

NOS1: A Susceptibility Gene for Reduced Level of FEV₁ in the Setting of Pesticide Exposure



To the Editor:

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by airway obstruction caused by complex interactions between genes and environmental factors (1). Recently, there has been growing evidence showing that pesticide exposure is associated with poorer respiratory outcomes, such as chronic bronchitis and an impaired level of lung function compatible with airway obstruction (2, 3). Different types of pesticides have distinct physicochemical properties, and may cause direct damage to the cells of the bronchial mucosa, or may cause indirect damage via interaction with proinflammatory receptors, for example, transient receptor potential ion channels on airway chemosensory nerves (4). Genetic susceptibility to the adverse effects of pesticide exposure has been implicated in several diseases, such as cancer (5) and Parkinson's disease (6). Whether genetic susceptibility is of importance for the effects of pesticide exposure in the lungs is largely unknown. Therefore, in the current study, we performed a genome-wide interaction study to assess genetic susceptibility to the effects of occupational pesticide exposure in relation to the FEV₁, a measurement of lung function.

We used data from two general population-based cohorts from The Netherlands, the LifeLines and the Vlagtwedde-Vlaardingen general population-based cohort studies. In these cohorts, we have previously shown adverse effects of occupational pesticide exposure on the levels of FEV₁ and FEV₁/FVC (3). The LifeLines cohort study started in 2006 and includes subjects from the three northern provinces of The Netherlands (7). The Vlagtwedde-Vlaardingen longitudinal cohort study started in 1965, and subjects were followed for 25 years until the last survey in 1989/1990 (8). In the current study, we used data from the last survey. Occupational pesticide exposure in both cohorts was assessed using the ALOHA+ job exposure matrix (JEM), estimating no, low, or high exposure to pesticides (including herbicides and insecticides) based on self-reported job titles and functions (3). Genome-wide genotyping in both cohorts was performed using IlluminaCytoSNP-12 arrays (for detailed information on the measurements, genotyping platform, quality control, and genomic inflation factors, see the online supplement). The LifeLines and the Vlagtwedde-Vlaardingen cohorts include only white subjects.

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Author Contributions: K.d.J. participated in the study design, analysis and interpretation of the data, and drafting of the manuscript, tables and figures; H.M.B., D.S.P., and J.M.V. obtained funding, determined the study design, participated in the analysis and interpretation of data, and supervised writing of the manuscript; H.K. and R.V. designed and provided the ALOHA+ job exposure matrix and participated in writing of the manuscript. All authors read and approved the final version of the manuscript.

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First, in both cohorts separately, single-nucleotide polymorphism (SNP)-by-exposure interactions on the level of FEV₁ were assessed using linear regression adjusted for sex, age, height, and smoking status (never/ever smoker). Pesticide exposure was coded by dummy variables, and both the SNP-by-low exposure and SNP-by-high exposure interactions were included in the model. To have a clear exposure contrast, we focused on SNP-by-high exposure interactions only. SNPs were tested in an additive genetic model. Subsequently, we meta-analyzed all SNP-by-high pesticide exposure interactions using the software package, PLINK version 1.07 (9). Meta-analyzed SNP-by-high exposure interactions with a *P* value less than 2.26×10^{-7} (i.e., 0.05/221,444 SNPs available in both cohorts) were considered genome-wide significant.

Within the LifeLines cohort, data were available for 12,400 subjects with a median age of 47 years (range, 18–89 yr) in 2006/2011; 41% were males, 59% were ever smokers, and only 1% had high occupational exposure to pesticides. Within the Vlagtwedde-Vlaardingen cohort, data were available for 1,436 subjects; median age was 53 years (range, 35–79 yr) in 1989/1990, 54% were males, 70% were ever smokers, and 12% had high occupational exposure to pesticides.

Interactions of four SNPs with high occupational exposure to pesticides reached genome-wide significance in the meta-analysis (Table 1). There were no significant main effects of these SNPs or interaction effects with low exposure to pesticides on the level of FEV₁ (see Table E1 in the online supplement). Two SNPs were located in *phospholipase C, zeta 1 (PLCZ1)*. This gene has been mainly studied in relation to embryonic development (i.e., expression of this protein increases calcium release during fertilization of mammalian eggs [10]). The two SNPs in *PLCZ1* were in high linkage disequilibrium (LD) ($R^2 = 0.99$), and effect estimates from the two samples (i.e., LifeLines and Vlagtwedde-Vlaardingen) were quite heterogeneous ($I^2 = 68$ and 71%, respectively) (11). Meta-analysis using the random effects model showed less significant *P* values. Another significant SNP after meta-analysis was located near the gene coding for mannosidase, endo- α , a protein that processes oligosaccharides in the Golgi apparatus (12).

The most plausible SNP involved in the adverse effects of pesticide exposure in the lungs was located in the gene *nitric oxide synthase 1 (NOS1)*. Subjects carrying the minor allele of the SNP were more susceptible to high levels of occupational exposure to pesticides, as indicated by a lower level of FEV₁ (Figure 1). Interestingly, a recent study showed that three SNPs in *NOS1* increased the susceptibility for the effects of pesticide exposure on the risk for Parkinson's disease (13). These SNPs (rs12829185, rs10774910, and rs2682826) were not in LD with the SNP (rs482555, $R^2 < 0.1$) identified in the current study. SNP rs482555 was not associated with the level of FEV₁ independently of pesticide exposure ($b = -5$ ml FEV₁; $P = 0.471$; model adjusted for sex, age, height, and smoking status), which is in line with a study that showed no associations between *NOS1* SNP rs41279104 (LD with rs482555, $R^2 < 0.1$) with baseline lung function level and 5-year decline in a cohort of smokers (14).

The *NOS1* gene encodes for neuronal NOS that synthesizes endogenous nitric oxide (NO) from arginine. In the human lung, *NOS1* was found in submucosal nerves and endothelial cells (15).

Table 1. Single-Nucleotide Polymorphism (Additive)–by-High Occupational Pesticide Exposure Interactions in Relation to the Level of FEV₁ (ml), Adjusted for Sex, Age, Height, and Ever Smoking (No/Yes)

SNP	CHR	Minor Allele		Annotation	LifeLines Cohort (n = 12,400)			Vlagtwedde–Vlaardingen Cohort (n = 1,436)			Meta-analysis					
		A1	A2		b	P Value	MAF	b	P Value	MAF	P _r Value	P _r Value	b _r	b _r	Q	I ²
rs4764419	12	G	T	PLCZ1 (intronic)	286	1.37 × 10 ^{−6}	0.46	151	2.37 × 10 ^{−3}	0.45	5.51 × 10 ^{−8}	1.51 × 10 ^{−3}	206	215	0.079	68
rs10459067	12	T	C	PLCZ1 (intronic)	290	1.29 × 10 ^{−6}	0.43	145	4.32 × 10 ^{−3}	0.42	1.11 × 10 ^{−7}	3.26 × 10 ^{−3}	205	214	0.064	71
rs482555	12	C	T	NOS1 (intronic)	−283	8.05 × 10 ^{−5}	0.25	−217	3.60 × 10 ^{−4}	0.23	1.30 × 10 ^{−7}	1.30 × 10 ^{−7}	−244	−244	0.484	0
rs2145067	6	T	C	MANEA (769 kb 5′)	−310	8.60 × 10 ^{−5}	0.17	−242	5.87 × 10 ^{−4}	0.19	2.15 × 10 ^{−7}	2.15 × 10 ^{−7}	−271	−271	0.521	0

Definition of abbreviations: b = beta for FEV₁ (ml); CHR = chromosome; f = fixed effects model; I² = percentage of variation across studies; MAF = minor allele frequency; MANEA = mannosidase, endo-α; NOS1 = nitric oxide synthase 1; PLCZ1 = phospholipase C, zeta 1; Q = P value for Cochran’s Q (11); r = random effects model; SNP = single-nucleotide polymorphism. Interaction effects are shown for the Lifelines cohort, Vlagtwedde–Vlaardingen cohort, and the two cohorts meta-analyzed. MAF is given for minor allele A1.

Messenger RNA and protein levels of *NOS1* were increased in peripheral lung tissue of patients with moderate to very severe COPD compared with healthy smokers and nonsmoking control subjects, and expression levels increased with increasing COPD severity, as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria (16). NO has been implicated in several ways in the toxicity of paraquat, a commonly used herbicide. Paraquat may activate NF-κβ, thereby inducing an increased expression of *inducible NOS*, which subsequently increases cytoplasmic NO and enhances nitrosative stress (17). Second, NO may react with the superoxide anion (O₂^{•−}) generated by the redox cycling of paraquat, thereby increasing peroxynitrite (ONOO[−]) levels (17). Interestingly, increased production of NO was shown to be neuronal NOS dependent in patients with COPD and potentially increases the production of peroxynitrite (16). Increased production of peroxynitrite amplifies nitrosative stress, and thereby induces expression of other *NOS* isoforms, resulting in increased expression of NO (16). This mechanism was suggested to be involved in inflammation and progression of disease

pathogenesis in COPD (16) and to underlie the effects of pesticide exposure in the lungs (17). In the current genome-wide interaction study, we aimed to identify novel susceptibility loci for occupational exposure to pesticides in relation to FEV₁. We have used the ALOHA+ JEM to estimate pesticide exposure as no, low, or high. Using JEM-based estimates is an efficient way of exposure assessment in large samples, yet chemical specificity is lacking. Further research should elucidate the role of *NOS1* in the development of impaired lung, and consequently the development of COPD, and the role of exposure to specific chemicals in this process. To conclude, with the current study, using a hypothesis-free approach and meta-analyzing data from two independent cohorts, we identified four SNPs in three genes. The most plausible candidate was *NOS1* as a novel susceptibility gene for the adverse effects of pesticide exposure in relation to the level of lung function. Interestingly this gene has been implicated in pesticide toxicity, as well as in COPD pathogenesis. Excess release of NO may underlie pesticide toxicity in the lungs, and

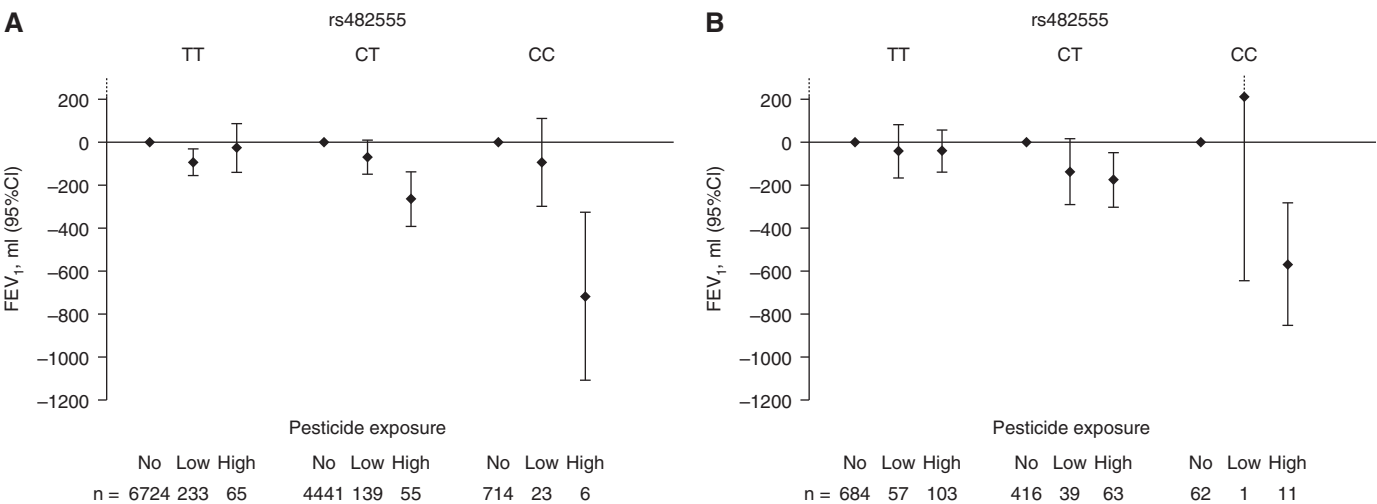


Figure 1. Associations of no, low, and high occupational exposure to pesticides and the level of FEV₁ (ml) in the LifeLines cohort (A) and Vlagtwedde–Vlaardingen cohort (B) stratified for *nitric oxide synthase 1* rs482555 genotype. No exposure was set as reference category. Associations were adjusted for sex, age, height, and ever smoking (no/yes). CI = confidence interval.

subsequently lead to an impaired lung function, a hallmark of COPD. ■

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LifeLines Cohort Study

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Proximity to a Major Road, Vitamin D Insufficiency, and Severe Asthma Exacerbations in Puerto Rican Children



To the Editor:

Traffic-related air pollution (TRAP) causes asthma morbidity, and vitamin D insufficiency (a plasma 25[OH]D level < 30 ng/ml) is associated with severe asthma exacerbations in Puerto Rican (PR) children (1). Because vitamin D has antioxidant effects, we examined whether proximity to a major road (a marker of TRAP) is associated with increased risk for severe asthma exacerbations

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Author Contributions: G.C. and J.C.C. participated in study design and implementation; F.R., J.M.B., E.F., K.S.K., and J.C.C. participated in data analysis; E.A.-P. participated in data generation; F.R. and J.C.C. wrote the initial draft of the manuscript; and all authors participated in the review of the manuscript and approved its final version.

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***NOS1*: a susceptibility gene for reduced level of FEV₁ in relation to pesticide exposure?**

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SUPPLEMENTARY MATERIAL

METHODS

LifeLines cohort

Genotyped individuals from the LifeLines cohort study with full data on all covariates were included (n = 12,400). At baseline all participants filled in a standardized questionnaire and were subject to a medical examination. The questionnaire included questions regarding personal characteristics, smoking habits, job title and description of current or last held job. The medical examination included pre-bronchodilator spirometry according to a standardized protocol following ATS guidelines using a Welch Allyn Version 1.6.0.489, PC-based SpiroPerfect with Ca Workstation software.

Vlagentwedde-Vlaardingen cohort

For replication of our initial finding we included 1,436 subjects with full data on genotypes and covariates from the Vlagentwedde-Vlaardingen cohort, a prospective general population based cohort including Caucasians from Dutch decent only. Pre-bronchodilator spirometry was performed according to a standardized protocol following ERS guidelines with a water-sealed spirometer (Lode Instruments, the Netherlands). Reported jobs were coded according to ISCO-88 classification and job specific exposures were estimated with the ALOHA+ JEM, similar to the identification sample.

Occupational exposure

Job title and description were coded according to the International Standard Classification of Occupations version 1988 (ISCO-88)(1). These four-digit classification codes were used to estimate job-specific exposures to pesticides using the ALOHA+ Job Exposure Matrix (JEM) (2, 3). The ALOHA+ JEM classifies subjects based on the ISCO-88 job codes into no, low, and high exposure categories (0/1/2, respectively). Jobs were averaged and rounded to the nearest integer in case a participant reported two different jobs simultaneously (0.5 = 1 and 1.5 = 2).

Genotyping and quality control

In both cohorts, genotyping was performed using IlluminaCytoSNP-12 arrays. The IlluminaCytoSNP-12 is an oligonucleotide chip designed to have a uniform spacing of

markers across all chromosomes, with the far majority of the markers on this chip reflecting common SNPs: 93% of the 301,232 markers on this chip reflect bi-allelic SNP markers with callable polymorphic genotypes. Applicability of the CytoSNP12 LifeLines data has been shown before (4).

In the LifeLines cohort 227,981 SNPs fulfilled the quality control criteria: genotype call-rate $\geq 95\%$, minor allele frequency $\geq 1\%$, and Hardy-Weinberg equilibrium cut-off p-value $\geq 10^{-4}$. Non-Caucasian samples and first-degree relatives were excluded. In the Vlagtwedde-Vlaardingen cohort, 242,926 SNPs fulfilled the quality control criteria.

Statistical model

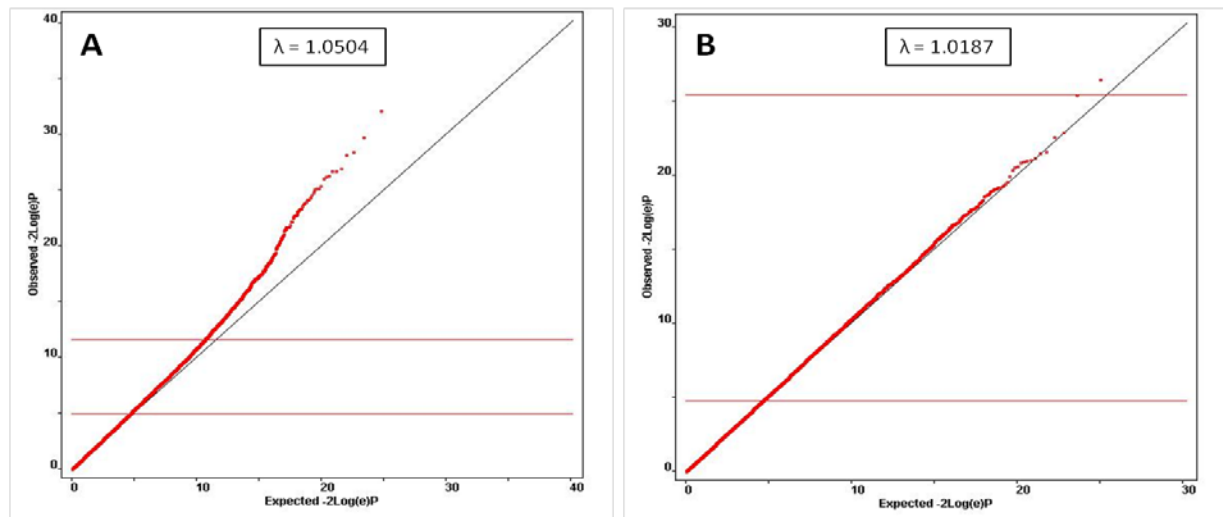
The statistical model was specified as: $FEV_1 = \text{SNP} + \text{low exposure (no/yes)} + \text{high exposure (no/yes)} + \text{SNP} * \text{low exposure} + \text{SNP} * \text{high exposure} + \text{covariates}$. Thus both SNP-by-low exposure and SNP-by-high exposure interactions were included in the model. In order to have a clear exposure contrast we focussed on SNP-by-high exposure interactions only. SNPs were tested in an additive genetic model. All SNP-by-high pesticide exposure interactions from both cohorts were meta-analysed using the software package PLINK version 1.07 (5). Meta-analyzed SNP-by-high exposure interactions with a p-value $< 2.26 * 10^{-7}$ (i.e. $0.05/221,444$ SNPs available in both cohorts) were considered genome-wide significant.

Ethical approval

Both the LifeLines cohort study and the Vlagtwedde-Vlaardingen studies were approved by the Medical Ethics Committee of the University Medical Center Groningen, Groningen, The Netherlands. All subjects gave written informed consent.

Genomic inflation factors for marginal associations

QQ-plots for the marginal association between the SNPs and level of FEV₁ in the LifeLines (A) and Vlagtwedde-Vlaardingen samples (B), adjusted for sex, age, height and ever smoking (no/yes).



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SUPPLEMENTARY TABLE 1. Estimates for the effects of SNPs, pesticide exposure (low and high versus no exposure) and their interaction on the level of FEV₁ (ml) using linear regression models adjusted for sex, age, height and smoking status (never/ever).

						LifeLines cohort (n = 12,400)				Vlagtwedde-Vlaardingen cohort (n = 1,436)			
SNP	CHR	A1	A2	Annotation	Predictor	B	95% CI		P	B	95% CI		P
rs4764419	12	G	T	PLCZ1 (intronic)	SNP (additive)	-10	-22	2	1.19E-01	-24	-63	15	2.22E-01
					Low exposure	-65	-140	11	9.18E-02	-154	-313	5	5.84E-02
					High exposure	-430	-567	-293	7.33E-10	-255	-369	-141	1.25E-05
					SNP*Low exposure	-22	-90	45	5.16E-01	84	-54	221	2.33E-01
					SNP*High exposure	286	170	402	1.37E-06	151	54	248	2.37E-03
rs10459067	12	T	C	PLCZ1 (intronic)	SNP (additive)	-11	-23	1	6.54E-02	-24	-63	15	2.34E-01
					Low exposure	-56	-128	16	1.27E-01	-163	-314	-11	3.57E-02
					High exposure	-408	-538	-279	6.74E-10	-242	-353	-130	2.26E-05
					SNP*Low exposure	-35	-103	32	3.04E-01	99	-36	234	1.52E-01
					SNP*High exposure	290	173	407	1.29E-06	145	45	244	4.32E-03
rs482555	12	C	T	NOS1 (intronic)	SNP (additive)	-3	-17	11	6.91E-01	31	-14	75	1.77E-01
					Low exposure	-90	-150	-30	3.31E-03	-43	-166	80	4.96E-01
					High exposure	-12	-123	100	8.39E-01	-17	-110	77	7.25E-01
					SNP*Low exposure	14	-64	91	7.33E-01	-78	-261	105	4.02E-01
					SNP*High exposure	-283	-423	-142	8.05E-05	-217	-336	-98	3.60E-04
rs2145067	6	T	C	MANEA (769kb 5')	SNP (additive)	-3	-18	13	7.51E-01	38	-10	87	1.23E-01
					Low exposure	-112	-168	-56	8.36E-05	-86	-198	26	1.34E-01
					High exposure	-59	-156	39	2.37E-01	-33	-122	57	4.74E-01
					SNP*Low exposure	90	-2	181	5.48E-02	21	-131	173	7.85E-01
					SNP*High exposure	-310	-463	-155	8.60E-05	-242	-379	-104	5.87E-04