

## LETTER TO THE EDITOR

# Association between antipsychotic agents and risk of lung cancer: a nested case-control study

Dear Editor,

Antipsychotics are a class of psychotropic medication primarily used for the treatment of schizophrenia and a range of other psychotic disorders. They are antagonists of multiple receptors, such as dopamine D<sub>1</sub>, dopamine D<sub>2</sub>, serotonin 5HT<sub>2A</sub>, and serotonin 5HT<sub>1A</sub> receptors. Serotonin antagonists have been identified as growth-inhibiting agents in cancer cells, and they not only inhibit the growth of cancer cells but may also induce apoptosis in these cells [1]. Several studies have examined the association between antipsychotics and certain cancers, but the relationship between antipsychotics and lung cancer remains largely unknown.

Here, we conducted a population-based nested case-control study, consisting of 38,318 lung cancer cases diagnosed from November 2011 to December 2019, and matched 191,590 population controls. Detailed descriptions of the study can be found in the Supplementary Materials and Methods section, Supplementary Table S1-S3, and Supplementary Figure S1. Briefly, exposure to antipsychotics was obtained from medication records and medical insurance databases. The exposure level was measured by olanzapine equivalent doses (OEDs). The odds ratios (ORs) for lung cancer associated with antipsychotics were estimated using the conditional logistic regression models. The effects of different classes of antipsychotics and individual antipsychotics on lung cancer risk were also assessed. The restricted cubic spline (RCS) with 3 knots was used to fit the nonlinear association between antipsychotics and lung cancer risk, and ANOVA for the nonlinearity test. We also conducted three sensitivity analyses to test the robustness of the main findings.

The median age was 66 [inter quartile range (IQR), 59-74] years in the entire cohort, and 60.09% of the study subjects were males. A total of 1077 subjects (0.47%) had

received antipsychotics before the index date (Supplementary Table S4). Compared with non-users of antipsychotics, the adjusted ORs for lung cancer risk associated with short-term and long-term use of antipsychotics were 0.82 (95% CI, 0.64-1.06) and 0.55 (95% CI, 0.40-0.74), respectively (Table 1). Higher exposure to antipsychotics tended to be associated with a lower risk of lung cancer, with OR decreasing from 0.85 (95% CI, 0.63-1.14) for limited use (1-3000 mg OEDs) to 0.41 (95% CI, 0.25-0.70) for use of more than 15,000 mg OEDs. We further analyzed the association between the antipsychotic classes and lung cancer risk, and our results showed that exposure to second-generation antipsychotics (SGAs) was associated with a decreased lung cancer risk, with an adjusted OR of 0.65 (95% CI, 0.46-0.92) for short-term use and an adjusted OR of 0.47 (95% CI, 0.32-0.67) for long-term use. There was an inverse dose-response relationship between SGAs and lung cancer risk ( $P$  for trend < 0.05). Also, the dose-response relationship between SGAs exposure and lung cancer risk was nonlinear ( $P = 0.014$ ) (Supplementary Figure S2). When the SGAs exposure exceeded 10000 mg OEDs, the slope of the relationship tended to be zero. The association between exposure to first-generation antipsychotics (FGAs) and lung cancer risk was not statistically significant ( $P > 0.05$ ), with an adjusted OR of 0.91 (95% CI, 0.67-1.22) for short-term use and an adjusted OR of 0.84 (95% CI, 0.56-1.25) for long-term use.

Long-term use of risperidone, olanzapine, clozapine, and perphenazine were all associated with a reduced risk of lung cancer. The corresponding ORs were 0.40 (95% CI, 0.24-0.67;  $P < 0.001$ ), 0.43 (95% CI, 0.22-0.84;  $P = 0.014$ ), 0.38 (95% CI, 0.16-0.88;  $P = 0.023$ ), and 0.39 (95% CI, 0.15-0.98;  $P = 0.046$ ), respectively. No significant association was observed between long-term use of quetiapine, sulpiride, and chlorpromazine and lung cancer risk (Supplementary Table S5). The adjusted ORs for antipsychotics with high affinity to serotonin 5-HT<sub>1A</sub> (OR: 0.60, 95%CI: 0.43-0.85), serotonin 5-HT<sub>2A</sub> (OR: 0.59, 95% CI: 0.42-0.82), adrenergic alpha 2 (OR: 0.65, 95% CI: 0.46-0.92), and histaminel receptor (OR: 0.74, 95% CI: 0.56-0.97) are

**Abbreviations:** OED, olanzapine equivalent dose; IQR, Inter Quartile Range; OR, odds ratio; RCS, restricted cubic spline; SGA, second-generation antipsychotic; FGA, first-generation antipsychotic; cDDD, cumulative defined daily dose

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TABLE 1 Association between antipsychotics exposure and lung cancer risk

Exposure group*	Controls (cases)	Adjusted ORs (95% CI) <sup>a</sup>	P	Adjusted ORs (95% CI) <sup>b</sup>	P	P for trend <sup>†</sup>
<b>Antipsychotics</b>						<0.001
Non-use	190,670 (38,161)	1 (ref)		1 (ref)		
Short-term use	439 (87)	0.87 (0.68-1.12)	0.283	0.82 (0.64-1.06)	0.126	
Long-term use	481 (70)	0.60 (0.45-0.81)	<0.001	0.55 (0.40-0.74)	<0.001	
Cumulative use						<0.001
1-3,000mg	290 (57)	0.87 (0.65-1.17)	0.362	0.85 (0.63-1.14)	0.278	
3,001-10,000 mg	361 (62)	0.74 (0.55-0.99)	0.043	0.67 (0.49-0.90)	0.009	
10,001-15,000 mg	116 (20)	0.71 (0.43-1.18)	0.184	0.65 (0.39-1.08)	0.096	
≥15,001 mg	153 (18)	0.49 (0.29-0.81)	0.006	0.41 (0.24-0.70)	0.001	
<b>FGAs</b>						0.305
Non-use	191,137 (38,231)	1 (ref)		1 (ref)		
Short-term use	278 (56)	0.97 (0.72-1.30)	0.848	0.91 (0.67-1.22)	0.526	
Long-term use	175 (31)	0.84 (0.56-1.24)	0.376	0.84 (0.56-1.25)	0.382	
Cumulative use						0.213
1-3,000mg	199 (39)	0.94 (0.66-1.33)	0.717	0.91 (0.64-1.30)	0.606	
3,001-10,000 mg	163 (32)	0.95 (0.64-1.40)	0.791	0.88 (0.59-1.30)	0.508	
10,001-15,000 mg	47 (9)	0.90 (0.44-1.85)	0.77	0.92 (0.44-1.92)	0.823	
≥15,001 mg	44 (7)	0.75 (0.33-1.68)	0.485	0.71 (0.31-1.66)	0.431	
<b>SGAs</b>						<0.001
Non-use	190,989 (38,231)	1 (ref)		1 (ref)		
Short-term use	275 (45)	0.69 (0.49-0.97)	0.031	0.65 (0.46-0.92)	0.015	
Long-term use	326 (42)	0.52 (0.37-0.75)	<0.001	0.47 (0.32-0.67)	<0.001	
Cumulative use						<0.001
1-3,000mg	185 (25)	0.58 (0.37-0.89)	0.013	0.57 (0.36-0.88)	0.011	
3,001-10,000 mg	236 (42)	0.74 (0.52-1.05)	0.091	0.67 (0.46-0.96)	0.029	
10,001-15,000 mg	86 (11)	0.52 (0.27-0.99)	0.047	0.47 (0.24-0.91)	0.026	
≥15,001 mg	94 (9)	0.39 (0.19-0.78)	0.008	0.32 (0.16-0.67)	0.002	

OEDs, olanzapine equivalent doses; FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; ORs, odds ratios; CI, confidence interval;

\*Drug dose usage was standardized using olanzapine equivalents. Short-term use was defined as a cumulative OEDs between 0 mg to 5000mg; Long-term use was defined as a cumulative exposure of 5000 mg OEDs;

<sup>†</sup>We performed the trend tests by entering the grade variable representing the antipsychotics exposure subgroup as a continuous variable in the model. The trend in this study refers to that the risk of lung cancer decreased as the exposure dose increased.

<sup>a</sup>Adjusted for smoking, and schizophrenia;

<sup>b</sup>Adjusted for smoking, drinking, type of residential area, hypertension, diabetes, hyperlipidemia, statin, nonsteroidal anti-inflammatory drugs (NSAIDs), chronic obstructive pulmonary disease (COPD), cirrhosis, pneumonia, schizophrenia, depressive disorder, anxiety disorder, and other psychotic disorders. Type of residential area refers to rural or urban.

significantly lower than those of antipsychotics with low affinity to the above four receptors (Supplementary Table S6).

Sensitivity analyses showed that our main findings were robust. In the first sensitivity analysis, similar association patterns to the main findings were observed when the exposure to antipsychotics was measured using cumulative defined daily doses (cDDD) (Supplementary Table S7-S8). The ORs for short-term and long-term use of SGAs were 0.63 (95% CI, 0.45-0.88) and 0.48 (95% CI, 0.33-0.70), respectively. The second sensitivity analysis showed that changing the lag-time from 1 year to 2 years had no signif-

icant effects on the association estimates. (Supplementary Table S9-S11). The adjusted ORs for lung cancer risk associated with short-term and long-term use of SGAs were 0.65 (95% CI, 0.45-0.94) and 0.40 (95% CI, 0.25-0.63), respectively. In the third sensitivity analysis, after adjusting for common risk factors of lung cancer, E values for short-term and long-term use of SGAs were 2.45 and 3.68, respectively. These indicated that our main findings are relatively robust.

Many previous studies have evaluated the association between schizophrenia and lung cancer, but the results remained inconsistent [2]. Our study showed that SGAs

were associated with a decreased risk of lung cancer with a dose-response pattern, while FGAs did not. Also, the associations between different individual antipsychotics and lung cancer were inconsistent. Based on the results of this study, it can be reasonably inferred that studies with more patients using SGAs would more likely to conclude that patients with schizophrenia could have a lower risk of lung cancer.

Although the exact mechanisms of the relationship between antipsychotics and lung cancer are still unclear, some previous studies have provided possible explanations. Wiklund *et al.* [3] found that antipsychotics such as olanzapine and haloperidol could selectively inhibit the viability of non-small cell carcinoma cancer cell lines. It has been reported that serotonin receptors can induce angiogenesis in lung cancer [4, 5], and the mRNA expression of 5HT<sub>2A</sub> receptors in tumors was 3.12 times higher than that in surrounding healthy tissues [6]. On the other hand, Hejazi *et al.* [7] showed that 5HT<sub>2A</sub> antagonists could cause apoptosis of human breast cancer cells (MCF-7) and had an inhibitory effect on the proliferation of these cells. The results of our affinity study are consistent with the above studies. The underlying mechanism of the relationship between antipsychotics and the occurrence and development of lung cancer needs to be further studied.

Our study also has several limitations. First, there may still be residual confounding in this study. Smoking is a major risk factor for lung cancer, but as the data on the number of cigarettes smoked by the participants was unavailable, thus, we could not further adjust the intensity of smoking in the multivariate model, but the E value showed that the results of this study were stable. Second, the relatively small number of people exposed to antipsychotics may lead to insufficient statistical power in the analysis of individual antipsychotics. Although the confidence interval for OR is wide, all three sensitivity analyses showed that our results are robust.

In summary, we found a significant association between SGAs and lung cancer risk with a dose-dependent pattern, whereas no such association pattern was found between FGAs and lung cancer risk. The anti-lung cancer effects of antipsychotics may be mediated by serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, adrenergic  $\alpha_2$ , and histamine 1 receptors.

## DECLARATIONS

## FUNDING

This work was supported by the National Key Research and Development Program of China (2020YFC2003500), Shandong Province Major Science and Technology Innovation Project (2018CXGC1210), the Major Science and Technology Projects of Shandong province (2018YFJH0506-2), and the National Natural Science Foundation of China (71804093). All authors report no conflicts of interest.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the ethics committee of the School of Public Health, Shandong University. Informed consent was waived as this was a non-interventional study using routinely collected data.

## COMPETING INTERESTS

The authors declare no potential conflicts of interest.

## DATA AVAILABILITY STATEMENT

Datasets can be obtained by making reasonable requests to corresponding authors.

## AUTHORS' CONTRIBUTIONS

JL and FX have the conception. JL did the statistical analyses and drafted the initial manuscript. All authors participated in the interpretation of the results, edited and reviewed the manuscript.


## ACKNOWLEDGMENTS

The authors thank the participants included in this study and doctors of the community health service center for their efforts in data collection. We are also very grateful to the engineers of the Healthcare Big Data Research Institute of Shandong University for their help in data collection and processing.

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