A MIXTURE APPROACH TO ADDRESS THE ROLE OF OCCUPATIONAL EXPOSURES ON PARKINSON'S DISEASE AND PARKINSONISM IN A MATCHED CASE-CONTROL STUDY

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Introduction
The province of Brescia, northern Italy, was characterized by historical metallurgic and ferromanganese industrial activities. A higher prevalence of Parkinsonism has been observed among municipalities closer to ferromanganese plants compared to other province municipalities [1].

Objectives
Through this work, we aimed to test the association between occupational exposure including metals, pesticides, aromatic and chlorinated solvents, mineral dust and gas, and fumes on the risk of developing Parkinson's disease (PD) or parkinsonism among subjects enrolled in the heavily industrialized Brescia province in northern Italy.

Methods
The study population consisted of 876 individuals. The case definition not only included idiopathic PD but it was extended to the broader classification of Parkinsonism defined by the presence of at least two of the following features: bradykinesia, akinesia, rigidity, tremor, and postural instability. The controls were matched to cases based on sex, age (±5 years), and occupational life until the PD diagnosis (matched controls follow-up was stopped accordingly). We included 668 subjects (334 between cases and controls) for the analysis. Direct interviews provided information on lifetime occupational exposure and tobacco smoking besides demographic information. The job-exposure matrix ALOHA [2] was used to assess the years and the levels to which individuals were exposed to compounds. All participants were tested for genotyping of synuclein alpha (SNCA: rs356219) with TaqMan real-time PCR. Conditional logistic regression and Weighted Quantile Sum (WQS) regression [3] with repeated holdout [4] were used to assess the effect of the exposures on PD adjusting for covariates as single elements and as a mixture, respectively. Smoking status, parent history of PD, and SNCA were considered as covariates in the regression models.

Results
Conditional logistic regression showed a significant association between a high level of cumulative exposure to pesticides and the probability of PD or Parkinsonism (OR: 2.98, 95%CI 1.23, 7.25, p-value 0.016). When we stratified the analysis by considering PD or Parkinsonism separately, we were still able to find the same significant association for PD (OR: 3.56, 95%CI 1.25 10.15, p-value 0.018) but not for Parkinsonism (OR: 1.87, 95%CI 0.24, 14.33, p-value 0.548). Through WQS regression we were able to observe a significant association between the mixture and the onset of PD (OR: 1.15, 95%CI 1.001, 1.32) (Figure 1) where pesticides and metals showed the higher contribution (pesticides weight = 0.434, metals weight = 0.210) covering almost 65% of the mixture effect. No statistically significant association was

found in the stratified analysis, but the magnitude of the effects was similar (OR: 1.12 and OR: 1.19 for PD and Parkinsonism respectively) (Figure 1).

Figure 1. Odds ratios (OR) and relative 95% Confidence Intervals (95% CI) estimated through the repeated holdout Weighted Quantile Sum (WQS) regression.
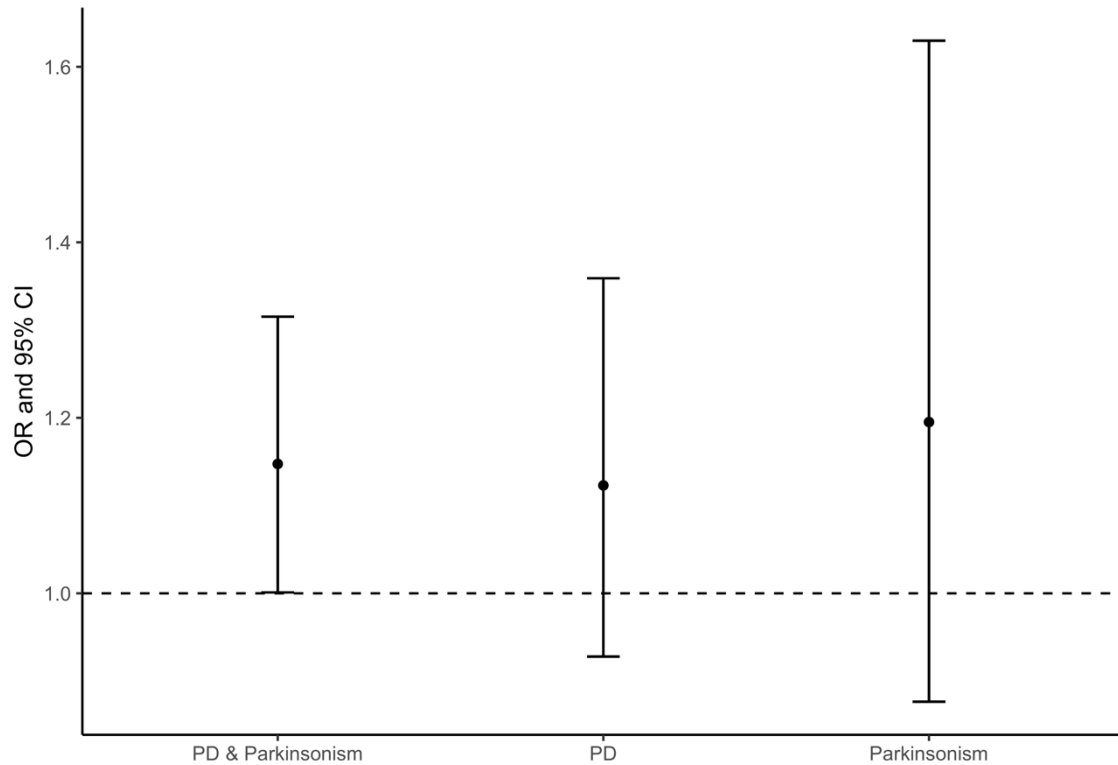
Conclusions
Through this study, we assessed the effect of occupational exposure on PD and Parkinsonism and identified pesticides and metals as the elements of major risk for the onset of the disease. This agrees with the previous literature, however, to our knowledge, this is the first study that tests the effect of occupational exposures on PD as a mixture of different elements. Future studies can be performed to identify windows of susceptibility to the exposures during the occupational life of a worker.

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