

## Parkinson's in Farmers, Could it be Caused by the Paraquat Herbicide Exposure?

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### Abstract

Many studies have been carried out to assess the safety of the widespread use of pesticides in agriculture with diseases in farmers. A 52-year-old female farmer suffered Parkinson's after working 27 years using paraquat herbicide. This study was conducted to obtain answers about the impact of paraquat exposure on the incidence of Parkinson's in farmers through evidence-based case reports (EBCR) derived from a literature review.

The review was conducted through the search and selection method of articles in PubMed, ProQuest, and Cochrane Library to answer research questions. The article search process used the keywords "paraquat AND Parkinson AND farmer". Article selection was carried out using predetermined inclusion and exclusion criteria. In the initial search, 35 articles were retrieved and through the selection process three articles of the meta-analysis systematic review were selected.

Selected articles from Tangamornsuksan and Vaccari show a statistically significant association between paraquat exposure and the incidence of Parkinson's disease (PD) in workers, with a pooled OR of 1.70 and 1.24. Meanwhile, Yan's study shows that duration of exposure to pesticides increases the risk of PD. The result showed a 5 and 10 years of duration exposure to pesticide were associated with a 5% and 11% augment in the risk of PD. All studies applied validation to reduce bias and heterogeneity effects or inadequate statistical methods.

Based on the results of this evidence-based case report, it shows that the epidemiological studies taken can prove the possibility that Parkinson's disease in this farmer is caused by exposure to paraquat.

**Keywords:** parkinson's disease, paraquat, farmer

### Abstrak

Sudah banyak penelitian dilakukan untuk mengetahui keamanan penggunaan pestisida dengan munculnya penyakit pada petani. Seorang petani wanita usia 52 tahun menderita penyakit Parkinson setelah bekerja selama 27 tahun dengan menggunakan herbisida paraquat. Tulisan ini dilakukan untuk mendapatkan jawaban tentang dampak paparan paraquat pada kejadian Parkinson pada petani melalui laporan kasus berbasis bukti yang berasal dari tinjauan literatur.

Laporan kasus ini diawali dengan metode pencarian dan pemilihan artikel dari PubMed, ProQuest, dan Cochrane Library untuk menjawab pertanyaan penelitian. Proses pencarian artikel menggunakan kata kunci "Paraquat dan Parkinson dan Petani". Pemilihan artikel dilakukan dengan menggunakan kriteria inklusi dan eksklusi yang telah ditentukan. Pada pencarian awal didapatkan 35 artikel, setelah melalui proses seleksi, maka dipilih tiga artikel dari tinjauan sistematis meta-analisis untuk ditelaah.

Artikel dari Tangamornsuksan dan Vaccari menunjukkan terdapat hubungan yang bermakna secara statistik antara paparan paraquat dengan kejadian munculnya penyakit Parkinson, dengan nilai pooled OR sebesar 1,70 dan 1,24. Adapun artikel dari Yan menunjukkan bahwa lamanya paparan pestisida juga akan meningkatkan risiko Parkinson. Dimana durasi paparan selama 5 dan 10 tahun menggunakan pestisida akan meningkatkan risiko Parkinson dari 5% menjadi 11%. Semua penelitian yang diambil menerapkan validasi untuk mengurangi efek bias, heterogenitas atau metode statistik yang tidak memadai.

Berdasarkan hasil laporan kasus berbasis bukti ini, menunjukkan bahwa studi epidemiologis yang diambil dapat membuktikan bahwa kemungkinan penyakit Parkinson pada petani ini disebabkan oleh paparan paraquat.

**Kata kunci:** penyakit parkinson, paraquat dan petani

## Introduction

The agricultural is still major sector that plays an important role in the national economy in absorbing labor, as a source of economic growth, and a contributor to foreign exchange. In 2018, the Central Statistics Agency (BPS) held The Inter-Census Agricultural Survey between the 2013 and 2023 Agricultural Censuses, hereinafter referred to as the 2018 Inter-Census Agricultural Survey (SUTAS). The results of the survey found that the total number of farmers in Indonesia was 33.5 million people, accounting for nearly 20% of all Indonesian workers. The large number of farmers will certainly increase the number of occupational diseases on this sector.<sup>1</sup>

One of the occupational diseases in agriculture that is suspected of being due to exposure to paraquat herbicides is Parkinson's Disease (PD). PD affects 1-2 per 1000 population at any time and its prevalence increases with age where 1% occurs in the population over 60 years. Onset in persons younger than 40 years is relatively rare.<sup>2</sup>

Genetic factor plays a more important role in determining the occurrence of PD than environmental risk factors, although it may also occur in people without a family history. The environment may induce Parkinson's in someone who may be genetically susceptible to it. Many epidemiological studies have shown that environmental factors such as rural living, agriculture, well water consumption, and pesticides are particularly associated with an increased risk of PD. Environmental exposures such as paraquat are thought to increase the risk of PD by a very small amount, depending on the dose and frequency of exposure.<sup>3</sup>

The aim of this study was to obtain information on the association between Parkinson's disease in farmers and paraquat exposure through an evidence-based case reports (EBCR) derived from a literature review.

## Case Report

A 52-year-old female patient came with complaints of trembling hands on the left side and often experience muscle stiffness/ cramps, a little difficulty to start moving, and getting tired easily in the past 3 months. Patients sometimes had to wait a little time to moves. There is no history of trauma capitis or trauma medulla

spinalis. There is no family history of suffering from the same disease.

The patient has been with this company for 27 years, and during her work, she fertilizes and uses pesticides, herbicides (paraquat), and fungicides in her work. Keeps seeds fertile and prevents diseases and weeds that interfere with plants. Work without using personal protective equipment and take breaks from eating and drinking in the huts around the nursery area. As a farmer, the patient is at risk for paraquat exposure. Work 8 hours every day for 6 days a week.

Based on physical examination, it is known that there are resting tremors. The patient was referred to a neurologist for further diagnostic and treatment. The neurologist decided to conduct CT scan and MRI tests to assess and check for abnormal findings in the brain. While waiting for the results of the examination based on the patient's clinical symptoms leading to Parkinson's, the neurologist gave levodopa drug therapy to see the response to therapy. After taking levodopa for 2 weeks and the results of the investigations were there, the patient came back to the neurologist to report the medication. Results of the CT-Scan showed no hydrocephalus or brain tumor appearance. But the MRI test showed the absence of a swallowtail sign on the right side of the brain.<sup>4</sup>

Based on PD cardinal sign, the good response of levodopa therapy, and supporting test MRI, the neurologist concluded that she met the criteria for Parkinson's disease.

The data above, raises the clinical question "*Is there any association between paraquat exposure and Parkinson's disease in farmers?*"

## Methods

The literature search was performed to answer the clinical question via electronic databases from PubMed, ProQuest, and Cochrane Library. The keywords used were worker, farmer, herbicide, paraquat, Parkinson's disease, parkinsonism, and PD The searching was done on June 12<sup>th</sup>, 2021, at 02:52. (Table 1).

The inclusion criteria of this searching strategy were Systematic Review and Meta-Analysis, Cohort Study, Case-control Study, Cross-sectional Study. The exclusion criteria were inaccessible article, review article, case report, the article is not in English, animal studies,

and statistical value data is not available (Figure 1).

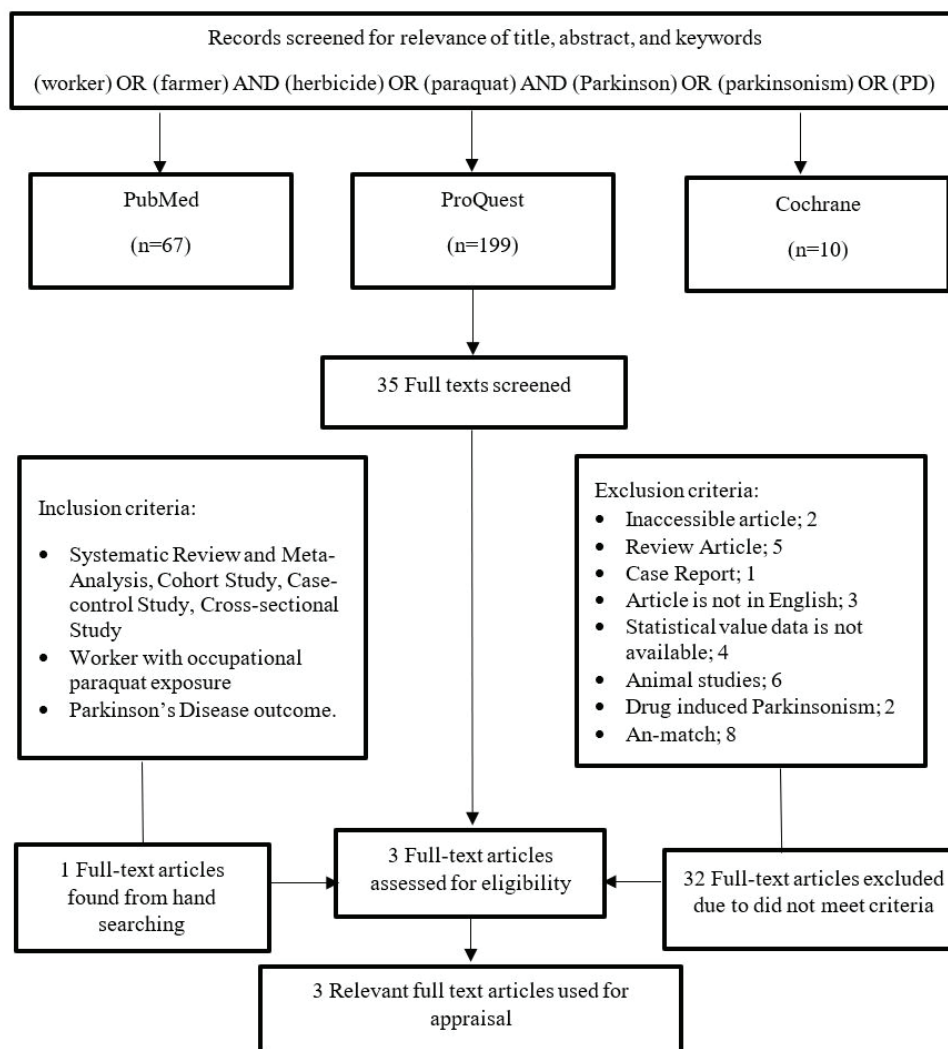
After obtaining articles based on screening through the inclusion and exclusion criteria then these articles were critically appraise for etiological study based on

Oxford Centre for Evidence-Based Medicine.<sup>5</sup>

The results of the appraisal are presented in Tables 2, 3 and 4.

**Table 1.** Searching Strategy Uses Electronic Database

Database	Searching Strategy	Finding
PubMed	Search: (((worker) OR (farmer)) OR (occupation)) AND ((paraquat [Title/Abstract]) OR (herbicide[Title/Abstract])) AND (((Parkinson[Title/Abstract]) OR (PD[Title/Abstract])) OR (parkinsonism[Title/Abstract]))	67
ProQuest	paraquat AND Parkinson AND farmer	199
Cochrane Library	(farmer) OR (worker) AND (herbicide) OR (paraquat) AND (Parkinson) OR (disease)	10



**Figure 1.** Literature Searching Chart

**Table 2.** Critical appraisal checklist for article 1

Article	Tangamornsuksan W, et al. (2018) <sup>6</sup>		
	Paraquat Exposure and Parkinson's Disease: A Systematic Review and Meta-Analysis.		
Level	1 (Systematic Review studies) <sup>9</sup>		
Questions	Does the systematic review address a focused question (PICO)?	Yes	The main question being addressed clearly stated.  Population: general and occupational populations  Intervention: paraquat exposure  Comparison: -  Outcome: Parkinson's disease
Find	Did the research find all the relevant evidence?	Yes	The study performed systematic searches of the following databases: PubMed, Cochrane libraries, EMBASE, Scopus, ISI Web of Knowledge, and TOXLINE. All databases were searched from their inception to May of 2018.  Search terms used were, Paraquat OR Pesticides AND parkinsonian disorders OR Parkinson's disease OR Parkinson disease. Languages of the published papers were not restricted, and only human studies were included.
Appraise	Have the studies been critically appraised and was the overall quality adequate?	Yes	This article described about the quality of each study assessed using quality criteria appropriate to the type of clinical question including. Two authors (WT and RS) separately extracted data from selected studies, and discrepancies were resolved through discussion and consensus. To assess the quality of the study, they used the Newcastle-Ottawa quality assessment scale (NOS). <sup>10</sup>
Synthesize	Have the results been synthesized with appropriate summary tables and plot?	Yes	The results were presented as a forest plot and tables.
	Were the results similar between studies?	Yes	The results of different studies were homogenous ( $i^2 = 31.3\%$ , $p = 0.126$ ).
Result	What measure was used, how large was the effect (could it have been due to chance?)	Yes	OR = 1.70  95% CI (1.28-2.25)

## Results

The research design found by the authors in this study is three systematic review meta-analysis, where this is the best research design as a reference so that the quality of the three studies is high with a level of evidence 1.<sup>5</sup> The study conducted by Tangamornsuksan, et al. (2018)<sup>6</sup> was a systematic review and meta-analysis study of

previously published studies that aimed to investigate the association between paraquat exposure and risk of Parkinson's Disease.

The study showed that there is a significant association between paraquat exposures and PD, with a pooled OR of 1.70 (95% CI: 1.28, 2.25;  $i^2 = 31.3\%$ ,  $p = 0.126$ ). The value indicated that PD occurrence was 70 % higher in participants exposed to paraquat.

There was no apparent publication bias as revealed by Begg’s test ( $p = 0.429$ ) and Egger’s test ( $p = 0.294$ ). In the sensitivity analyses of the quality of the selected studies determined by NOS (New Castle-Ottawa Scale) criteria were evaluated.<sup>10</sup>

The study conducted by Vaccari, et al. (2019)<sup>7</sup> was also a systematic review and meta-analysis study that aimed to investigate the association between paraquat exposure and risk of Parkinson’s Disease. Based on the random-effects meta-analysis, the study showed that there is a significant association between paraquat

exposures and PD, with a pooled OR of 1.24 (95% CI: 1.03, 1.49;  $i^2 = 16\%$ ,  $p = 0.002$ ). The value indicated that PD occurrence was 24 % higher in participants exposed to paraquat, and the occurrence of PD increased to 43% in participants who had long-term exposure to paraquat. In addition, the investigations were searched in a wide range of databases, without language restriction, and no conflict of interest was detected.

Exposure and clinical outcome were assessed in the same way between two study groups, in the meta-analysis studies. They used the Newcastle-Ottawa

**Table 3.** Critical appraisal checklist for article 2

Article		Vaccari C, et al. (2019) <sup>7</sup>	
Paraquat and Parkinson’s Disease: A Systematic Review and Meta-Analysis of Observational Studies.			
Level	1 (Systematic Review studies) <sup>9</sup>		
Questions	Does the systematic review address a focused question (PICO)?	Yes	The authors analyzed the association between exposure paraquat and PD. The authors applied the focused questions to select the most relevant articles.
Find	Did the research find all the relevant evidence?	Yes	Original peer-reviewed studies were searched in the following electronic databases: PubMed, Embase, ISI Web of Science, TOXLINE (one of the TOXNET databases), and LILACS (Latin American & Caribbean Health Sciences Literature), regardless of the language or the year the articles were published. The last search was conducted on May 5th, 2019. MeSH terms and free terms related to “Parkinson’s Disease”, “herbicides”, and “paraquat” were combined.
Appraise	Have the studies been critically appraised and was the overall quality adequate?	Yes	Two reviewers (CV and HG) independently screened all the titles and abstracts identified by the literature search, obtained, and read the full text articles of all the potentially eligible studies, and evaluated all of them for eligibility. Disagreements were resolved by consensus or, if necessary, with third party adjudication (RED or JLVC). The modified New-Castle Ottawa Scale (NOS) (Guyatt and Busse 2019) tools for cohort and case-control studies were adapted to assess the methodological quality of the included studies.
Synthesize	Have the results been synthesized with appropriate summary tables and plot?	Yes	The results were presented as a forest plot and tables.
	Were the results similar between studies?	Yes	The results of different studies were homogenous ( $i^2 = 16\%$ , $p = 0.3$ ).
Result	What measure was used, how large was the effect (could it have been due to chance?)	Yes	OR = 1.24 95% CI (1.03-1.49)

quality assessment Scale (NOS) as an assessment of exposures and outcomes.<sup>10</sup> Sensitivity analyses based on quality of study, quality of analyses, study design, types of exposure, and criteria of cases selection were performed. A study with occupational exposure is defined as a study with participants in the study directly exposed to paraquat in their workplace. Whereas a study with environmental exposure is defined as a study with participants in the study indirectly exposed to paraquat. Describe the history, physical examination, laboratory tests and imaging, treatment, and follow-up of each case.

For the 3rd study by Yan (2018)<sup>8</sup>, the best of our knowledge, the present study is the first dose-response meta-analysis study using duration exposure to investigate the relationship between pesticide exposure and PD. The results suggested a positive association of pesticides duration exposure with PD risk, which was consistent with a few previous meta-analyses designed to analyse the relationship qualitatively between them.

Meanwhile, the sensitivity analyses did not substantially modify the conclusion of this meta-analysis, indicating the conclusion of the meta-analysis

**Table 4.** Critical appraisal checklist for article 3

Article	Yan D, et al. (2018) <sup>8</sup>		
	Pesticide exposure and risk of Parkinson's disease: Dose-response meta-analysis of observational studies.		
Level	1 (Systematic Review studies) <sup>9</sup>		
Questions	Does the systematic review address a focused question (PICO)?	Yes	The main question being addressed clearly stated to select the most relevant articles and applied the focused questions.
Find	Did the research find all the relevant evidence?	Yes	They conducted a literature search of PubMed and Web of Science databases for cohort and case-control studies examining the association between pesticide exposure and risk of PD in peer-reviewed journals through June 2017. PubMed search terms were ("Parkinson Disease" OR "Parkinsonism" OR "Parkinson Disease" [Mesh]) AND ("exposure" OR "Occupational Exposure" [Mesh] OR "Environmental Exposure" [Mesh] OR "Pesticides" [Mesh] OR "Herbicides" [Mesh] OR "Fungicides" [Mesh] OR "Insecticides" [Mesh] OR "Rodenticides" [Mesh] OR "farming" OR "rural living" OR "well water") AND "Risk". Similar search terms were used for Web of Science.
Appraise	Have the studies been critically appraised and was the overall quality adequate?	Yes	Data extraction was carried out independently by two authors (D.Y. and Y.Z.) using a standard form. They extracted the following information from each article: authors, year of publication, study location, study design, source of case/exposure and control, participants' characteristics, exposure assessment method, number of cases, adjusted covariates, and effect sizes (95% CI) for the category of "pesticide".
Synthesize	Have the results been synthesized with appropriate summary tables and plot?	Yes	The results were presented as a forest plot and tables.
	Were the results similar between studies?	Yes	The results of different studies were heterogenous ( $i^2 = 50\%$ , $p = 0.03$ ).
Result	What measure was used, how large was the effect (could it have been due to chance?)	Yes	OR = 1.05 (5 years) 95%CI (1.02-1.09) OR = 1.11 (10 years) 95%CI (1.05-1.18)

was relatively stabilized. Different from other available meta-analyses, this study was conducted to investigate the dose-response relationship between pesticide exposure and PD risk that showed a 5 and 10 years of duration exposure to pesticide were associated with a 5% (OR = 1.05; 95% CI: 1.02–1.09) and 11% (OR = 1.11, 95% CI: 1.05–1.18) augment in the risk of PD, respectively.

## Discussion

There have been many studies conducted to find the association between exposure to paraquat and the incidence of Parkinson's disease (PD). The three studies we took above showed a strong association between paraquat and PD. We selected two recent systematic review meta-analyzes specifically on paraquat exposure with PD by involving nearly 300,000 research subjects about workers and their work environment. Also, third studies from systematic review studies there was a measurement of the duration of pesticide exposure with the incidence of PD.

The similarities between the patient and the articles they were all farmer that exposed with the paraquat herbicide. For the complaints of our patient also similar with the subject in the article. PD is diagnosed based on the cardinal sign that appear. The effect of paraquat exposure on the incidence of PD is described in all articles showing a statistically significant association.

Some of the limitations of the results found were first regarding dose-response, most of the included studies did not report the actual level and duration of paraquat exposure so it was not possible to calculate the dose and duration especially in the first and second studies. Although that has been complemented by a recent third study by calculating the exposure dose. The two research subjects included in each study were still considered a mixed population of occupational and environmental exposures even though they were dominated by workers. The third drawback is that the subject may also be exposed to other pesticides in the workplace (combined exposure) not only by exposure to paraquat, or in an environment of which they are not aware, so appropriate subgroup analysis is required. And lastly, the above studies did not carry out laboratory measurements of paraquat or its metabolites to estimate the amount of exposure received.

## Conclusion

Answering PICO clinical questions; according to the working population, exposure, and disease occurrence; Could paraquat cause PD in farmers? Based on the results of this evidence-based case report, it shows that the epidemiological studies taken can prove that is Parkinson's disease in this farmer is caused by paraquat exposure. This evidence-based case report study that uses systematic steps can prove or become one way to help find answers to clinical problems encountered at health care facilities. Further epidemiologic studies need to be conduct that is more specific on measuring the dose, duration, and metabolite of paraquat exposure on PD risk.

## Conflict of Interest

“The authors declare no conflict of interest”.

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## Author contribution

AA contributed to conceptualization and methodology. AA, DY and LC contributed to preparing and writing the original draft. DY and LC contributed to supervision. AA contributed to review and editing. All authors have read and approved the final manuscript.

## References

1. Team SUTAS (Ed.). 2018. *The Result of Inter-Census Agricultural Survey 2018*. Jakarta: BPS-Statistics Indonesia.
2. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna)*. 2017 Aug;124(8):901-905. doi: 10.1007/s00702-017-1686-y. Epub 2017 Feb 1. PMID: 28150045.
3. Grosset DG, Macphee GJ, Nairn M; Guideline Development Group. Diagnosis and pharmacological management of Parkinson's disease: summary of SIGN guidelines. *BMJ*. 2010 Jan 12;340:b5614. doi: 10.1136/bmj.b5614. PMID: 20068048.

4. Schwarz ST, Afzal M, Morgan PS, Bajaj N, Gowland PA, Auer DP. The 'swallow tail' appearance of the healthy nigrosome - a new accurate test of Parkinson's disease: a case-control and retrospective cross-sectional MRI study at 3T. *PLoS One*. 2014 Apr 7;9(4):e93814. doi: 10.1371/journal.pone.0093814. PMID: 24710392; PMCID: PMC3977922.
5. Evidence Base Medicine Toolbox. Critical Appraisal Log Book [Internet]. Juni 22, 2021. Available from: Critical Appraisal tools — Centre for Evidence-Based Medicine (CEBM), University of Oxford
6. Tangamornsuksan W, Lohitnavy O, Sruamsiri R, Chaiyakunapruk N, Norman Scholfield C, Reisfeld B, Lohitnavy M. Paraquat exposure and Parkinson's disease: A systematic review and meta-analysis. *Arch Environ Occup Health*. 2019;74(5):225-238. doi: 10.1080/19338244.2018.1492894. Epub 2018 Nov 25. PMID: 30474499.
7. Vaccari C, El Dib R, Gomaa H, Lopes LC, Camargo JL. Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. *J Toxicol Environ Health B Crit Rev*. 2019;22(5-6):172-202. doi: 10.1080/10937404.2019.1659197. Epub 2019 Sep 2. PMID: 31476981.
8. Yan D, Zhang Y, Liu L, Shi N, Yan H. Pesticide exposure and risk of Parkinson's disease: Dose-response meta-analysis of observational studies. *Regul Toxicol Pharmacol*. 2018 Jul; 96:57-63. doi: 10.1016/j.yrtph.2018.05.005. Epub 2018 May 3. PMID: 29729297.
9. Center for Evidence Based Medicine. Oxford Centre for Evidence-based Medicine- Levels of Evidence [Internet]. June 22, 2020. Available from: <https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf>.
10. Newcastle-Ottawa Scale (N-O-S) for observational studies. Thresholds for Quality Assessment [Internet]. June 25, 2021. Available from: Thresholds for Quality Assessment - Closing the Quality Gap: Revisiting the State of the Science (Vol. 3: Quality Improvement Interventions to Address Health Disparities) - NCBI Bookshelf (nih.gov).