterminants de la Santé"), Ministry of Health (DGS), Environmental Programme PRIMEQUAL-PREDIT, Agence de la Maîtrise de l'Energie (ADEME), Mutuelle Générale de l'Education Nationale (MGEN), Agence Française de Sécurité Sanitaire de l'Environnement et du Travail (AFSSET), and Association Nationale pour les Traitements À Domicile, les Innovations et la Recherche (ANTADIR)] and the fellowship of Erasmus Mundus External Cooperation Window (EM ECW) for China, lot 14 coordinated by Lund University.

References

- Zeka A, Melly SJ, Schwartz J. The effects of socioeconomic status and indices of physical environment on reduced birth weight and preterm births in Eastern Massachusetts. *Environ Health* 2008;7:60.
- Chen E, Schreier HM, Strunk RC, Brauer M. Chronic traffic related air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environ Health Perspect* 2008;116:970–5.
- Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic related air pollution on childhood asthma incidence. *Proc Natl Acad Sci U S A* 2009;106:12406–11.
- Rappold AG, Cascio WE, Kilanu VJ, Stone SL, Neas LM, Devlin RB, et al. Cardio respiratory outcomes associated with exposure to wildfire smoke are modified by measures of community health. *Environ Health* 2012;11:71.
- Wright RJ. Stress and childhood asthma risk: overlapping evidence from animal studies and epidemiologic research. *Allergy Asthma Clin Immunol* 2008;4:29–36.
- Feldman JM, Ortega AN, Koinis Mitchell D, Kuo AA, Canino G. Child and family psychiatric and psychological factors associated with child physical health problems: results from the Boricua youth study. *J Nerv Ment Dis* 2010;198:272–9.
- Tibosch MM, Verbaak CM, Merkus PJ. Psychological characteristics associated with the onset and course of asthma in children and adolescents: a systematic review of longitudinal effects. *Patient Educ Couns* 2011;82:11–9.
- Rand CS, Wright RJ, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Mediators of asthma outcomes. *J Allergy Clin Immunol* 2012;129(suppl):1365–415.
- Bockelbrink A, Heinrich J, Schäfer I, Zutavern A, Borte M, Herbarth O, et al. Atopic eczema in children: another harmful sequel of divorce. *Allergy* 2006;61:1397–402.
- Cooney CM. Stress pollution interactions: an emerging issue in children's health research. *Environ Health Perspect* 2011;119:A431–5.
- Pénard Morand C, Raberison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, et al. Long term exposure to close proximity air pollution and asthma and allergies in urban children. *Eur Respir J* 2010;36:33–40.
- Pénard Morand C, Armengaud A, Debotte G, Chretien E, Pellier S, Annesi Maesano I. Assessment of schoolchildren's exposure to traffic related air pollution in the French Six Cities Study using a dispersion model. *Atmospheric environment* 2006;40:2274–87.
- Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, et al. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* 2004;24:406–12.
- Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;40:1337–45.
- Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008;372:1039–48.
- Lødrup Carlsen KC, Håland G, Devulapalli CS, Munthe Kaas M, Pettersen M, Granum B, et al. Asthma in every fifth child in Oslo, Norway: a 10 year follow up of a birth cohort study. *Allergy* 2006;61:454–60.
- Burgess JA, Lowe AJ, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *J Asthma* 2009;46:429–36.
- Shojaei T, Wazana A, Pitrou I, Kovess V. The strengths and difficulties questionnaire: validation study in French school aged children and cross cultural comparisons. *Soc Psychiatry Psychiatr Epidemiol* 2009;44:740–7.
- Preisser JS, Koch GG. Categorical data analysis in public health. *Annu Rev Public Health* 1997;18:51–82.
- Gowers AM, Cullinan P, Ayres JG, Anderson HR, Strachan DP, Holgate ST, et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence: a review. *Respirology* 2012;17:887–98.
- Carlsten C, Melén E. Air pollution, genetics, and allergy: an update. *Curr Opin Allergy Clin Immunol* 2012;12:455–60.
- Gruzdeva O, Bergström A, Hulchiy D, Kull I, Lind T, Melén E, et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology* 2013;24:54–61.
- Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Krämer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic related air pollution in children. *Am J Respir Crit Care Med* 2008;177:1331–7.
- Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356:982–7.
- Calam R, Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems antecede the development of wheeze in childhood: a birth cohort study. *Am J Respir Crit Care Med* 2005;171:323–7.
- Bakoula C, Kolaitis G, Veltsista A, Gilka A, Chrousos GP. Parental stress affects the emotions and behaviour of children up to adolescence: a Greek prospective, longitudinal study. *Stress* 2009;12:486–98.
- Egliston KA, McMahon C, Austin MP. Stress in pregnancy and infant HPA axis function: conceptual and methodological issues relating to the use of salivary cortisol as an outcome measure. *Psychoneuroendocrinology* 2007;32:1–13.
- Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. *Curr Opin Allergy Clin Immunol* 2005;5:23–9.
- Suglia SE, Duarte CS, Sandel MT, Wright RJ. Social and environmental stressors in the home and childhood asthma. *J Epidemiol Community Health* 2010;64:636–42.
- World Health Organization. A conceptual framework for action on the social determinants of health. Geneva: World Health Organization; 2010.
- Madrigano J, Baccarelli A, Mittleman MA, Sparrow D, Spiro 3rd A, Vokonas PS, et al. Air pollution and DNA methylation: interaction by psychological factors in the VA Normative Aging Study. *Am J Epidemiol* 2012;176:224–32.
- Terry MB, Delgado Cruzata L, Vin Raviv N, Wu HC, Santella RM. DNA methylation in white blood cells: association with risk factors in epidemiologic studies. *Epigenetics* 2011;6:828–37.
- Clougherty JE, Kubzansky LD. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect* 2009;117:1351–8.
- Ingram JL, Kraft M. IL 13 in asthma and allergy disease: asthma phenotypes and targeted therapies. *J Allergy Clin Immunol* 2012;130:829–42.
- Wright RJ, Visness CM, Calatroni A, Grayson NH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine response in an inner city cohort. *Am J Respir Crit Care Med* 2010;182:25–33.
- Nakamura Y, Miyata M, Ohba T, Ando T, Hattushika K, Suenaga F, et al. Cigarette smoke extract induces thymic stromal lymphopoietin expression, leading to T(H)2 type immune responses and airway inflammation. *J Allergy Clin Immunol* 2008;122:1208–14.
- Islam T, Urman R, Gauderman WJ, Milam J, Lurmann F, Shankardass K, et al. Parental stress increase the detrimental effect of traffic exposure on children's lung function. *Am J Respir Crit Care Med* 2011;184:822–7.
- Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am* 2011;31:19–39.

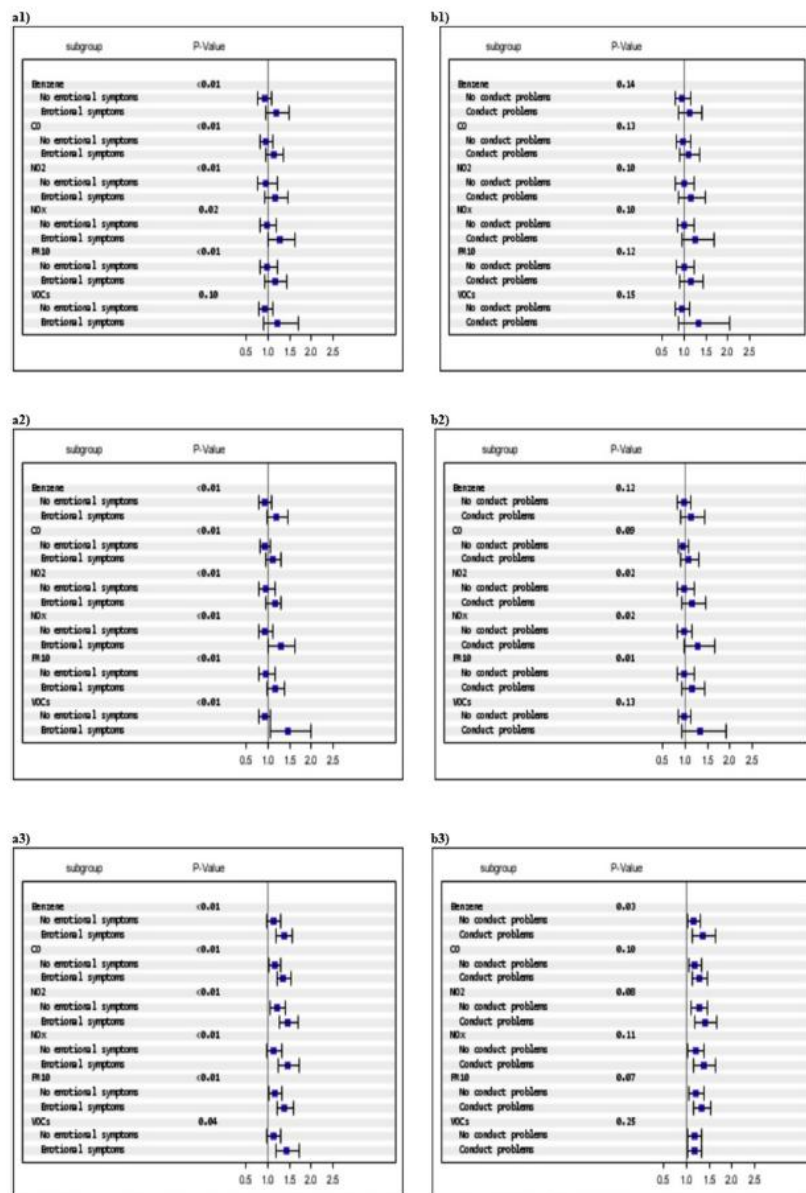


Fig. S1. (A) Emotional symptoms as a modifier for the between ambient air pollutants and asthma phenotypes and eczema. (B) Conduct problems as a modifier for the relationships between ambient air pollutants and asthma phenotypes and eczema.

Table S1

Characteristics of the study population according to the six study centers

Characteristics	Creteil (n = 841)	Reims (n = 487)	Marseille (n = 672)	Strasbourg (n = 778)	Clermont Ferrand (n = 720)	Bordeaux (n = 711)	P*
Gender, n (%)							.71
Male	415 (49)	257 (53)	343 (51)	383 (49)	355 (49)	344 (48)	
Female	426 (51)	230 (47)	329 (49)	395 (51)	365 (51)	367 (52)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Ethnic origin, n (%)							<.01
Metropolitan France	462 (55)	408 (85)	0 (0)	595 (79)	549 (78)	604 (87)	
French overseas departments and foreign countries	372 (45)	71 (15)	659 (100)	161 (21)	159 (22)	93 (13)	
Total	834 (100)	479 (100)	659 (100)	756 (100)	708 (100)	697 (100)	
Parental education attainment, n (%)							<.01
Low (primary or secondary)	407 (53)	265 (60)	302 (48)	371 (51)	370 (54)	259 (37)	
High (tertiary)	367 (47)	174 (40)	323 (52)	350 (49)	310 (45)	433 (63)	
Total	774 (100)	439 (100)	625 (100)	721 (100)	680 (100)	692 (100)	
Preterm birth†, n (%)							.05
Yes	80 (10)	50 (10)	50 (7)	69 (9)	43 (6)	69 (10)	
No	761 (90)	437 (90)	622 (93)	709 (90)	677 (94)	642 (90)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Siblings (>1), n (%)							<.10
Yes	638 (76)	377 (77)	467 (69)	605 (78)	536 (74)	517 (73)	
No	203 (24)	110 (23)	205 (31)	173 (22)	184 (26)	194 (27)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Family history of asthma, n (%)							.13
Yes	186 (22)	121 (25)	132 (20)	168 (22)	133 (18)	150 (21)	
No	655 (78)	366 (75)	540 (80)	610 (78)	587 (82)	561 (79)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Prenatal parental smoking, n (%)							<.01
Yes	248 (29)	158 (32)	231 (34)	277 (34)	267 (37)	265 (37)	
No	593 (71)	329 (68)	441 (66)	501 (64)	453 (63)	446 (63)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Dampness in the house during the first year of life, n (%)							<.01
Yes	145 (20)	90 (21)	99 (16)	111 (16)	76 (12)	146 (23)	
No	595 (80)	329 (79)	533 (84)	586 (84)	578 (88)	503 (77)	
Total	740 (100)	419 (100)	632 (100)	697 (100)	654 (100)	649 (100)	
Contact with pets during the first year of life, n (%)							<.01
Yes	208 (25)	170 (35)	184 (27)	215 (28)	215 (30)	230 (32)	
No	633 (75)	317 (65)	488 (73)	563 (72)	505 (70)	481 (68)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Emotional symptoms, n (%)							.22
Yes	142 (17)	66 (14)	97 (14)	97 (12)	102 (14)	100 (14)	
No	699 (83)	421 (86)	575 (86)	681 (88)	618 (86)	611 (86)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Conduct problems, n (%)							.10
Yes	82 (10)	57 (12)	72 (11)	88 (11)	62 (9)	55 (8)	
No	759 (90)	430 (88)	600 (89)	690 (89)	658 (91)	656 (92)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
ECFs, n (%)							.39
Yes	111 (13)	56 (11)	73 (11)	89 (11)	71 (10)	74 (10)	
No	730 (87)	431 (89)	599 (89)	689 (89)	649 (90)	637 (90)	
Total	841 (100)	487 (100)	672 (100)	778 (100)	720 (100)	711 (100)	
Current doctor diagnosed asthma, n (%)							.66
Yes	40 (5)	20 (4)	33 (5)	34 (5)	28 (4)	41 (6)	
No	742 (95)	434 (96)	594 (95)	694 (95)	623 (96)	622 (94)	
Total	782 (100)	454 (100)	627 (100)	728 (100)	651 (100)	663 (100)	
Current wheezing, n (%)							.29
Yes	52 (6)	32 (7)	50 (8)	47 (6)	45 (6)	63 (9)	
No	763 (94)	449 (93)	612 (92)	721 (94)	658 (94)	643 (91)	
Total	815 (100)	481 (100)	662 (100)	768 (100)	703 (100)	706 (100)	
Current eczema, n (%)							.36
Yes	114 (14)	45 (10)	83 (13)	90 (12)	97 (14)	89 (13)	
No	701 (86)	408 (90)	566 (87)	661 (88)	605 (86)	604 (87)	
Total	815 (100)	453 (100)	649 (100)	751 (100)	702 (100)	793 (100)	
Maternal age at recruitment (y), mean (SD)	39.11 (5.15)	38.32 (5.07)	38.85 (4.65)	38.67 (5.13)	38.59 (4.83)	39.34 (5.04)	<.01
Age (y), mean (SD)	10.79 (0.67)	10.57 (0.63)	11.47 (0.52)	10.68 (0.65)	10.67 (0.61)	10.60 (0.60)	<.01
Birth weight (g), mean (SD)	3259 (557)	3314 (534)	3262 (485)	3253 (542)	3242 (484)	3255 (489)	.31

SD = standard deviation.

* The value of P for the differences of characteristics of study population among children in the six study centers.

† Maternal gestational age <37 wk and low birth weight (<2500 g).

Table S2

Concentrations of ambient air pollutants according to the six study centers, mean (SD)

Air pollutants	Creteil (n = 841)	Reims (n = 487)	Marseille (n = 672)	Strasbourg (n = 778)	Clermont Ferrand (n = 720)	Bordeaux (n = 711)	P*
Benzene ($\mu\text{g}/\text{m}^3$)	2.27 (0.51)	1.48 (0.20)	3.26 (0.85)	2.30 (0.75)	2.51 (0.87)	2.43 (0.87)	<.01
CO ($\mu\text{g}/\text{m}^3$)	608.83 (100.90)	382.84 (56.74)	631.41 (161.00)	556.06 (134.68)	595.26 (154.76)	518.39 (154.89)	<.01
NO ₂ ($\mu\text{g}/\text{m}^3$)	55.52 (4.44)	30.00 (5.39)	49.52 (5.71)	41.46 (5.56)	46.01 (10.72)	36.64 (9.38)	<.01
NO _x ($\mu\text{g}/\text{m}^3$)	102.91 (29.60)	51.04 (10.65)	84.97 (27.65)	69.93 (26.89)	83.36 (32.44)	68.66 (30.43)	<.01
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	29.08 (5.84)	19.59 (1.83)	32.84 (4.27)	24.00 (5.04)	26.04 (6.77)	26.42 (6.04)	<.01
VOCs ($\mu\text{g}/\text{m}^3$)	17.23 (15.47)	3.94 (4.30)	28.91 (22.26)	9.26 (13.51)	21.86 (18.43)	20.04 (17.88)	<.01

SD = standard deviation.

* The value of *P* for the differences of air pollutants concentrations among children in the six study centers.

5.2 Evidence from EDEN mother-child cohort study

5.2.1 Interaction between subjectively measured air pollutants in utero life and maternal depression during pregnancy in relation to asthma

We used GEE model to examine the interactions between exposures to reported maternal smoking during pregnancy and *in utero* exposure to traffic-related air pollution, and maternal depression during pregnancy in the first 5 years of life in children of the EDEN mother-child cohort study (results were presented in table 12).

Results showed that there was interaction between maternal smoking during pregnancy and maternal depression during pregnancy in relation to ever doctor-diagnosed asthma, while interaction was found between *in utero* exposure to traffic-related air pollution and maternal depression during pregnancy in relation to the development of wheezing in the first 5 years of life ($P < 0.20$). No interactions were found between the considered exposures and maternal depression during pregnancy in relation to doctor-diagnosed eczema and allergic rhinoconjunctivitis ($P > 0.20$).

Table 12— Health effects of subjectively measured air pollutants on health outcomes according to maternal depression during pregnancy

Healthoutcomes	Maternal depression, OR (95% CI) [†]		Interaction <i>P</i> value [§]
	Without maternal depression (n=609)	With maternal depression (n=113)	
Ever wheezing			
Maternal smoking during pregnancy	1.22 (0.99,1.50)	1.22 (0.99,1.50)	0.30
<i>In utero</i> exposure to traffic-related air pollution	1.13 (0.89,1.43)	1.68 (1.15,2.43)	0.08
Ever doctor-diagnosed asthma			
Maternal smoking during pregnancy	0.78 (0.45,1.33)	1.56 (0.74,3.29)	0.14
<i>In utero</i> exposure to traffic-related air pollution	1.16(0.77,1.76)	1.16(0.77,1.76)	0.93
Ever doctor-diagnosed eczema			
Maternal smoking during pregnancy	1.27(0.92,1.77)	1.27(0.92,1.77)	0.32

In <i>utero</i> exposure to traffic-related air pollution	1.19(0.89,1.61)	1.19(0.89,1.61)	0.48
Ever allergic rhinoconjunctivitis			
Maternal smoking during pregnancy	1.11 (0.71,1.71)	1.11 (0.71,1.71)	0.60
In <i>utero</i> exposure to traffic-related air pollution	1.71 (1.16,2.51)	1.71 (1.16,2.51)	0.38

aOR, adjusted odds ratio; CI, confidence interval;

[†]aOR:odds ratio adjusted by potential confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

5.2.2 Interaction between objectively measured air pollutants in *utero* life and maternal depression during pregnancy in relation to asthma and allergies

We used GEE model to examine the interactions between exposures to objectively measured air pollutants, namely benzene, CO, NO₂, PM₁₀, SO₂, VOCs in *utero* life, and maternal depression during pregnancy in relation to health outcomes in the first 5 years of life in children of the EDEN mother-child cohort study (results were presented in table 13).

Results showed that interaction was found between exposure to benzene and maternal depression during pregnancy in relation to doctor-diagnosed eczema ($P<0.20$).

Table 13— Health effects of air pollutants on health outcomes according to maternal depression during pregnancy

		Maternal depression, OR (95% CI) [†]		Interaction <i>P</i> value [§]
	IQR (µg/m ³)	Without maternal depression (n=609)	With maternal depression(n=113)	
Everwheezing				
Benzene	2.10-2.21	1.02 (0.97,1.07)	1.02 (0.97,1.07)	0.87
CO	494.07-580.88	1.03 (0.88,1.19)	1.03 (0.88,1.19)	0.58
NO ₂	17.84-24.04	1.03(0.95,1.12)	1.03 (0.95,1.12)	0.54
PM ₁₀	17.78-21.67	0.98(0.85,1.13)	0.97 (0.83,1.14)	0.76
SO ₂	2.67-3.31	0.98(0.89,1.08)	0.98(0.89,1.08)	0.89
VOCs	4.02-6.08	1.03 (0.99,1.07)	1.03 (0.99,1.07)	0.92
Ever doctor- diagnosed asthma				
Benzene	2.10-2.21	0.89 (0.77,1.03)	0.89 (0.77,1.03)	0.35
CO	494.07-580.88	0.93 (0.70,1.23)	0.93 (0.70,1.23)	0.79
NO ₂	17.84-24.04	1.11 (0.94,1.31)	1.11 (0.94,1.31)	0.95
PM ₁₀	17.78-21.67	0.94 (0.69,1.27)	0.94 (0.69,1.27)	0.53

SO ₂	2.67-3.31	1.10 (0.91,1.32)	1.10 (0.91,1.32)	0.92
VOCs	4.02-6.08	0.99 (0.91,1.08)	0.99 (0.91,1.08)	0.47
Ever doctor-diagnosed eczema				
Benzene	2.10-2.21	0.99 (0.92,1.06)	1.00 (0.93,1.08)	0.17
CO	494.07-580.88	1.04(0.83,1.29)	1.04 (0.83,1.29)	0.21
NO ₂	17.84-24.04	0.95 (0.83,1.09)	0.95 (0.83,1.09)	0.82
PM ₁₀	17.78-21.67	0.99 (0.81,1.20)	0.99 (0.81,1.20)	0.71
SO ₂	2.67-3.31	0.98 (0.87,1.11)	0.98 (0.87,1.11)	0.58
VOCs	4.02-6.08	0.99 (0.92,1.06)	0.99 (0.92,1.06)	0.29
Ever allergic rhinoconjunctivitis				
Benzene	2.10-2.21	1.01 (0.94,1.09)	1.01 (0.94,1.09)	0.53
CO	494.07-580.88	0.84 (0.64,1.11)	0.84 (0.64,1.11)	0.79
NO ₂	17.84-24.04	0.89 (0.69,1.14)	0.89 (0.69,1.14)	0.81
PM ₁₀	17.78-21.67	0.89 (0.69,1.14)	0.89 (0.69,1.14)	0.22
SO ₂	2.67-3.31	0.95 (0.81,1.10)	0.95 (0.81,1.10)	0.80
VOCs	4.02-6.08	1.00 (0.93,1.07)	1.00 (0.93,1.07)	0.76

aOR, adjusted odds ratio; CI, confidence interval;

[†]aOR:odds ratio adjusted by potential confounders of study center, maternal educational attainment, maternal smoking during pregnancy, maternal age at recruitment, maternal pre-pregnancy body mass index, siblings, gender of the new-born, and family history of asthma, eczema, allergic rhinitis or food allergy.

6. Discussion

We discuss here the validity of our results in terms of exposure assessment, health outcome identification, and the relationships of environmental and psychological factors with childhood asthma and the potential mechanisms.

6.1 The measurement of air pollutants

In previous studies, both subjective measurement and objective measurement of air pollutants were used. Some studies showed that the subjectively measured exposure was weakly associated with the objectively assessed exposure¹⁴⁷. However, other investigations argued that results of the two kinds of measurement are moderately or strongly related¹⁴⁸⁻¹⁴⁹. We present here the different results of the studies included simultaneously the subjective and objective measurements (see table 14).

Table 14 — Studies on the relationships between subjectively measured and objectively measured indicators of air pollutants

study	Study population	Subjective measured indicators	Objective measured indicators	Relationships between subjective and objective measurement
Cesaroni Get al ¹⁴⁹ , 2008	948825 59-year-old Rome residents, Italy	Self-reported traffic intensity	Distance from busy roads from geographical information system; area-based emission of particulate matter; estimated concentration of nitrogen dioxide from a land-use regression (LUR) model	Moderately correlated to one another

Gauderman WJ et al ¹⁴⁸ , 2005	208 children (average age=10 years) from 10 southern California communities, USA	Distance to freeway; Traffic volume within 150 metres	CALINE4 (CALifornia LINE Source Dispersion Model, version 4) dispersion model based freeway-related air pollution	Strongly correlated to one another
Heinrich Jet al ¹⁴⁷ , 2005	2633 and 673 infants from Dutch and the German-Munich cohort	Total traffic at home address; Buses/trucks at home address	Geographical information system model based estimates of concentrations of PM _{2.5} and NO ₂	Weakly correlated to one another

For subjective measurement of air pollutants, most of the studies used questionnaires to investigate the exposures. Self-reported traffic intensity, distance to freeway or main road were indicators commonly assessed as subjective measurement of air pollutants. In recent years, however, objective measurement tools, such as dispersion modelling and land-use regression modelling have been widely used as objective tools to estimate exposures to air pollution^{13, 150-151}. Of note, although misclassification or reporting bias may be existed in subjective measurement of air pollutants, more research is need to clarify the sensitivity and speciality of different measurement tools, including both subjective tools and objective tools, in detecting a health effect. Forastiere F et al¹⁵² indicated that both subjective and objective measurement had their advantages, and that no single method could be considered as the gold standard.

In the thesis, both subjective and objective indicators of exposures to air pollution were used in the data set of EDEN mother-child cohort study, and results showed that the subjective measurement was strongly associated with the objective measurement¹⁵³.

6.2 Identification of health outcomes

The health outcomes in the thesis were assessed by standard ISAAC questionnaires completed by the parents. The major limitation of the assessment of health outcomes is the recall bias. In the French 6 Cities study, the information on the health outcomes in the past 12 months was collected by the parents. In the EDEN mother-child cohort study, asthma symptoms were reported by the parents every 3 months in the first year of life of the children and every 12 months afterward. However, the assessment of asthma outcomes by ISAAC questionnaire normally with a recall period of 12 months has showed consistent validity in diverse populations. Nwaru BI et al¹⁵⁴ have found that the ISAAC questionnaire-based investigation had highly valid information on the prevalence of parent-reported childhood asthma for epidemiological purposes in Finland (both the sensitivity and specificity are 98 %). Another study showed also adequate validity of the ISAAC questionnaire to distinguish between asthmatic and non-asthmatic children aged 6- to 7-year-old in Brazil, indicating that the sensitivity and specificity for “asthma ever” indicators were 87.2 % and 100 %, respectively¹⁵⁵.

6.3 Relationships between air pollutants and childhood asthma

We found that both subjectively measured air pollutants and objectively measured air pollutants are related to childhood asthma, eczema, and allergic rhinitis. In schoolchildren of the French 6 cities study, allergic sensitization was related to dispersion model based exposure to residential proximity fine particles¹²⁷, asthma (lifetime and past year) was related to exposures to benzene, SO₂, PM₁₀, NO_x, and CO, eczema (lifetime and past year) was associated with exposures to benzene, PM₁₀, NO₂, NO_x, and CO, and lifetime allergic rhinitis was associated with exposure to PM₁₀¹³. In the first year of life in children of the EDEN mother-child cohort study, both single and multi-dimensional asthma phenotypes were positively related to the first year of life exposures to passive smoking, traffic related air pollution and dampness, but negatively associated with contact with cats and domestic wood heating. Results persisted for *in utero* exposures to passive smoking and traffic-related air pollution. In addition, traffic-related air pollution *in utero* life and in the first year of life had a greater impact than other pollutants on the health outcomes¹⁵³. In the first 5 years of life of child in the EDEN mother-child cohort study, maternal smoking during pregnancy was related to the development of wheezing, while *in utero* exposure to traffic-related air pollution was related to the development of wheezing and allergic rhinoconjunctivitis. Compared to maternal smoking during pregnancy, *in utero* exposure to traffic-related air pollution had greater impacts on the development of respiratory health outcomes according to the values of aPARs. However, no significant relationships were found between objectively measured outdoor air pollutants and the development of asthma and allergies in the first 5 years of life in children of the EDEN mother-child cohort study.

Both indoor and outdoor air pollutants have been found to be related to childhood asthma and allergies in previous studies^{13, 57, 156-158}. In our study, the data from French 6 cities studies also showed that outdoor air pollutants (SO₂, PM₁₀, NO₂, NO_x, CO)¹³ and indoor air pollutants (formaldehyde,

PM_{2.5}, acrolein and NO₂)⁵⁷ were related to the prevalence of asthma and allergies in schoolchildren. In our longitudinal data, results showed that indoor air pollutants (*in utero* life passive smoking, dampness in the first year of life) were positively related to asthma phenotypes in the first year of life, that domestic wood heating in the first year of life was negatively related to asthma phenotypes in the first year of life, and that *in utero* life passive smoking was positively related to wheezing in the first 5 year of life.

The potential mechanism for the effects of air pollutants on childhood asthma and allergies has been explored increasingly in the previous studies. Firstly, air pollutants could have detrimental effects on the development of the lung^{106, 159}, especially in early life which is a critical period for the lung development. One review on the relationship between air pollutants and the development of lung has concluded that the air pollutants of environment tobacco smoke, ozone, and particulate matter affect the development of lung and the structure of the respiratory system¹⁰⁶. Secondly, air pollutants could have negative effects on the lung function, thus favoring the development of asthma and allergies. Air pollutants, such as ozone¹⁵⁷, NO₂^{128, 160}, NO_x¹²⁸, PM_{2.5}¹²⁸, PM₁₀¹⁶⁰, traffic-related air pollution^{107, 161-162} were identified as factors that impact on the lung function in children. One nonhuman primate study has showed that ozone-exposed infant monkeys had four fewer nonalveolarized airway generations, hyperplastic bronchiolar epithelium, and altered smooth muscle bundle orientation in terminal and respiratory bronchioles, comparing with control infants¹⁶³. Thirdly, the relationships between air pollutants and childhood asthma and allergies could be explained by the interaction between air pollutants and genes, thus increase the genetic susceptibility to be asthmatic or allergenic. Blekic M et al¹⁶⁴ has examined the interaction between early-life indoor air pollutants (environmental tobacco smoke and furry pets ownership) and genes in 17q12-21 region in relation to asthma in schoolchildren. Results indicate that several genes in 17q12-21 region interacted with the early-life air pollutants to impact on the development of asthma in schoolchildren.

6.4 Relationships between psychological features and childhood asthma

Psychological disorders (behavioral problems in French 6 cities study and maternal depression in the EDEN mother-child cohort study) were found to be related to asthma and allergies both in our study population. In children of the French 6 cities study, emotional or conduct problems were found to be related to asthma, eczema, severe asthma and asthma early onset (before the age of 4 years). In children of the EDEN mother-child cohort study, maternal depression during pregnancy was associated with the development of allergic rhinoconjunctivitis in the first 5 years of life, but no significant relationships were found between maternal depression during pregnancy and the development of wheezing, doctor-diagnosed asthma and doctor-diagnosed eczema.

Psychological features have been well documented in literature as important influencing factors of childhood asthma and allergies. Chang HY et al¹⁶⁵ has found that psychological and behavioral problems are weakly associated with asthma and strongly associated with allergic rhinitis and atopic dermatitis in Korean preschoolers. In Puerto Rican children, paternal and maternal psychological factors (posttraumatic stress disorder, depressive symptoms, and antisocial behavior) and childhood abuse were indicated to influence asthma morbidity¹⁶⁶⁻¹⁶⁷. In children of United States, studies have showed that violence and stress are associated with increased childhood asthma¹⁶⁸⁻¹⁶⁹. In children of European Union, the number of studies on the relationships between psychological features and asthma and allergies are increasing, but evidence on the relationships still lacked. In Italian children, data showed that foetal exposure to maternal stressful events moderately increased the risk of having wheezing, asthma, eczema and allergic rhinitis⁷⁵. In Swedish children, results showed that maternal bereavement shortly before and during pregnancy, a proxy for prenatal stress, was positively related to childhood asthma^{15, 142}. In children of United Kingdom, data indicated that

negative life events increase the risk of children's asthma attacks over the coming few weeks¹⁷⁰, and that behavior problems measured by the Behavior Screening questionnaire related to asthma in children with atopic dermatitis¹⁷¹. In children of Rotterdam, Netherlands, studies showed that maternal psychological distress during pregnancy assessed by the Brief Symptom Inventory questionnaire was associated with increased risk of wheezing in the first 6 years of life independent of paternal psychological distress during pregnancy and maternal and paternal psychological distress after delivery⁷⁸. In French children, Lefevre F et al¹⁷² found that there was a link between maternal depression (investigated by the questionnaire of the Beck Depression Inventory short form) and infants' wheezing and its severity, using a case-control study design. In our study conducted in France, we further described this relationship by using longitudinal data. In addition, our data also showed a significant relationship between maternal depression during pregnancy and the development of allergic rhinoconjunctivitis in the first 5 years of life.

One possible explanation for the relationships of psychological features and childhood asthma and allergies is that psychological disorders could be associated with detrimental changes in the structure of airway. One review has indicated that stress and injury may relate to a phenotypic shift in the epithelium of asthmatic airway, with likely direct transformation of epithelial cells into mesenchymal cells¹⁰⁸. Another explanation could be that psychological factors reduce children's lung function. Suglia SF et al¹⁰⁹ studied the relationships between psychological factors (reported community violence and interparental conflict by mothers) and childhood lung function. Results showed that both community violence and interparental conflict were associated with decreased childhood lung function independent of socioeconomic status, tobacco smoke exposure, birthweight, and respiratory illness history. The plausible pathway for the relationships between psychological factors and asthma and allergies could be that psychological disorders produce changes in the Hypothalamo-Pituitary-Adrenal (HPA) axis regulation and thence dysregulation of immune system functioning, favoring the development of asthma and allergies¹³⁷. In an animal study, results

implicated that prenatal stress produces long-term changes in the HPA axis responses in the offspring of rats, with elevated plasma corticosterone which elicited aberrant immune functions¹⁷³. Wright RJ et al¹⁷⁴ have found that higher prenatal stress was related to increase IL-8 (Interleukin 8) production after microbial stimuli and increased tumor necrosis factor-alpha to microbial stimuli, and also was associated with increased IL-13 after dust mite stimulation and reduced phytohemagglutinin-induced IFN-gamma.

6.5 Interactions between air pollutants and psychological features in relation to childhood asthma

Our results showed that there were interactions between air pollutants and psychological features in relation to childhood asthma and allergies. Children with emotion and conduct problems had 1.17 to 1.51 times higher adjusted odds ratios for the associations between outdoor air pollutants (benzene, CO, NO₂, NO_x, PM₁₀, VOCs), and asthma phenotypes and current eczema than children without emotion and conduct problems in the case of French 6 cities study. In children of the EDEN mother-child cohort study, interaction was found between maternal smoking during pregnancy and maternal depression during pregnancy in relation to ever doctor-diagnosed asthma in the first 5 years of life. There was also interaction between *in utero* exposure to traffic-related air pollution and maternal depression during pregnancy in relation to the development of wheezing in the first 5 years of life ($P < 0.02$). No interactions were found between subjectively measured air pollutants and maternal depression during pregnancy in relation to doctor-diagnosed eczema and allergic rhinoconjunctivitis ($P > 0.02$). As for the objectively measured air pollutants, interaction was only found between exposure to benzene and maternal depression during pregnancy in relation to doctor-diagnosed eczema in the first 5 years of life ($P < 0.20$).

Few studies have explored the interactions between psychological features and air pollutants in relation to childhood asthma and allergies. Clougherty JE et al¹⁰² examined the synergistic effects of long-term exposure to traffic-related air pollution using geographic information system and exposure to violence on urban childhood asthma. Results showed that an interaction was found between traffic-related air pollution and violence exposure in relation to elevated risk of childhood asthma. Chen E et al¹⁰⁴ NO₂ interacted with high family stress to increase over time in symptoms in children with asthma. indicated that Shankardass K and coworkers¹⁷ presented that the risk of asthma

attributable to traffic-related air pollution was significantly higher for children with high parental stress (Hazard Ratio 1.51 across the interquartile range for traffic-related air pollution; 95 % CI 1.16-1.96) than children with low parental stress (Hazard Ratio 1.05 across the interquartile range for traffic-related air pollution; 95 % CI 0.74-1.49, interaction P value 0.05). In our cross-sectional study, interactions were found between behavioral problems and exposures to outdoor air pollutants (benzene, CO, NO₂, NO_x, PM₁₀, VOCs) in relation to asthma phenotypes (current wheezing and current doctor-diagnosed asthma) and current eczema in children of French 6 cities study. These interactions were further demonstrated on childhood wheezing and doctor-diagnosed asthma etiology by using our longitudinal data of EDEN mother-child cohort study, although the psychological indicator is different from the French 6 cities study.

One explanation could be that psychological disorders may increase the susceptibility of the detrimental effects of air pollutants on childhood lung structure. Both psychological disorders and air pollutants have detrimental effects on lung structure^{106, 108}, contributing to the development of asthma and allergies. Another explanation could be that there are interactions between psychological features and air pollutants in relation to children's lung function. Islam T et al¹⁷⁵ indicated that a high-stress home environment was associated with increased susceptibility to children's lung function effects of air pollution both at home and at school. The potential mechanism could also be explained by the combined effects of those two kinds of factors on altering the immune system responses, increasing susceptibility of having asthma and allergies¹⁷⁶.

6.6 Potential mechanisms for the impacts of environmental and psychological factors on childhood

6.6.1 Lung structure and function changes

Fig. 5 briefly summarized the principal stages of lung development in humans (included 5 stages of Embryonic, Pseudoglandula, Canalicular, Saccular, and Alveolar) that commence in the fetus and continue postnatally¹⁰⁶. The impaired lung growth (changed lung structure and function), especially in early life, are believed to predispose the development of childhood asthma and allergies. Haland G and coworkers¹⁷⁷ presented that reduced lung function measured shortly after birth is associated with an increased risk of asthma by 10 years of age. In addition, diminished lung function has been found as a predisposing factor for the development of a first wheezing illness in infants¹⁷⁸.

In previous studies, both psychological features and air pollutants are identified as factors influencing the lung development^{106, 108-109, 128}. However, few studies examined the likely critical periods that susceptible to the psychological disorders and air pollutants in relation to childhood asthma and allergies, which will give important empirical evidence for identifying the vulnerable age groups of children that need to be given priority to access to the pulmonary health care.

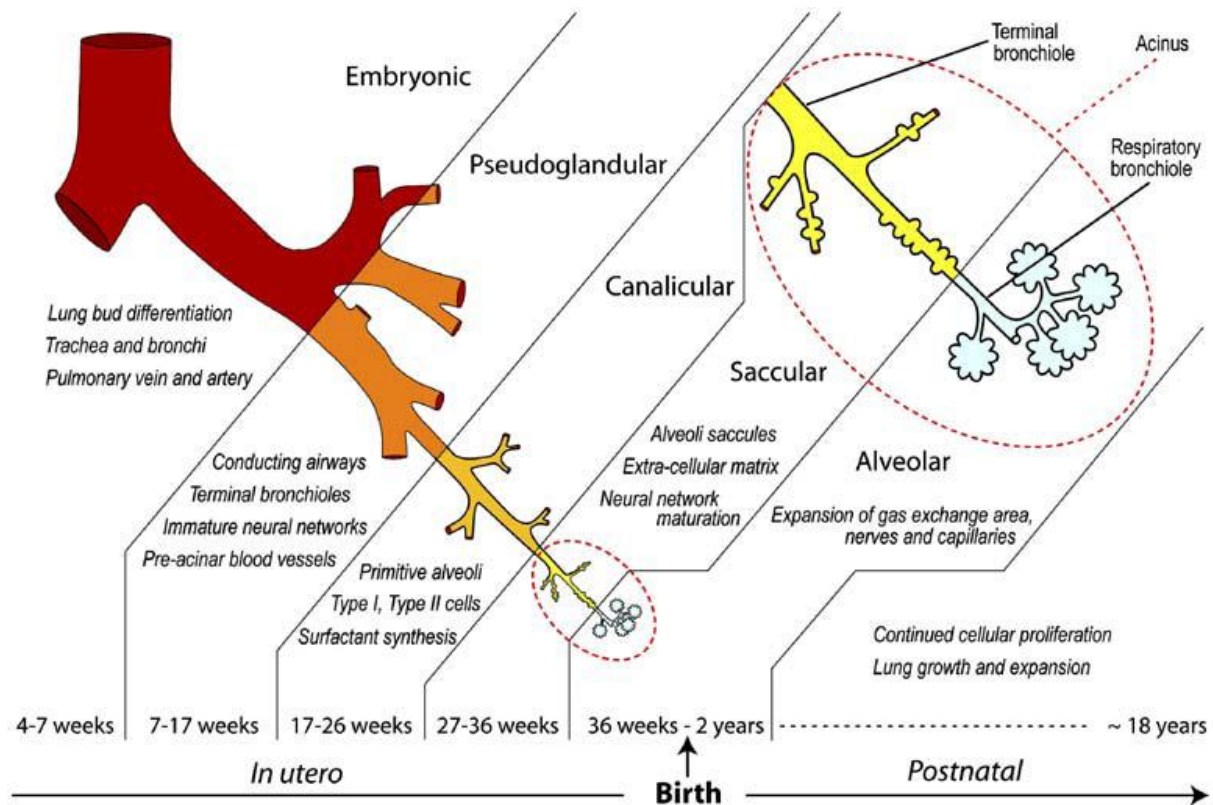


Fig. 5: Principal stages of lung development in humans [Kajekar R et al ¹⁰⁶]

6.6.2 Altered immune system responses

Psychological disorders and air pollutants could elicit altered immune system responses, mainly including Th1 (T helper type 1) /Th2 imbalance and increased production of IgE.

Th1/Th2 imbalance plays an important role in immune system responses in relation to asthma and allergies. Cytokine products of Th1 and Th2 cells are mutually inhibitory¹⁷⁹. The Th1/Th2 imbalance could increase the production of cytokines that contribute to the development of asthma and allergies^{174, 180}. There is ample evidence on the impacts of cytokine production changes on the development of asthma and allergies. Studies indicated that IL-4 (Interleukin 4) and IL-13 (Interleukin

13) are key factors that contribute to the airway remodeling by acting on human lung fibroblasts¹⁸¹, thus increased the risk of having asthma and allergies. Recently, IL-23 has been found to be inversely related to lung function¹⁸², a preceding pathway for asthma and allergies development.

An IgE interaction could result in the release of the mediators contained in mast cells. Those mediators trigger bronchoconstriction and airway hyperresponsiveness, which is common pathway leading to asthma and allergies. Chen E and coworkers¹⁰⁴ have found that NO₂ interacted with chronic family stress in predicting increased IgE level (interaction *P* value=0.02).

6.7 Conclusion

In conclusion, our results showed that both air pollutants and psychological factors are related to childhood asthma, and that air pollutants may interact with psychological features on the health outcomes, implying to consider children with psychological problems as a susceptible population to the detrimental impacts of air pollutants on asthma and to take into account these two kinds of factors simultaneously into the paradigm of childhood asthma prevention.

7. Strengths and limitations

7.1 Strengths

- 1) The study sample was large and drawn from the general population;
- 2) Both preschool children (in the EDEN mother-child cohort study) and schoolchildren (in the French 6 Cities study) were recruited as the study sample;
- 3) Both cross-sectional and longitudinal data were used to show the empirical evidence of the relationships between exposures and health outcomes;
- 4) Both subjective and objective exposures to air pollutants were assessed;
- 5) Standardized questionnaire were implemented to assess both exposures and health outcomes;
- 6) Marginal models were used to take into account of the non-independence of data of children measured repeatedly in different survey waves for the longitudinal dataset, or children living in the same community;
- 7) Adjusted Population Attributable Risk (aPAR) was estimated to examine the impact of each exposure on health outcomes to provide information for further public health interventions;
- 8) The effects of early life exposures on childhood asthma and allergies were estimated, which is thought to be critical to the development of childhood asthma and allergies;
- 9) Both outdoor and indoor air pollutants were assessed;
- 10) Asthma phenotypes covering large spectrum were considered in the analysis thus reducing misclassification of asthmatic cases.

7.2 Limitations

1) In the cross-sectional study (French 6 cities study), the study sample are school children aged 10-12 years, not allowing us to explore the aetiology of childhood asthma and allergies in schoolchildren. In study sample we included in the longitudinal study (EDEN mother-child cohort study) was preschool children that followed up from birth to 5 years old. Therefore, the results of our study could only be extrapolated to the general population aged 0-5 years and 10-12 years in France;

2) In the French 6 cities study, our investigation assessed exposures to air pollution at school addresses instead of at home, where children spend most of their time. Although the school addresses in metropolitans of France are within 500 meters away from the houses of the schoolchildren, exposure assessments errors might have occurred;

3) In the EDEN mother-child cohort study, the prevalence of maternal depression during pregnancy is lower than the general population in France, thus the effect may be underestimated.

4) Recall bias may existed for the investigation of subjectively exposures and health outcomes through standard questionnaires.

8. Perspectives

1) The gene-environment interactions between air pollutants, psychological factors and genes need to be further examined to fully understand the biological mechanism of the development of asthma and allergies;

2) The relationship between exposures (air pollutants, psychological factors) and lung structure and function need to be further explored, taking into account of the interaction between air pollutants and psychological disorders;

3) The spatial correlation between physical environment (air pollution) and social environment (psychological feature) could be taken into account to disentangle the effects of the two kinds of exposures and better understand the interactions between them;

4) The relationships between exposures and severity of health outcomes need further be elucidated in order to take countermeasures to reduce clinical symptoms in children.

5) In the long term the EXPOSOME approach and the EWAS (Environment-wide Associations Study) have to be applied to better understand asthma. This strategy will be conducted in the HEALS (Health and Environment-wide Association based on Large population Surveys) project funded in the frame of the FP7_ENV of the EC of which the EPAR team is coordinator (see Fig. 6).

Genes, Environment, and Health Initiative

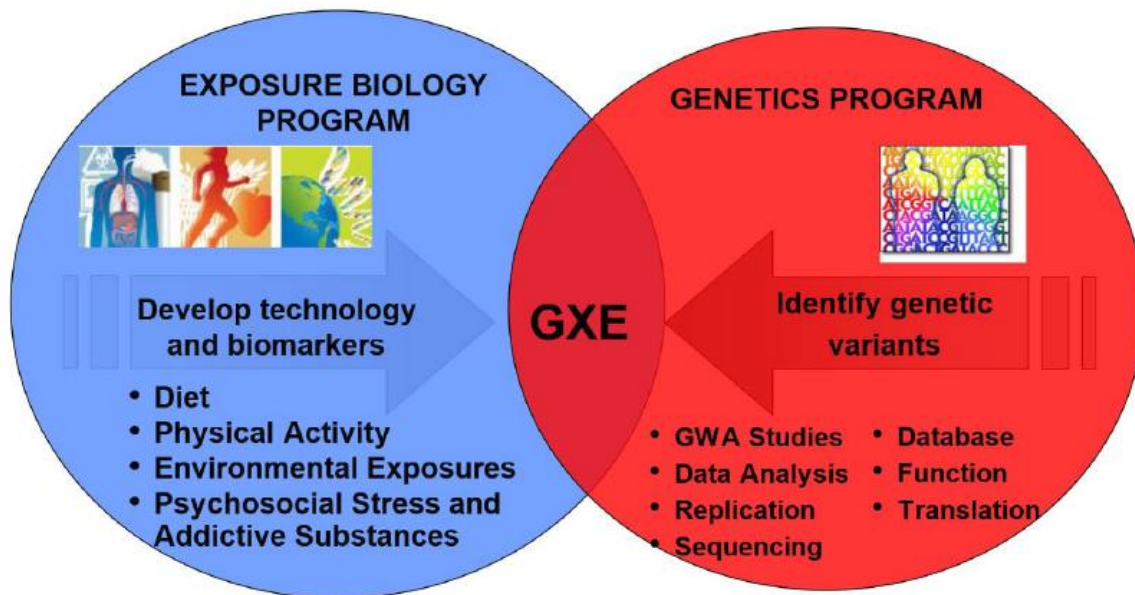


Fig. 6: EXPOSME approach and the EWAS in relation to childhood asthma (From David M. Balshaw, making the case for advancing the EXPOSOME (or EWAS))

References

1. Global initiative for asthma (GINA). Global strategy for asthma management and prevention. 2006.
2. Baiz N, Annesi-Maesano I. Is the Asthma Epidemic Still Ascending? *Clinics in Chest Medicine* 2012;33(3):419-29.
3. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226-35.
4. Russell G. The childhood asthma epidemic. *Thorax* 2006;61(4):276-8.
5. Duggan EM, Sturley J, Fitzgerald AP, Perry IJ, Hourihane JO. The 2002-2007 trends of prevalence of asthma, allergic rhinitis and eczema in Irish schoolchildren. *Pediatric Allergy and Immunology* 2012;23(5):464-471.
6. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368(9537):733-743.
7. Zollner IK, Weiland SK, Piechotowski I, et al. No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992-2001. *Thorax* 2005;60(7):545-548.
8. Johnson CC, Ownby DR, Zoratti EM, Alford SH, Williams LK, Joseph CL. Environmental epidemiology of pediatric asthma and allergy. *Epidemiol Rev* 2002;24(2):154-75.
9. Subbarao P, Becker A, Brook JR, et al. Epidemiology of asthma: risk factors for development. *Expert Rev Clin Immunol* 2009;5(1):77-95.
10. Gruziova O, Bergstrom A, Hulchiy O, et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology* 2013;24(1):54-61.
11. Chen YC, Tsai CH, Lee YL. Early-life indoor environmental exposures increase the risk of childhood asthma. *Int J Hyg Environ Health* 2011;215(1):19-25.
12. Heinrich J. Influence of indoor factors in dwellings on the development of childhood asthma. *International Journal of Hygiene and Environmental Health* 2011;214(1):3-27.
13. Penard-Morand C, Raherison C, Charpin D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Eur Respir J* 2010;36(1):33-40.
14. dos Santos LM, dos Santos DN, Rodrigues LC, Barreto ML. Maternal mental health and social support: effect on childhood atopic and non-atopic asthma symptoms. *Journal of Epidemiology and Community Health* 2012;66(11):1011-1016.
15. Fang F, Hoglund CO, Arck P, et al. Maternal Bereavement and Childhood Asthma-Analyses in Two Large Samples of Swedish Children. *Plos One* 2011;6(11).
16. Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedon JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *Journal of Allergy and Clinical Immunology* 2011;127(3):734-U373.
17. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106(30):12406-12411.
18. Milam J, McConnell R, Yao L, Berhane K, Jerrett M, Richardson J. Parental stress and childhood wheeze in a prospective cohort study. *Journal of Asthma* 2008;45(4):319-323.
19. European, Environment, Agency. Air quality in Europe-2013 report. In. Luxembourg: Publications Office of the European Union; 2013.
20. Sonnenschein-van der Voort AMM, de Kluizenaar Y, Jaddoe VWV, et al. Air pollution, fetal and infant tobacco smoke exposure, and wheezing in preschool children: a population-based prospective birth cohort. *Environmental Health* 2012;11.

21. Carlsten C, Melen E. Air pollution, genetics, and allergy: an update. *Current Opinion in Allergy and Clinical Immunology* 2012;12(5):455-460.
22. Salam MT, Byun HM, Lurmann F, et al. Genetic and epigenetic variations in inducible nitric oxide synthase promoter, particulate pollution, and exhaled nitric oxide levels in children. *Journal of Allergy and Clinical Immunology* 2012;129(1):232-U338.
23. Philip-Joet F. Respiratory effects of pollution. *Biomed Pharmacother* 1990;44(9):443-6.
24. Viegi G, Simoni M, Scognamiglio A, et al. Indoor air pollution and airway disease. *International Journal of Tuberculosis and Lung Disease* 2004;8(12):1401-1415.
25. Habre R, Coull B, Moshier E, et al. Sources of indoor air pollution in New York City residences of asthmatic children. *J Expo Sci Environ Epidemiol* 2013.
26. Yu CH, Morandi MT, Weisel CP. Passive dosimeters for nitrogen dioxide in personal/indoor air sampling: a review. *J Expo Sci Environ Epidemiol* 2008;18(5):441-51.
27. Zou B, Wilson JG, Zhan FB, Zeng Y. Air pollution exposure assessment methods utilized in epidemiological studies. *J Environ Monit* 2009;11(3):475-90.
28. Ozkaynak H BL, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. *J Expo Sci Environ Epidemiol* 2013;23(6):566-72.
29. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *Journal of Allergy and Clinical Immunology* 2008;121(5):1133-1139.
30. Yamazaki S, Shima M, Ando M, Nitta H. Modifying Effect of Age on the Association between Ambient Ozone and Nighttime Primary Care Visits Due to Asthma Attack. *Journal of Epidemiology* 2009;19(3):143-151.
31. Nastos PT, Paliatsos AG, Anthracopoulos MB, Roma ES, Priftis KN. Outdoor particulate matter and childhood asthma admissions in Athens, Greece: a time-series study. *Environmental Health* 2010;9.
32. Iskandar A, Andersen ZJ, Bønnelykke K, Ellermann T, Andersen KK, H B. Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. *Thorax* 2012;67(3):252-7.
33. Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptom severity and medication use in children with asthma. *Annals of Allergy Asthma & Immunology* 2003;91(4):346-353.
34. Patel MM, Miller RL. Air pollution and childhood asthma: recent advances and future directions. *Current Opinion in Pediatrics* 2009;21(2):235-242.
35. Erbas B, Lowe AJ, Lodge CJ, et al. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. *Clinical and Experimental Allergy* 2013;43(3):337-343.
36. Laumbach RJ, Kipen HM. Respiratory health effects of air pollution: update on biomass smoke and traffic pollution. *J Allergy Clin Immunol* 2012;129(1):3-11; quiz 12-3.
37. D'Amato G, Cecchi L, D'Amato M, Liccardi G. Urban Air Pollution and Climate Change as Environmental Risk Factors of Respiratory Allergy: An Update. *Journal of Investigational Allergology and Clinical Immunology* 2010;20(2):95-102.
38. Shima M, Nitta Y, Ando M, Adachi M. Effects of air pollution on the prevalence and incidence of asthma in children. *Archives of Environmental Health* 2002;57(6):529-535.
39. Lin S, Liu X, Le LH, Hwang SA. Chronic Exposure to Ambient Ozone and Asthma Hospital Admissions among Children. *Environmental Health Perspectives* 2008;116(12):1725-1730.
40. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359(9304):386-391.
41. Nordling E, Berglund N, Melen E, et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 2008;19(3):401-408.
42. Gehring U, Wijga AH, Brauer M, et al. Traffic-related Air Pollution and the Development of Asthma and Allergies during the First 8 Years of Life. *American Journal of Respiratory and Critical Care Medicine* 2010;181(6):596-603.

43. McConnell R, Islam T, Shankardass K, et al. Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School. *Environmental Health Perspectives* 2010;118(7):1021-1026.
44. Gasana J, Dillikar D, Mendy A, Forno E, Vieira ER. Motor vehicle air pollution and asthma in children: A meta-analysis. *Environmental Research* 2012;117:36-45.
45. Bernstein DI. Traffic-Related Pollutants and Wheezing in Children. *Journal of Asthma* 2012;49(1):5-7.
46. Gruziova O BA, Hulchiy O, Kull I, Lind T, Melén E, et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology* 2013;24:54-61.
47. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 2008;177(12):1331-7.
48. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: A prospective cohort study with individual exposure measurement. *Environmental Health Perspectives* 2008;116(10):1433-1438.
49. Kramer U, Sugiri D, Ranft U, et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *Journal of Dermatological Science* 2009;56(2):99-105.
50. Oftedal B, Nystad W, Brunekreef B, Nafstad P. Long-Term Traffic-Related Exposures and Asthma Onset in Schoolchildren in Oslo, Norway. *Environmental Health Perspectives* 2009;117(5):839-844.
51. Ryan PH, Bernstein DI, Lockey J, et al. Exposure to Traffic-related Particles and Endotoxin during Infancy Is Associated with Wheezing at Age 3 Years. *American Journal of Respiratory and Critical Care Medicine* 2009;180(11):1068-1075.
52. Clark NA, Demers PA, Karr CJ, et al. Effect of Early Life Exposure to Air Pollution on Development of Childhood Asthma. *Environmental Health Perspectives* 2010;118(2):284-290.
53. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occup Environ Med* 2011;68(4):291-5.
54. Patel MM, Quinn JW, Jung KH, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. *Environmental Research* 2011;111(8):1222-1229.
55. Organization WH. A conceptual framework for action on the social determinants of health. In. Geneva: World Health Organization; 2010.
56. Zhao ZH, Zhang Z, Wang ZH, Ferm M, Liang YL, Norback D. Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. *Environmental Health Perspectives* 2008;116(1):90-97.
57. Annesi-Maesano I, Hulin M, Lavaud F, et al. Poor air quality in classrooms related to asthma and rhinitis in primary schoolchildren of the French 6 Cities Study. *Thorax* 2012;67(8):682-8.
58. Hulin M, Simoni M, Viegi G, Annesi-Maesano I. Respiratory health and indoor air pollutants based on quantitative exposure assessments. *Eur Respir J* 2012;40(4):1033-45.
59. Hansel NN, Breyse PN, McCormack MC, et al. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environ Health Perspect* 2008;116(10):1428-32.
60. Henderson J, Sherriff A, Farrow A, Ayres JG. Household chemicals, persistent wheezing and lung function: effect modification by atopy? *Eur Respir J* 2008;31(3):547-54.
61. Krauss-Etschmann S, Niedermaier S, Beyer J, et al. Current use of room disinfectants and allergic symptoms at the age of 4 years. *Journal of Allergy and Clinical Immunology* 2009;123(5):1176-1178.
62. Iossifova YY, Reponen T, Ryan PH, et al. Mold exposure during infancy as a predictor of potential asthma development. *Annals of Allergy Asthma & Immunology* 2009;102(2):131-137.
63. Karvonen AM, Hyvarinen A, Roponen M, et al. Confirmed Moisture Damage at Home, Respiratory Symptoms and Atopy in Early Life: A Birth-Cohort Study. *Pediatrics* 2009;124(2):E329-E338.

64. Kerkhof M, Wijga AH, Brunekreef B, et al. Effects of pets on asthma development up to 8 years of age: the PIAMA study. *Allergy* 2009;64(8):1202-8.
65. Raaschou-Nielsen O, Hermansen MN, Loland L, et al. Long-term exposure to indoor air pollution and wheezing symptoms in infants. *Indoor Air* 2010;20(2):159-167.
66. McCormack MC, Breyse PN, Matsui EC, et al. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Annals of Allergy Asthma & Immunology* 2011;106(4):308-315.
67. Tischer C, Gehring U, Chen CM, et al. Respiratory health in children, and indoor exposure to (1,3)-beta-D-glucan, EPS mould components and endotoxin. *Eur Respir J* 2011;37(5):1050-9.
68. Jung KH, Hsu SI, Yan BZ, et al. Childhood exposure to fine particulate matter and black carbon and the development of new wheeze between ages 5 and 7 in an urban prospective cohort. *Environment International* 2012;45:44-50.
69. Reponen T, Lockey J, Bernstein DI, et al. Infant origins of childhood asthma associated with specific molds. *J Allergy Clin Immunol* 2012;130(3):639-644 e5.
70. Neuman A, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med* 2012;186(10):1037-43.
71. Carlsen KCL, Roll S, Carlsen KH, et al. Does Pet Ownership in Infancy Lead to Asthma or Allergy at School Age? Pooled Analysis of Individual Participant Data from 11 European Birth Cohorts. *Plos One* 2012;7(8).
72. Bunyavanich S, Silberg JL, Lasky-Su J, et al. A twin study of early-childhood asthma in Puerto Ricans. *PLoS One* 2013;8(7):e68473.
73. Tischer CG, Hohmann C, Thiering E, et al. Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy* 2011;66(12):1570-9.
74. Su MW, Tung KY, Liang PH, Tsai CH, Kuo NW, Lee YL. Gene-Gene and Gene-Environmental Interactions of Childhood Asthma: A Multifactor Dimension Reduction Approach. *Plos One* 2012;7(2).
75. de Marco R, Pesce G, Girardi P, et al. Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood. *Pediatric Allergy and Immunology* 2012;23(8):724-729.
76. Calam R, Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems antecede the development of wheeze in childhood. *American Journal of Respiratory and Critical Care Medicine* 2005;171(4):323-327.
77. Macri F, Rossi FP, Lambiase C, di Castelbianco FB, Frassanito A. Psychological factors in childhood asthma. *Pediatr Pulmonol* 2008;43(4):366-70.
78. Guxens M, Sonnenschein-van der Voort AM, Tiemeier H, et al. Parental psychological distress during pregnancy and wheezing in preschool children: The Generation R Study. *J Allergy Clin Immunol* 2013.
79. Liu X, Olsen J, Agerbo E, et al. Psychological Stress and Hospitalization for Childhood Asthma- a Nationwide Cohort Study in Two Nordic Countries. *PLoS One* 2013;8(10):e78816.
80. Feldman JM, Ortega AN, Koinis-Mitchell D, Kuo AA, Canino G. Child and Family Psychiatric and Psychological Factors Associated With Child Physical Health Problems Results From the Boricua Youth Study. *Journal of Nervous and Mental Disease* 2010;198(4):272-279.
81. Suglia SF, Duarte CS, Sandel MT, Wright RJ. Social and environmental stressors in the home and childhood asthma. *Journal of Epidemiology and Community Health* 2010;64(7):636-642.
82. Wright RJ. Epidemiology of Stress and Asthma: From Constricting Communities and Fragile Families to Epigenetics. *Immunology and Allergy Clinics of North America* 2011;31(1):19-+.
83. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. *Int J Epidemiol* 2002;31(6):1091-3.
84. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24(4):385-96.

85. Long KA, Ewing LJ, Cohen S, et al. Preliminary Evidence for the Feasibility of a Stress Management Intervention for 7- to 12-Year-Olds with Asthma. *Journal of Asthma* 2011;48(2):162-170.
86. Wright RJ, Mitchell H, Visness CM, et al. Community violence and asthma morbidity: the Inner-City Asthma Study. *Am J Public Health* 2004;94(4):625-32.
87. Kovacs M. The Children's Depression Inventory Manual. North Tonawanda, NY: Multi-Health Systems; 1992.
88. Beck AT, Rial WY, Rickels K. Short form of depression inventory: cross-validation. *Psychol Rep* 1974;34(3):1184-6.
89. Lefevre F, Moreau D, Semon E, Kalaboka S, Annesi-Maesano I, Just J. Maternal depression related to infant's wheezing. *Pediatr Allergy Immunol* 2011;22(6):608-13.
90. Apter AJ, Garcia LA, Boyd RC, Wang XM, Bogen DK, Ten Have T. Exposure to community violence is associated with asthma hospitalizations and emergency department visits. *Journal of Allergy and Clinical Immunology* 2010;126(3):552-557.
91. Spielberger C. State-Trait Anxiety Inventory for Children. New York: Consulting Psychologist Press; 1973.
92. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *Journal of Allergy and Clinical Immunology* 2009;123(4):847-853.
93. Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol* 1988;61 (Pt 3):255-66.
94. Turyk ME, Hernandez E, Wright RJ, et al. Stressful life events and asthma in adolescents. *Pediatric Allergy and Immunology* 2008;19(3):255-263.
95. Achenbach TM, Edelbrock C. Manual for the child behavior checklist and revised child behavior profile. Burlington, VT: Department of Psychiatry, University of Vermont; 1983.
96. Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy - A prospective birth-cohort study. *American Journal of Respiratory and Critical Care Medicine* 2002;165(3):358-365.
97. Shankardass K, Jerrett M, Milam J, Richardson J, Berhane K, McConnell R. Social environment and asthma: associations with crime and No Child Left Behind programmes. *Journal of Epidemiology and Community Health* 2011;65(10):859-865.
98. Turney K. Perceived instrumental support and children's health across the early life course. *Soc Sci Med* 2013;95:34-42.
99. Marin TJ, Chen E, Munch JA, Miller GE. Double-Exposure to Acute Stress and Chronic Family Stress is Associated With Immune Changes in Children With Asthma. *Psychosomatic Medicine* 2009;71(4):378-384.
100. Kozyrskyj AL, Bahreinian S, Azad MB. Early life exposures: impact on asthma and allergic disease. *Current Opinion in Allergy and Clinical Immunology* 2011;11(5):400-406.
101. Wright RJ, Steinbach SF. Violence: An unrecognized environmental exposure that may contribute to greater asthma morbidity in high risk inner-city populations. *Environmental Health Perspectives* 2001;109(10):1085-1089.
102. Clougherty JE, Levy JI, Kubzansky LD, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environmental Health Perspectives* 2007;115(8):1140-1146.
103. Chiu YH, Coull BA, Sternthal MJ, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J Allergy Clin Immunol* 2013.
104. Chen E, Schreier HMC, Strunk RC, Brauer M. Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environmental Health Perspectives* 2008;116(7):970-975.
105. Peters JL CS, Staudenmayer J, Hosen J, Platts-Mills TA, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. *Allergy* 2012;67(4):545-51.

106. Kajekar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther* 2007;114(2):129-45.
107. Eenhuizen E, Gehring U, Wijga AH, et al. Traffic-related air pollution is related to interrupter resistance in 4-year-old children. *European Respiratory Journal* 2013;41(6):1257-1263.
108. Bai TR. Evidence for airway remodeling in chronic asthma. *Current Opinion in Allergy and Clinical Immunology* 2010;10(1):82-86.
109. Suglia SF, Ryan L, Laden F, Dockery DW, Wright RJ. Violence exposure, a chronic psychosocial stressor, and childhood lung function. *Psychosom Med* 2008;70(2):160-9.
110. Madrigano J, Baccarelli A, Mittleman MA, et al. Air Pollution and DNA Methylation: Interaction by Psychological Factors in the VA Normative Aging Study. *American Journal of Epidemiology* 2012;176(3):224-232.
111. Penard-Morand C, Charpin D, Raheison C, et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clinical and Experimental Allergy* 2005;35(10):1279-1287.
112. Weiland SK, Bjorksten B, Brunekreef B, et al. Phase II of the international study of asthma and allergies in childhood (ISAAC II): rationale and methods. *European Respiratory Journal* 2004;24(3):406-412.
113. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry* 1997;38(5):581-6.
114. Shojaei T WA, Pitrou I, Kovess V. The strengths and difficulties questionnaire: validation study in French school-aged children and cross-cultural comparisons. *Soc Psychiatry Psychiatr Epidemiol* 2009;44:740-7.
115. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1(1977):385-401.
116. Fuhrer R RF. La version française de l'échelle CES-D (Center for Epidemiology Studies-Depression Scale). Description et traduction de l'échelle d'auto-évaluation. *Psychiatrie et Psychobiologie* 1989;4:163-6.
117. Scafidi FA FT, Prodromidis M, Abrams SM. Low beck depression scores and "faking good" MMPI profiles. *Adolescence* 1999;34:61-8.
118. Orr ST, Miller CA. Maternal Depressive Symptoms and the Risk of Poor Pregnancy Outcome - Review of the Literature and Preliminary Findings. *Epidemiologic Reviews* 1995;17(1):165-171.
119. Orr ST, Blazer DG, James SA, Reiter JP. Depressive symptoms and indicators of maternal health status during pregnancy. *J Womens Health (Larchmt)* 2007;16(4):535-42.
120. Melchior M, Ferrie JE, Alexanderson K, et al. Using Sickness Absence Records to Predict Future Depression in a Working Population: Prospective Findings From the GAZEL Cohort. *American Journal of Public Health* 2009;99(8):1417-1422.
121. Beasley R, Clayton T, Crane J, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008;372(9643):1039-1048.
122. Carlsen KCL, Haland G, Devulapalli CS, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006;61(4):454-460.
123. Burgess JA LA, Matheson MC, Varigos G, Abramson MJ, Dharmage SC. Does eczema lead to asthma? *J Asthma* 2009;46:429-36.
124. Omar RZ, Wright EM, Turner RM, Thompson SG. Analysing repeated measurements data: a practical comparison of methods. *Stat Med* 1999;18(13):1587-603.
125. Preisser JS, Koch GG. Categorical data analysis in public health. *Annual Review of Public Health* 1997;18:51-82.
126. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985;122(5):904-14.
127. Annesi-Maesano I, Moreau D, Caillaud D, et al. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respiratory Medicine* 2007;101(8):1721-1729.

128. Gehring U, Gruzieva O, Agius RM, et al. Air Pollution Exposure and Lung Function in Children: The ESCAPE Project. *Environ Health Perspect* 2013.
129. Yang IV, Schwartz DA. Epigenetic mechanisms and the development of asthma. *Journal of Allergy and Clinical Immunology* 2012;130(6):1243-1255.
130. Peters JL, Boynton-Jarrett R, Sandel M. Prenatal environmental factors influencing IgE levels, atopy and early asthma. *Current Opinion in Allergy and Clinical Immunology* 2013;13(2):187-192.
131. Algert CS, Bowen JR, Lain SL, Allen HD, Vivian-Taylor JM, Roberts CL. Pregnancy exposures and risk of childhood asthma admission in a population birth cohort. *Pediatric Allergy and Immunology* 2011;22(8):836-842.
132. Apter G, Devouche E, Gratier M. Perinatal mental health. *J Nerv Ment Dis* 2011;199(8):575-7.
133. Apter G, Devouche E, Garez V, et al. Pregnancy, somatic complaints and depression: a French population-based study. *Eur J Obstet Gynecol Reprod Biol* 2013;171(1):35-9.
134. Tandon SD, Cluxton-Keller F, Leis J, Le HN, Perry DF. A comparison of three screening tools to identify perinatal depression among low-income African American women. *Journal of Affective Disorders* 2012;136(1-2):155-162.
135. Wood RA, Bloomberg GR, Kattan M, et al. Relationships among environmental exposures, cord blood cytokine responses, allergy, and wheeze at 1 year of age in an inner-city birth cohort (Urban Environment and Childhood Asthma study). *Journal of Allergy and Clinical Immunology* 2011;127(4):913-U136.
136. Trueba AF, Ritz T. Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology. *Brain Behav Immun* 2013;29:11-27.
137. Wright RJ. Prenatal maternal stress and early caregiving experiences: implications for childhood asthma risk. *Paediatric and Perinatal Epidemiology* 2007;21:8-14.
138. Bloomberg GR, Chen E. The relationship of psychologic stress with childhood asthma. *Immunology and Allergy Clinics of North America* 2005;25(1):83-+.
139. Wright RJ. Perinatal stress and early life programming of lung structure and function. *Biological Psychology* 2010;84(1):46-56.
140. Lock M, McGillick EV, Orgeig S, McMillen IC, Morrison JL. Regulation of fetal lung development in response to maternal overnutrition. *Clin Exp Pharmacol Physiol* 2013.
141. Mandal M, Donnelly R, Elkabes S, et al. Maternal immune stimulation during pregnancy shapes the immunological phenotype of offspring. *Brain Behav Immun* 2013;33:33-45.
142. Khashan AS, Wicks S, Dalman C, et al. Prenatal stress and risk of asthma hospitalization in the offspring: a Swedish population-based study. *Psychosom Med* 2012;74(6):635-41.
143. Yonas MA, Lange NE, Celedon JC. Psychosocial stress and asthma morbidity. *Curr Opin Allergy Clin Immunol* 2012;12(2):202-10.
144. Keita SO, Payne P, PascaleV AK, Roya C. Fetal programming and early childhood growth insult: Neglected in discussions of the causation of US adult health disparities. *American Journal of Human Biology* 2007;19(2):261-262.
145. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr* 2001;4(2B):611-24.
146. Drever N, Saade GR, Bytautiene E. Fetal Programming: Early-life Modulations that Affect Adult Outcomes. *Current Allergy and Asthma Reports* 2010;10(6):453-459.
147. Heinrich J, Gehring U, Cyrus J, et al. Exposure to traffic related air pollutants: self reported traffic intensity versus GIS modelled exposure. *Occupational and Environmental Medicine* 2005;62(8):517-523.
148. Gauderman WJ, Avol E, Lurmann F, et al. Childhood asthma and exposure to traffic and nitrogen dioxide. *Epidemiology* 2005;16(6):737-743.
149. Cesaroni G, Badaloni C, Porta D, Forastiere F, Perucci CA. Comparison between various indices of exposure to traffic-related air pollution and their impact on respiratory health in adults. *Occupational and Environmental Medicine* 2008;65(10):683-690.

150. Wu J, Wilhelm M, Chung J, Ritz B. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. *Environmental Research* 2011;111(5):685-692.
151. Molter A, Lindley S, de Vocht F, Simpson A, Agius R. Modelling air pollution for epidemiologic research - Part II. Predicting temporal variation through land use regression. *Science of the Total Environment* 2010;409(1):211-217.
152. Forastiere F, Galassi C. Self report and GIS based modelling as indicators of air pollution exposure: is there a gold standard? *Occupational and Environmental Medicine* 2005;62(8):508-509.
153. Zhou CL, Baiz N, Zhang TH, et al. Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. *Bmc Public Health* 2013;13.
154. Nwaru BI, Lumia M, Kaila M, et al. Validation of the Finnish ISAAC questionnaire on asthma against anti-asthmatic medication reimbursement database in 5-year-old children. *Clin Respir J* 2011;5(4):211-8.
155. Valle SO, Kuschnir FC, Sole D, Silva MA, Silva RI, Da Cunha AJ. Validity and reproducibility of the asthma core International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire obtained by telephone survey. *J Asthma* 2012;49(4):390-4.
156. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. *Curr Opin Pediatr* 2013;25(2):232-9.
157. Altug H, Gaga EO, Dogeroglu T, et al. Effects of air pollution on lung function and symptoms of asthma, rhinitis and eczema in primary school children. *Environ Sci Pollut Res Int* 2013;20(9):6455-67.
158. Carlsten C, Melen E. Air pollution, genetics, and allergy: an update. *Curr Opin Allergy Clin Immunol* 2012;12(5):455-60.
159. Gauderman WJ, Vora H, McConnell R, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007;369(9561):571-577.
160. Molter A, Agius RM, de Vocht F, et al. Long-term Exposure to PM10 and NO2 in Association with Lung Volume and Airway Resistance in the MAAS Birth Cohort. *Environ Health Perspect* 2013;121(10):1232-8.
161. Schultz ES, Gruzieva O, Bellander T, et al. Traffic-related Air Pollution and Lung Function in Children at 8 Years of Age A Birth Cohort Study. *American Journal of Respiratory and Critical Care Medicine* 2012;186(12):1286-1291.
162. Rosenlund M, Forastiere F, Porta D, De Sario M, Badaloni C, Perucci CA. Traffic-related air pollution in relation to respiratory symptoms, allergic sensitisation and lung function in schoolchildren. *Thorax* 2009;64(7):573-580.
163. Fanucchi MV, Plopper CG, Evans MJ, et al. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *Am J Physiol Lung Cell Mol Physiol* 2006;291(4):L644-50.
164. Blekic M, Kljaic Bukvic B, Aberle N, et al. 17q12-21 and asthma: interactions with early-life environmental exposures. *Ann Allergy Asthma Immunol* 2013;110(5):347-353 e2.
165. Chang HY SJ, Kim HY, Kwon JW, Kim BJ, Kim HB, et al. Allergic diseases in preschoolers are associated with psychological and behavioural problems. *Allergy Asthma Immunol Res* 2013;5(5):315-21.
166. Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedon JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J Allergy Clin Immunol* 2011;127(3):734-40 e1-7.
167. Cohen RT, Canino GJ, Bird HR, Celedon JC. Violence, abuse, and asthma in Puerto Rican children. *American Journal of Respiratory and Critical Care Medicine* 2008;178(5):453-459.
168. Suglia SF, Duarte CS, Sandel MT, Wright RJ. Social and environmental stressors in the home and childhood asthma. *J Epidemiol Community Health* 2010;64(7):636-42.
169. Williams DR, Sternthal M, Wright RJ. Social Determinants: Taking the Social Context of Asthma Seriously. *Pediatrics* 2009;123:S174-S184.
170. Sandberg S, Paton JY, Ahola S, et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356(9234):982-987.

171. Stevenson J, ETAC Study Group. Relationship between behavior and asthma in children with atopic dermatitis. *Psychosomatic Medicine* 2003;65(6):971-975.
172. Lefevre F, Moreau D, Semon E, Kalaboka S, Annesi-Maesano I, Just J. Maternal depression related to infant's wheezing. *Pediatric Allergy and Immunology* 2011;22(6):608-613.
173. Henry C, Kabbaj M, Simon H, Le Moal M, Maccari S. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *J Neuroendocrinol* 1994;6(3):341-5.
174. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182(1):25-33.
175. Islam T, Urman R, Gauderman WJ, et al. Parental Stress Increases the Detrimental Effect of Traffic Exposure on Children's Lung Function. *American Journal of Respiratory and Critical Care Medicine* 2011;184(7):822-827.
176. Clougherty JE, Rossi CA, Lawrence J, et al. Chronic social stress and susceptibility to concentrated ambient fine particles in rats. *Environ Health Perspect* 2010;118(6):769-75.
177. Geir Håland KCLC, Leiv Sandvik, Chandra Sekhar Devulapalli, Monica Cheng Munthe-Kaas, Morten Pettersen, et al. Reduced Lung Function at Birth and the Risk of Asthma at 10 Years of Age. *N Engl J Med* 2006;355:1682-9.
178. Fernando D. Martinez WJM, Anne L. Wright, Catharine J. Holberg, Lynn M. Taussig, and The Group Health Medical Associates Personnel. Diminished Lung Function as a Predisposing Factor for Wheezing Respiratory Illness in Infants. *N Engl J Med* 1988;319:1112-7.
179. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* 1996;17(3):138-46.
180. Nakamura Y, Miyata M, Ohba T, et al. Cigarette smoke extract induces thymic stromal lymphopoietin expression, leading to T(H)2-type immune responses and airway inflammation. *Journal of Allergy and Clinical Immunology* 2008;122(6):1208-1214.
181. Doucet C B-BD, Pottin-Clemenceau C, Canonica GW, Jasmin C, Azzarone B. Interleukin (IL)-4 and IL13 act on human lung fibroblasts. *J Clin Invest* 1998;101:2129-39.
182. Ciprandi G, Cuppari C, Salpietro AM, et al. Serum IL-23 strongly and inversely correlates with FEV1 in asthmatic children. *Int Arch Allergy Immunol* 2012;159(2):183-6.