DOI: 10.4149/BLL_2021_024

Bratisl Med J 2021; 122 (2)

158 – 160

CLINICAL STUDY

Association of polypharmacy and Parkinson's disease prevalence

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ABSTRACT

OBJECTIVE: Polypharmacy and multiple diseases are common in geriatric practice; however, such kind of multiple interventions might result in adverse effects. Some previous studies have found the association of polypharmacy and Parkinson's disease, to confirm this relationship, we conducted a meta-analysis to analyze this issue quantitively.

MATERIALS AND METHODS: In total, we included 8 studies, 165,689 polypharmacy subjects and 373,660 non-polypharmacy controls, and 5644 PD patients among these subjects and controls.

RESULTS: For model without any adjustment, polypharmacy group has a significantly higher prevalence than control, OR = 2.53, 95 %CI [2.00, 3.20] ($p < 0.001$). However, this model showed a very high heterogeneity ($I2 = 91$ %, $p < 0.001$). In age, gender and disease history adjusted model, polypharmacy group has a significantly higher prevalence than control, OR = 1.43, 95 %CI [1.35, 1.52], $p < 0.001$. The heterogeneity decreased to zero ($I^2 = 0$ %, $p < 0.45$).

CONCLUSION: In this study we have found an association between PD risk and polypharmacy, a better designed prospective long-term cohort study might be required for further discussion on this issue *(Tab. 1, Fig. 5, Ref. 14)*. Text in PDF www.elis.sk

KEY WORDS: polypharmacy, PD, Parkinson, meta-analysis.

Introduction

Majority of senior patients have multiple diseases; this coexistence of co-morbidity requires polypharmacy. In a previous study, 67 % of senior patients (≥ 65) had ≥ 2 chronic conditions, such prevalence even increased with age, up to 81.5 % for ≥ 85 years old subjects (1). There is no way for healthcare providers but to apply polypharmacy to cover the variable conditions. However, there are concerns about such way of prescription. Multiple medications would increase the risk of potential side effects and drug–drug interactions. A previous guideline showed that to take care of an older adult with 5 common diseases would need to prescribe twelve medications (2). Limited large-scale studies have been established through this issue, which might be due to the complexity of multi-drug interactions, the risk associated with polypharmacy for persons with various conditions are not well known.

Parkinson's disease (PD) is a progressive nervous system disorder that mainly affects the motor system. It starts gradually with debilitating symptoms by resting tremor. The cause of it is largely unclear, but several risk factors were found to be associated with PD, including pesticides, heavy metals, head injury, family history, and genetic factors (3). One of them is the impact of polypharmacy on PD as an adverse drug reaction observed in elderly people (1). To best of our knowledge, there was no study conducted as quantitively analysis for previous evidence.

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Material and methods

Data sources and searches

Electronic databases including PubMed, EMBASE, Cochrane Library, Clinicaltrial.gov were searched to identify studies that reported polypharmacy associated Parkinson's disease prevalence after 2000. Following search strategies were established in PubMed:

#1 Search ((Parkinson's disease [MeSH Terms]) OR Parkinsonism [MeSH Terms]) OR Lewy Body [MeSH Terms]

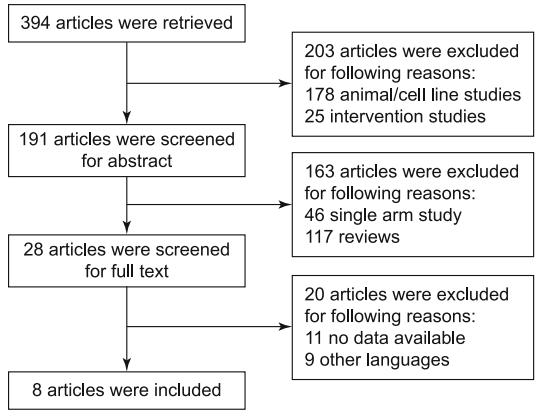

Fig. 1. Flow chart included articles.

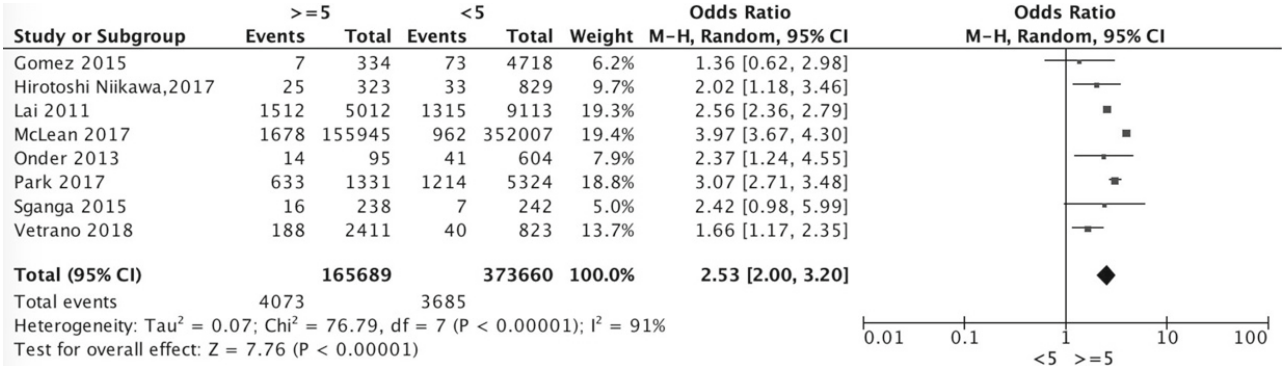

Fig. 2. Forest plot for polypharmacy vs control in PD prevalence, unadjusted model.

#2 Search ((Polypharmacy [MeSH Terms]) OR Polymedication [MeSH Terms]) OR Multiple medication [key words]

Search #1 AND #2

Similar strategy was conducted on EMBASE, Cochrane library and Clinicaltrial.gov.

Inclusion and exclusion criteria

Inclusion Criteria: According to the previous study, we define polypharmacy as over 5 medications taken simultaneously, and Parkinson's disease diagnosis based on criteria according to ICD-10. We included observational studies discussing PD and polypharmacy with control group (less than 5 medications), in whatever study design (retrospective or prospective); the full text of the research report should be obtained in English and it should be possible to extract data.

Exclusion Criteria: Multiple research reports of the same author at the same time as an independent study; Full text cannot be retrieved, incomplete data, or data that cannot be extracted. Animal study, reviews, Meta-analysis, etc. are not included in the study.

The flowchart is shown in Figure 1.

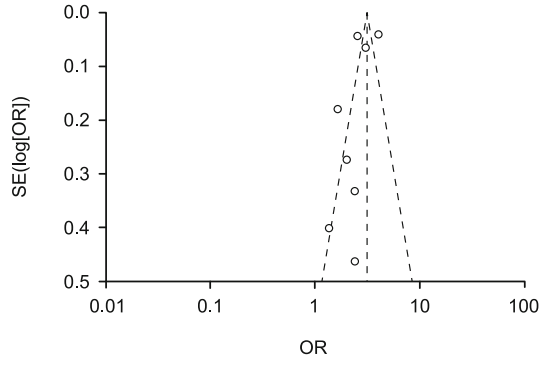

Fig. 3. Funnel plot for polypharmacy vs control in PD prevalence, unadjusted model.

Data extraction and statistical analysis

The main outcome was PD prevalence in each group (polypharmacy vs non-polypharmacy), also we collected subject number, study year, study design and population information for studies' baseline characteristic. Two reviewers (Yan Chen and Zhong Yu) independently conducted review for published literature. If there was any conflict in data extraction, the reviewer Zhong Yu would make a final decision. We used Revman ver 5.3 (from Cochrane library) to conduct this analysis. The heterogeneity of each study was estimated by X^2 test (if $p < 0.05$, the difference was considered as statistically significant, and the size of the heterogeneity was determined by Q-test according to I^2. If I^2 is greater than 50 %, we would define it as high heterogeneity. All analyses would be conducted in random effect model. Also, we conducted adjusted model for covariates, including age, gender, history of cardiovascular disease or cancer.

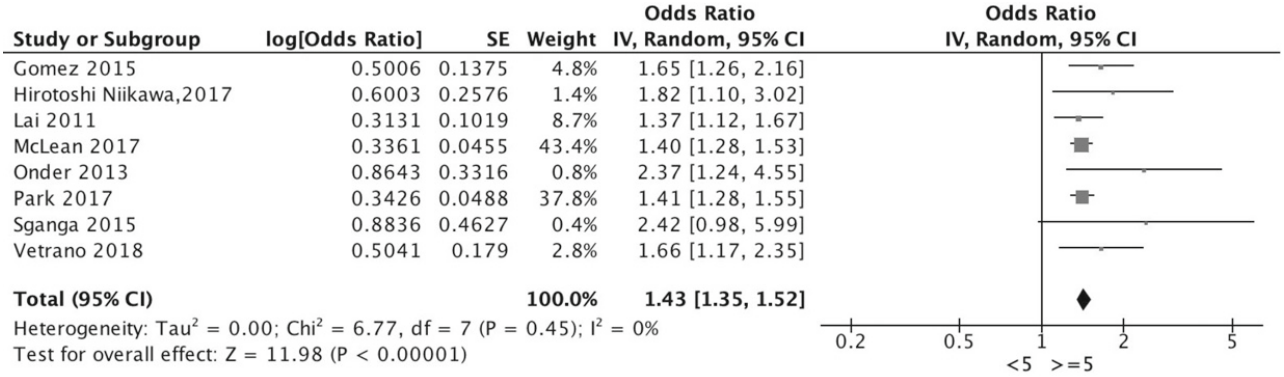

Fig. 4. Forest plot for polypharmacy vs control in PD prevalence, adjusted model.

Tab 1. Baseline characteristics for included studies.

Studies	Year	PD/Subject	PD/Control	Study design	Reference
Park et al	2017	633/1331	1214/5324	Retrospective Cohort	(5)
Vetrano et al	2018	188/2411	40/823	Prospective Cohort	(6)
McLean et al	2017	1678/155945	962/352007	Cross-section	(7)
Sganga et al	2015	16/238	7/242	Prospective Cohort	(8)
Onder et al	2013	14/95	41/604	Prospective Cohort	(9)
Gomez et al	2015	7/334	73/4718	Prospective Cohort	(10)
Lai et al	2011	1512/5012	1315/9113	Cross-section	(11)
Niikawa et al	2017	25/323	33/829	Cross-section	(12)

Results

In total, we included 8 studies, 165,689 polypharmacy subjects and 373,660 non-polypharmacy controls, and 5644 PD patients among these subjects and controls. The baseline characteristic are listed in Table 1.

For model without any adjustment, polypharmacy group has a significantly higher prevalence than control, OR = 2.53, 95 %CI [2.00, 3.20] ($p < 0.001$). However, this model showed a very high heterogeneity ($I^2 = 91$ %, $p < 0.001$), as shown in forest plot and funnel plot.

After adjustment, polypharmacy group has a significantly higher prevalence than control, OR = 1.43, 95 %CI [1.35, 1.52], $p < 0.001$. The heterogeneity decreased to zero ($I^2 = 0$ %, $p < 0.45$) in this model.

Discussion

In this study, we have found an association between polypharmacy and risk of PD, however, because of the nature of cross-sectional study, we cannot conclude any causality in it. There was a systematic review for UK clinical guidelines discussing the potential serious drug-disease and drug-drug interactions in 11 common chronic conditions (13). They concluded that such kind of interaction is uncommon, except for those who have chronic kidney diseases. However, only a few disease specific guidelines would discuss their target patients' comorbidity, or only one comorbidity at a time. They provided few specific recommendations about how to manage people with multiple comorbidities. To cover this issue, more and more evidence of studying this topic is available, a guideline recently summarized recommendations for managing multimorbid patients, moving the focus from the disease to the patient (14). However, it pointed out that we still lack reliable risk estimation models, feasible interventions, and consensus of future directions. And these guidelines often provided generic practice principles or tended to provide detailed recommendations, but shockingly they neglected cognitive dysfunction in general. This is surprising since cognitive condition is highly frequent and undiagnosed in senior population. Since then, this meta-analysis might be another piece of puzzle to state the polypharmacy potential risk for PD, although we still need a better designed longitudinal cohort study to prove this association.

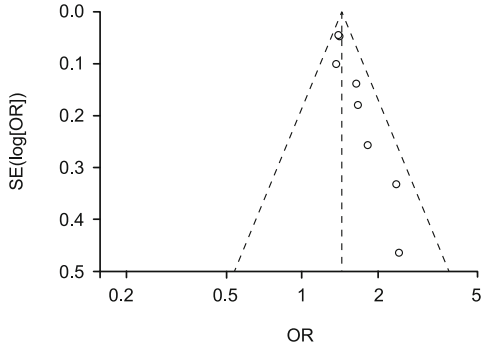

Fig. 5. Funnel plot for polypharmacy vs control in PD prevalence, adjusted model.

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Received June 21, 2020.
Accepted July 27, 2020.