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Maternal fine particulate matter exposure, polymorphism in xenobiotic-metabolizing genes and offspring birth weight

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ABSTRACT

We aimed to describe if polymorphisms in xenobiotics-metabolizing genes modify the effect of maternal exposure to fine particulate matter ($PM_{2.5}$) on offspring birth weight.

Among newborns from LISA cohort, we tested if polymorphisms of *GSTT1*, *GSTP1*, *GSTM1*, and *CYP2D6* genes modified the effect measure of $PM_{2.5}$ on term birth weight. Subsequently, we tested if polymorphisms modified the effect of other exposure factors with possibly similar pathways of action (active or passive smoking).

$PM_{2.5}$ exposure above the median value (reference, below) was associated with birth weight changes by 76 g in the *homozygous* wild type genotype ($n = 161$), −90 g in the *heterozygous* genotype ($n = 154$) and −168 g in children with *GSTP1 *1B/*1B mutant* genotype ($n = 39$, interaction test, $p = 0.05$). No effect measure modification with $PM_{2.5}$ was detected for *GSTT1*, *GSTM1* or *CYP2D6* polymorphisms ($p \geq 0.12$). No effect measure modification with *GSTP1* polymorphism was detected for active ($p = 0.71$) nor for passive smoking effects on birth weight ($p = 0.13$).

1. Introduction

Several studies reported associations between air pollution levels during pregnancy and measures of foetal size at birth (discussed e.g., by [1–4]). A few of these studies attempted to identify factors that could entail variations in the estimated sensitivity of foetal size to air pollutants; sensitivity factors considered include sex of the offspring [5–7], maternal parity [8], diet [9,10] and genetic polymorphisms [11]. The latter were considered in only one study based on 199 births, in which two polymorphisms of *CYP1A1* gene were assessed. No interaction tests have been reported, but birth weight changes associated with PM_{10} exposure above the 90th percentile (compared to below the 90th percentile) were not clearly in favor of an effect measure modification by any of the polymorphisms considered (see [11] and Table 1 of this paper). Therefore, there is currently very limited direct evidence for genetic polymorphisms modifying the effect measure of air pollutants on foetal growth in humans. Some genes implied in the metabolism of xenobiotics have been shown to modulate the action of drugs in the body [12–15], and they appear worth being considered in the context of the study of air pollution effects.

The metabolism of xenobiotics can schematically be seen as a process in two phases; phase 1 usually corresponds to a functionalisation of xenobiotics, which makes them more electrophilic or nucleophilic, thus allowing a conjugation step, corresponding to the phase 2 of metabolism, which eventually leads to more hydrophilic compounds that can be more easily eliminated from the body than the parent xenobiotics. Examples of enzymes implied in phase 1 metabolism include the cytochrome P450 (CYP) superfamily.

Abbreviations: CI, confidence interval; CY, cytochrome P 450; ETS, environmental tobacco smoke; GST, glutathione S-transferase; $PM_{2.5}$, fine particulate matter with an aerodynamical diameter below 2.5 μ.

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Table 1
Overview of previous gene–environment studies of effects of atmospheric pollutants or active or passive smoking on birth weight considering polymorphisms of xenobiotics-metabolizing genes.

Reference	Environmental factor	Genetic polymorphisms	Origin of DNA	Outcome	Type of model	Main results
Suh [11]	PM_{10} (above 90th centile vs. below 90th centile)	*CYP1A1* MspI *CYP1A1* NcoI	Maternal ($n = 199$)	Birth weight	Additive	Birth weight change associated with PM_{10}: −MspI: −349 g for *TT* genotype of *CYP1A1* MspI polymorphism and −394 g for *TC/CC* genotype; −NcoI: −261 g for *IleIle* genotype of *CYP1A1* NcoI polymorphism and −489 g for *IleVal/ValVal* genotype
Wang [19]	Maternal smoking during pregnancy	*CYP1A1* (AA: homozygous wild type; aa: homozygous variant type) *GSTT1*	Maternal ($n = 741$)	Birth weight	Additive (with a case-control sampling)	Birth weight change associated with smoking: *CYP1A1*: −252 g for *AA* polymorphism, −520 g for *Aa/aa* genotype (interaction test, $P = 0.06$) *GSTT1*: −285 g for *present* genotype, −642 g for *absent* genotype (interaction test, $P = 0.04$)
Grazuleviciene [52]	Maternal smoking during pregnancy	*GSTT1* *GSTM1*	Maternal ($n = 646$)	Birth weight < 2,500 g	Multiplicative	Interaction test between smoking and genetic polymorphisms: $P > 0.5$ for *GSTT1* and *GSTM1*
Infante-Rivard [39]	Maternal smoking during 3rd trimester of pregnancy	*GSTT1* *GSTM1* *CYP1A1*2A, 2B, 4* *XRCC3*	Newborn ($n = 465$)	Small-for gestational age (SGA) birth	Multiplicative	*GSTT1*: OR of SGA associated with smoking = 0.85 for +/+ genotype, 2.77 for −/+ and 1.42 for −/− genotypes (statistical interaction, $P = 0.01$). P for statistical interaction = 0.18 for *XRCC3*, $P = 0.66$ for *GSTM1*, $P = 0.98$ for *CYP1A1*2B*, $P = 0.06$ for *CYP1A1*4* *GSTT1*: OR of SGA associated with smoking = 1.39 for +/+ genotype, 1.93 for −/+ and 2.63 for −/− genotype (P for interaction, 0.46). *GSTM1*: P for interaction, 0.18. *CYP1A1*2B*: $P = 0.84$. *CYP1A1*4*: $P = 0.84$. *XRCC3*: $P = 0.03$
Infante-Rivard [39]	Maternal smoking during 3rd trimester of pregnancy	*GSTT1* *GSTM1* *CYP1A1*2A, 2B, 4* *XRCC3*	Maternal ($n = 465$)	Small-for gestational age (SGA) birth	Multiplicative	
Sasaki [53]	Maternal smoking during 2nd or 3rd trimester of pregnancy	*NQO1*, *CYP2E1*	Maternal ($n = 460$)	Birth weight (length and head circumference also considered)	Additive	Birth weight change associated with smoking: *NQO1*: beta = −77g for *Pro*/Ser** or *Ser/Ser* genotypes; beta = −199 g for *Pro/Pro* genotype (P for interaction, 0.05). *CYP2E1*: beta = −170 g for *c1/c2* or *c2/c2* genotypes and −195 g for *c1/c1* genotype (P for interaction, 0.63).