Occupational pesticide exposure increases risk for COPD
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Chronic obstructive pulmonary disease (COPD) is characterized by persistent and often progressive airflow obstruction caused by and abnormal inflammatory response to noxious particles and gases. Tobacco smoking is considered to be the main risk factor for COPD, yet a substantial proportion of 15–20% of all cases has been attributed to occupational exposures (1), with proportions up to 30% in never smokers (2). Because occupational exposures are common, yet also potentially modifiable contributors to the global burden of COPD, it is important to determine which occupational factors drive the development of this disease.

Within two Dutch general populations based cohorts, i.e. the LifeLines cohort study and the Vlagtwedde-Vlaardingen study, we estimated occupational exposure to amongst others pesticides using a job exposure matrix (JEM). The JEM classified subjects based on ISCO-88 job codes into no, low and high exposure categories (0/1/2).

First, we showed cross-sectional associations between pesticide exposure and lower levels of FEV_1 and FEV_1/FVC in 11,851 individuals from the LifeLines cohort study and 2,364 subjects included in the last survey (1989/1990) of the Vlagtwedde-Vlaardingen cohort (see figure 1 for associations in LifeLines). Subjects with high levels of exposure to pesticides had also an increased risk for COPD gold stage 2 and higher (OR = 1.95 (0.92 – 4.13) in LifeLines and OR = 1.78 (1.14 – 2.79) in Vlagtwedde-Vlaardingen) (3). There were no consistent associations between exposure to pesticides and the $FEF_{25-75\%}$, a marker of small airways obstruction (4).

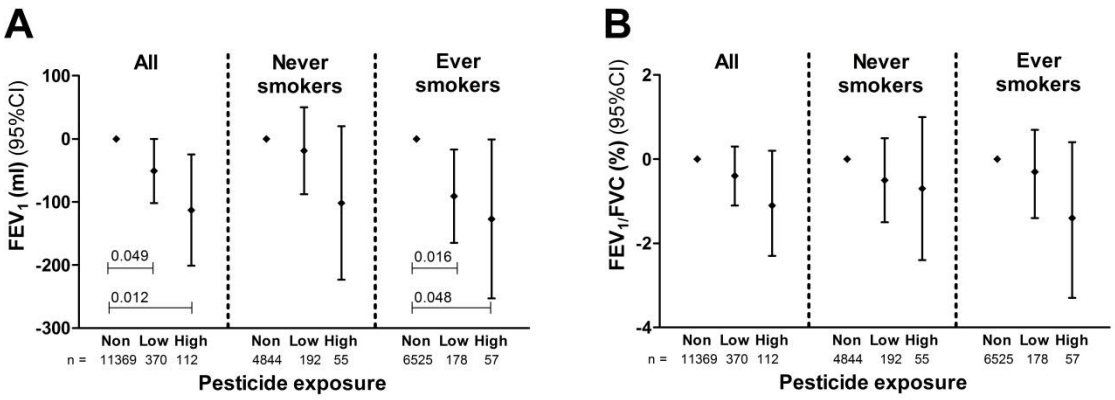

Figure 1. Cross-sectional associations between occupational pesticide exposure and the level of FEV_1 (A) and FEV_1/FVC (B), for the whole group and stratified according to smoking status (never/ever smoker) in the LifeLines cohort study. Associations with FEV_1 were significantly stronger ($p<0.05$) for ever compared to never smokers.

Additionally within 12,772 observations from 2,527 subjects assessed between 1965 and 1990 in the Vlagtwedde-Vlaardingen cohort we found that subjects with high pesticide exposure had an accelerated decline in FEV_1 and FEV_1%IVC (figure 2) (5). Especially within smokers these implied substantial losses of lung function, for example smokers with high exposure to pesticides had 7 ml/year larger decline in FEV_1 compared to smokers without pesticide exposure.

Interestingly, in both the cross-sectional (FEV_1) and longitudinal study (FEV_1 and FEV_1%IVC) we found significantly stronger associations in ever compared to never smokers, suggesting synergistic effects of tobacco smoke and pesticide exposure. For example for a pesticide like Paraquat the primary mechanism for toxicity is related to its cyclic redox reactions and consequently free radical generation resulting in oxidative damage of the lung tissue. It is very well likely that the effect of exposure to such a pesticide is more pronounced when anti-oxidant systems are already depleted by cigarette smoking and the lung is already damage by free radicals from tobacco smoke.

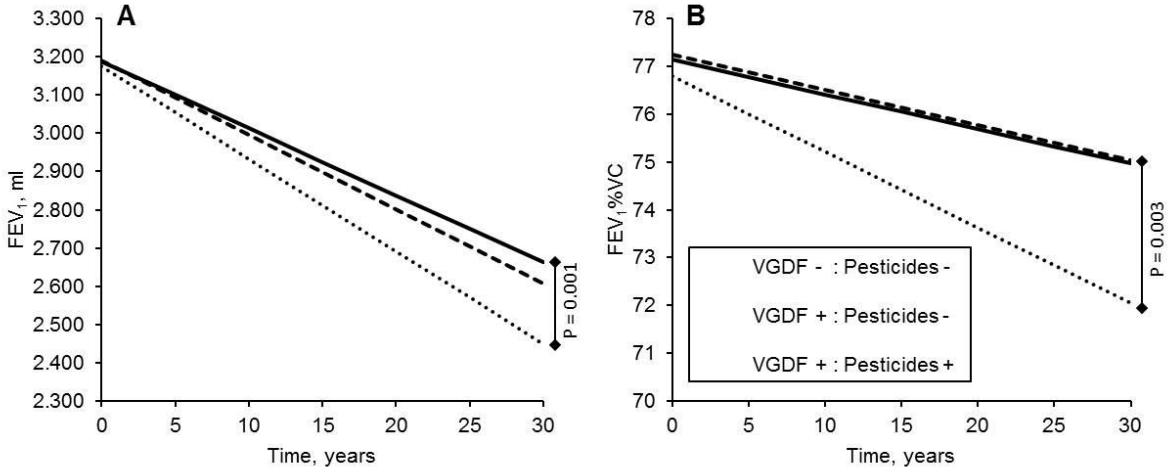

Figure 2. Estimated course of FEV_1 (A) and FEV_1%IVC (B) for subjects with high exposure to VGDF only (VGDF + : Pesticides -) and subjects with joint high exposure to VGDF and pesticides (VGDF + : Pesticides +) compared to unexposed subjects, modeled for time (years) since first survey after the age of 30 years in the Vlagtwedde-Vlaardingen cohort (1965-1990).

Finally common genetic variation may affect individual susceptibility to exposures such as pesticides. We therefore assessed interactions between single nucleotide polymorphisms and pesticide exposure on the level of FEV_1 in a genome-wide manner. We identified one common genetic variant (prevalence minor allele ~25%) in *NOS1* that increased susceptibility to high levels of pesticide exposure in both the LifeLines cohort study (12,400 subjects) and the Vlagtwedde-Vlaardingen study (1,436 subjects) (figure 3) (6).

The *NOS1* gene encodes for neuronal nitric oxide synthase that synthesizes endogenous nitric oxide (NO) from arginine. In the human lung, NOS1 was found in submucosal nerves and endothelial cells (7). Interestingly this gene has been implicated in pesticide toxicity as well as in COPD pathogenesis. This suggests that excess release of NO may underlie pesticide toxicity in the lungs and subsequently lead to an impaired lung function, a hallmark of COPD.

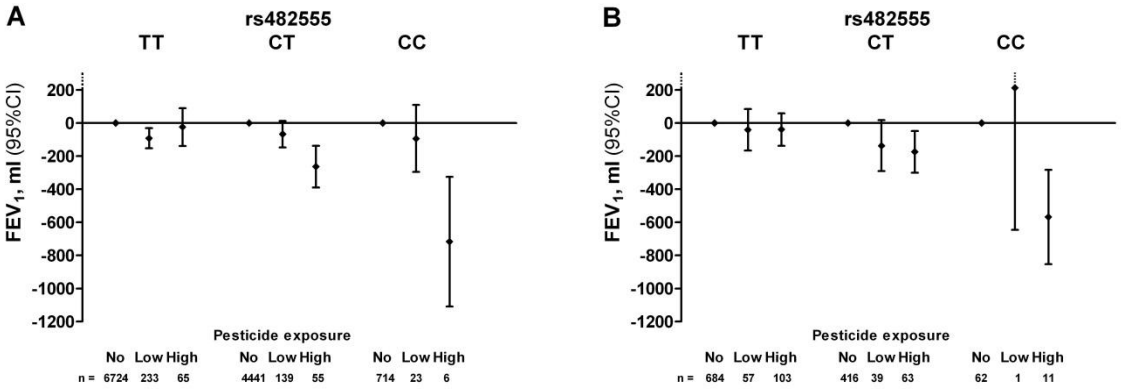

Figure 3. Associations of no, low and high occupational exposure to pesticides and the level of FEV_1 (ml) in the LifeLines cohort (A) and Vlagtwedde-Vlaardingen cohort (B) stratified for *NOS1* rs482555 genotype.

Apart from a few small scale cross-sectional studies that found associations between specific types of pesticides and lower levels of FEV_1 and FVC in occupationally exposed farmers from Sri-Lanka (8), South Korea (9) and Costa Rica (10), relatively few studies have focused on the effects of pesticide exposure on lung function (11). To our knowledge no studies thus far have shown associations between pesticide exposure and the longitudinal decline of lung function.

Globally, the agricultural sector employs more than 1.1 billion workers worldwide (about 34% of the global working force) (12) potentially putting a large amount of workers at risk for pesticide exposure. Additionally, people living in agriculture-intensive regions may be at risk for exposure due to pesticide drift (13). This may be especially relevant in a densely populated country as the Netherlands where large numbers of people live near greenhouses and pesticide-treated farmland. Little is known about the risks of people living in the vicinity of these pesticide-treated areas in the Netherlands, and such risks were not taken into account during the approval process for pesticides' entry on the Dutch market. Growing concerns about these risks have led to a first advisory report of a Committee of the Health Council of the Netherlands, and consequently the initiation of an exposure study among people living in the vicinity of greenhouses and pesticide-treated farmland that will be carried out in 2015 and 2016.

Publication of the above mentioned studies led to a reaction from the Dutch parliament, but the approval process for pesticides' entry of the Dutch marked will not be reconsidered based on these findings (14) (Rijksoverheid).

References

1. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American thoracic society statement: Occupational contribution to the burden of airway disease. American journal of respiratory and critical care medicine. 2003;167(5):787-97.

2. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the third national health and nutrition examination survey. American Journal of Epidemiology. 2002 October 15;156(8):738-46.

3. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM, et al. Pesticides and other occupational exposures are associated with airway obstruction: The LifeLines cohort study. Occup Environ Med. 2014 Feb;71(2):88-96.

4. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Vonk JM, Postma DS, et al. Occupational exposure to vapors, gases, dusts, and fumes is associated with small airways obstruction. Am J Respir Crit Care Med. 2014 Feb 15;189(4):487-90.

5. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. Am J Epidemiol. 2014 Jun 1;179(11):1323-30.

6. de Jong K, Vonk JM, Kromhout H, Vermeulen R, Postma DS, Boezen HM, et al. NOS1: A susceptibility gene for reduced level of FEV1 in the setting of pesticide exposure. Am J Respir Crit Care Med. 2014 Nov 15;190(10):1188-90.

7. Kobzik L, Bredt DS, Lowenstein CJ, Drazen J, Gaston B, Sugarbaker D, et al. Nitric oxide synthase in human and rat lung: Immunocytochemical and histochemical localization. Am J Respir Cell Mol Biol. 1993 Oct;9(4):371-7.

8. Peiris-John RJ, Ruberu DK, Wickremasinghe AR, van-der-Hoek W. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. Respir Med. 2005 10;99(10):1319-24.

9. Cha ES, Lee YK, Moon EK, Kim YB, Lee Y, Jeong WC, et al. Paraquat application and respiratory health effects among south korean farmers. Occupational and Environmental Medicine. 2012 June 01;69(6):398-403.

10. Schenker M, Stoecklin M, Lee K, Lupercio R, Zeballos RJ, Enright P, et al. Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. American journal of respiratory and critical care medicine. 2004;170(7):773-9.

11. Hoppin JA. Pesticides and respiratory health: Where do we go from here? Occup Environ Med. 2014 Feb;71(2):80,2013-101876. Epub 2013 Nov 12.

12. International Labour Office. Global employment trends 2012. Geneva: International Labour Organization; 2012. Report No.: ISBN 978-92-2-124924-5 (print).

13. Lee SJ, Mehler L, Beckman J, Diebolt-Brown B, Prado J, Lackovic M, et al. Acute pesticide illnesses associated with off-target pesticide drift from agricultural applications: 11 states, 1998-2006. Environ Health Perspect. 2011 Aug;119(8):1162-9.

14. Ministerie van Economische Zaken. Reactie op artikel werkgerelateerde longziekte COPD bij boeren en kwekers als gevolg van het gebruik van pesticiden. 3 December 2014.