Risk and Protective Factors Associated with Nuclear Sclerotic Cataract among Adults: Systematic Review

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Abstract:
Visual impairment is currently suffered by 253 million people and leads to blindness in 15% of cases. Among them, cataract is the main cause in the world and Indonesia (52%), which could be prevented. Although actions have been taken in-order to manage cataract, the number is increasing 0.1% yearly, thus we conducted a systematic review of 11,377 subjects in 11 case-control studies from PubMed and EBSCOhost in-order to know the risk factors of nuclear sclerotic cataract (NSC), the most common cataract in the world, hence reduce incidence and prevalence of it and blindness. Full article study texts were assessed with STROBE's criteria for further review. Within study, we concluded three preventable risk factors of NSC. Sunlight exposure which is gained by being outside for leisure (OR=1.45) or work (OR=1.75), could even elevate the risk up to 4.19 folds due to the glycation process which occurs with the help of UV light. Diabetes is also linked, both acute (OR=1.66) and more dangerous chronic (OR=3.71) because of the retinopathy mechanism. Furthermore, alcohol (OR=1.18) and smoking (OR=5.44) are also responsible for elevating the risk. However, a healthy diet with complete vitamins and low triglycerides, uric acid, and creatinine are proven to be able to cut the risk of NSC by half. Thus, we would like to increase awareness of primary health-care workers and the community itself to educate the community about the risk factors of NSC in-order to reduce its incidence and prevalence rate as a step to achieve WHO's "VISION 2020: The Right to Sight."

Keywords: cataract, lifestyle, nuclear sclerotic, protective factors, risk factors

Introduction:

Visual impairment, especially blindness is a prolonged-major problem worldwide among adults. According to the World Health Organization (WHO) and International Agency for the Prevention of Blindness (IAPB), 253 million world population are visually impaired, dominated by adults – 36 million are blind including 3 million Indonesians, highest in South-East Asia.[1,2] This could be caused by the fact that Indonesia is both a developing and tropical country, which speed up the occurrence of cataract by approximately 15 years. Among 1.5% blind Indonesians, 52% are caused by cataract which is acquired by 1.8% of the population and contribute to blindness more than any other diseases combined such as glaucoma and refractory impairment.[2]

However, 80% of blindness causes could be prevented and cured beforehand, including cataract. WHO has taken efforts to eliminate avoidable blindness through "VISION 2020: The Right to Sight" – a long-time aimed program by the end of the year. Indonesia's government has also done several steps in-order to support those programs, including donating US$ 72,762,237 yearly to fund a quarter of total 80,744 cataract operations performed yearly. Although actions have been taken, the number of blindness incidence in Indonesia is still climbing up to now with 210,000 (0.1%) additional population getting blind each year – which can be interpreted as one person going blind as a minute passes by.[2] Thus, we conducted a scientific review to identify risk and protective factors of cataract which could be prevented and applied to reduce incidence and prevalence of cataract which could lead to blindness. Moreover, we choose to study nuclear sclerotic cataract (NSC) further because it is three times more likely to occur than other types of cataracts, which makes it the most common cataract in the world and Indonesia.[3]

Since the early 1970s, interest in improving the end-of-life, palliative, and hospice care of patients has progressed from being the concern of a limited group of healthcare professionals to being the concern of the entire international healthcare community. While these three types of care are defined differently, they essentially comprise the idea of providing holistic care to patients who are about to succumb to death, as well as to their family members (1). The provision of this care is classified based on age (adult, geriatric, or pediatric patients) and occurs in settings such as hospitals, nursing homes, and patient homes. However,

the implementation of this care has been severely challenged during the COVID-19 pandemic due to the associated surge in patients needing palliative and hospice care.

Methods:

In order to determine factors contributing to development of nuclear sclerotic cataract among adults, we conducted a systematic review of large case-control studies based on PRISMA statement from PubMed and EBSCOhost using the keywords "nuclear OR sclerotic", "cataract", "risk factor OR risk OR cause", "case-control OR case control".4,5 Searching was done in November 2018. Afterward, inclusion criteria were set to filter the results including: case-control study, studying NSC, adult subject, study identifying preventable risk factors or applicable protective factors among adults population. In addition, exclusion criteria were also set: immunocompromised patients, unauthentic articles, not accessible articles, and written in languages other than English and Bahasa. We did not set a time range for selected studies to ensure sensitivity of our search. Subsequently, we set necessary data to be extracted from articles including: author and year of publication, study design, location of study, sample size and ratio, subject mean or range of age, method of analysis, and outcome which is picturized by odds ratio for each factor. Finally, the articles will be assessed through "Strengthening the Reporting of Observational Studies in Epidemiology" / STROBE's criteria of case-control study which includes 22 criteria in which 1 point is given for every criterion met. In this study, we did not find any potential confounding factor, thus matching was not necessary. The quality assessment was conducted by two reviewers collaboratively and concluded after consensus was reached.

Results:

The search was conducted via PubMed and EBSCOhost. Titles were screened for relevancy and duplication. Contents were screened for inclusion and exclusion criteria. Articles that went over criteria were fully assessed for eligibility and study design. Last, 11 suitable case-control articles were reviewed and included in this systematic review. Articles were assessed with STROBE's criteria to ensure it was in good quality. Due to limitation of page count, STROBE results of all articles could be seen in **Table 1.** The holistic process can be seen in **Figure 1,** while the included study design and characteristics are further shown in **Table 2**.

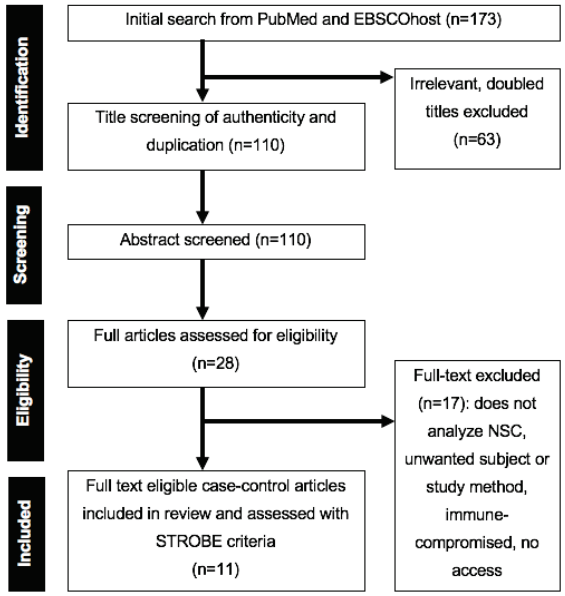

Figure 1. Flow chart of study search strategy for this systematic review

DISCUSSION

Analysis of the study

There are plenty of risk factors which are preventable and associated with NSC. However, considering the feasibility, page limitation, and importance based on the quality of previously assessed studies, we list three preventable risk factors and one feasible protective factor contributing largest towards NSC.

Sunlight exposure

Various studies showed that sunlight elevates the risk of NSC dramatically. Studies by Neale, Pastor-Valero, Rafnsson, Williams stated that exposure to sunlight enhances the risk by 2.80, 3.68, 4.19, 1.45 folds respectively. In addition, the risk also applies to occupational purposes which require daily outdoor activities – could be seen in studies held by Williams that job location in sunlight increases the risk by 1.75 times. More detailed occupations, such as pilot studies by Rafnsson and non-professional studies by Leske multiply the risk by 3.02 and 1.96 folds respectively. In addition, wearing no sunglasses outdoors elevates the risk by 1.30 folds according to Neale. However, according to Mohan, being in cloud cover could reduce the risk by 0.78 folds.

Those findings are proven to be true as chronic sunlight exposure could initiate and increase oxidative stress in the eye. Oxidative stress is a harmful chemical reaction which occurs as cells take oxygen to make energy. Eye lens consist mainly of water and proteins, lacking ~~of~~ organelles and oxygen, which minimize the risk of stress ~~to~~ happen. However, UV light contained in sunlight could replace oxygen role in oxidative reactions by damaging lens protein via glycation process, which could scramble and clump protein together to form a cloudy structure of cataract.[17] In addition, people who

Table 1. Studies quality assessment based on STROBE's Criteria

	Item No	Recommendation	Ghanavati M et al., 2015.[6]	Giuffre G et al., 2005.[7]	Leske MC et al., 1990.[8]	Miglior S et al., 1994.[9]	Mohan M et al., 1989.[10]	Neale RE et al., 2003.[11]	Pastor-Valero M et al., 2007.[12]	Phillips CI et al., 1996.[13]	Rafnsson V et al., 2005.[14]	Shao M et al., 2017.[15]	Williams SL et al., 2001.[16]
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Introduction													
Background/rationale	2	Explain the scientific backgrou	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		nd and rationale for the investigation being reported											
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods													
Study design	4	Present key elements of study design early in the paper	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		and data collection											
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		(*b*) For matched studies, give matching criteria and the number of controls per case	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Variables	7	Clearly define all outcomes, exposures, predictor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		s, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable											
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bias	9	Describe any	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No

		efforts to address potential sources of bias											
Study size	10	Explain how the study size was arrived at	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		confounding											
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		(*c*) Explain how missing data were addressed	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		(*d*) If applicable, explain how matching of cases and controls was addressed	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
		(*e*) Describe any sensitivity analyses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results													

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
		(b) Give reasons for non-participation at each stage	Yes	No	Yes	Yes	No	No	Yes	Yes	No	Yes	No
		(c) Consider use of a flow diagram	No	No	No	No	No	No	No	No	No	No	No
Descriptive data	14*	(a) Give characteristics of	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

		study participants (eg demographic, clinical, social) and information on exposures and potential confounders											
		(b) Indicate number of participants with missing data for each variable of interest	No	No	No	No	No	No	Yes	No	No	No	No
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
		(*b*) Report category boundaries when continuous variables were categorized	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No
Discussion													
Key results	18	Summarise key results with reference to study objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limitations	19	Discuss limitations of the study,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

		taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias											
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

Generalisability	21	Discuss the generalisability (external validity) of the study results	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Other information													
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
Total Score			18.17	16.43	19.17	20.17	19.50	18.83	20.17	18.17	18.63	19.67	17.63

Table 2. Included study designs and characteristics

Author and Year (STROBE's score)	Study Design	Location	Sample Size	Case: control ratio	Range/ mean of sample age	Method of analysis	Outcome
Ghanavati M et al, 2015.[6] **(18.17/22.00)**	Matched case-control study	Tehran	295	1:0.49	57.29 years	Kolmogorov-Smirnoff test, Chi-square test, WilcoxonMcNemar tests, Kruskal-Wallis test, logistic regression	Healthy eating index (OR=0.19)
Giuffre G et al., 2005.[7] **(16.43/22.00)**	Population-based case-control study	Sicily	1068	1:3.90	70.08 years	Univariate analysis	Diabetes >10 years (OR= 1.66), Refractive defects> -1.5D (OR= 7.81)
Leske MC et al, 1990.[8] **(19.17/22.00)**	Case-control study	Massachusetts	1380	2.17:1	64.43 years	Mantel-Haenszel test, Polychotomous logistic regression	Low education (OR=1.46), Use of multivitamin supplements (OR=0.63), Smoking (OR=1.68), Nonprofessional occupation (OR=1.96), Nutritional intake: vitamin A (OR=0.45), vitamin C (OR=0.48),

							vitamin E (OR=0.66), riboflavin (OR=0.72), niacin (OR=0.57), thiamine (OR=0.60), iron (OR=0.59)
Miglior S et al., 1994.[9] **(20.17/22.00)**	Case-control study	Milan	375	1:1.34	40-86 years	Standard logistic regression, chi-square test	Cigarettes >20 (OR= 5.44), Alcohol (OR= 1.06), Uric acid (OR= 1.72), Creatinine (OR= 2.16), Triglycerides (OR= 2.32), Diabetes >5 years (OR= 3.71), Gout (OR= 2.85)
Mohan M et al, 1989.[10]	Case-control study	New Delhi	1990	2.62:1	52.95 years	Polychotomous logistic regression	Gas as cooking fuel (OR=0.62), Higher level of education (OR=0.62), Increased dietary protein (OR=0.84), Increase exposure to cloud cover (OR=0.78)

Neale RE et al., 2003.[11] **(19.50/22.00)**	Conjunct case-control study	Nambour	354	1:0.82	58 years	Multiple categorical logistic regression	Not tertiary educated (OR= 6.67), Diabetes (OR= 1.66), Smoking (OR= 1.28), Medium sun exposure (OR= 2.80), No sunglasses (OR= 1.30)
Pastor-Valero M et al., 2007.[12] **(20.17/22.00)**	Frequency-matched case-control study	Valencia	677	1:0.97	66.35 years	Likelihood ratio test, logistic regression, stata 6 software	No secondary education (OR= 3.85), Sun exposure (OR= 3.68)
Phillips CI et al., 1996.[13] **(18.17/22.00)**	Stringent case-control study	Edinburgh	1848	1:0.87	>17 years	Conditional logistic regression, SAS statistical package	Heavy alcohol (OR= 1.18), Smoking (OR= 1.11)
Rafnsson V et al., 2005.[14] **(18.63/22.00)**	Population-based case control study	Reykjavik	445	1:0.19	67.46 years	Multivariate analysis, logistic regression, SPIDA calculation	Pilot (OR= 3.02), Smoking (OR= 1.92), Sun-radiation (OR= 4.19)
Shao M et al., 2017.[15] **(19.67/22.00)**	Case-control study	Shanghai	958	1:1.06	68.10 years	Kolmogorov-Smirnoff test, t-test, chi-square test, 1-way ANOVA test, ROC analysis, logical regression	BMI (OR= 1.22), Hypertension (OR=1.88), C3 levels (OR=0.92)

Williams SL et al., 2002.[16] **(17.63/22.00)**	Italian-American case-control study	Parma	1987	1: 0.47	45-79 years	Cox proportional hazard models, logistic regression	Smoking (OR= 1.74), No vitamin (OR= 1.72), Diabetes (OR= 1.25), Uneducated (OR= 1.30), Job location in sunlight (OR= 1.75), Leisure time in sunlight (OR= 1.45)

Note: OR, odds ratio; SAS, statistical analysis software; SPIDA, spatial intensity distribution analysis; ANOVA, analysis of variance; ROC, receiver operating characteristic

has either or both of light colored eyes, photosensitization drugs (eg: fluoroquinolones, tetracycline, birth control pills, anti-malarial, psoralens), previous cataract surgery should be extra careful as those traits enhance eye proneness towards UV light in sunlight.[18] Furthermore, outdoor occupations and living in tropical countries greatly enhances the amount of UV light received, thus could increase the risk of NSC.[19]

Diabetes

Diabetes is linked with the elevation of NSC risk. Studies by Giuffre, Neale, Williams concluded that diabetes could increase the risk slightly by 1.66, 1.66, and 1.25 folds respectively. However, prolonged diabetes increases the risk dramatically by 3.71 folds according to Miglior.

Diabetes can cause NSC through retinopathy, which is damage and proliferation of blood vessels which affect the backside of the eye called macula in the retina as a complication of blood sugar disease. Retinopathy could cause retinal detachment, permanent vision loss, and diabetic macular edema. However, retinopathy is suspected to affect the front side of the eye by secreting growth factors which supposedly are used to grow new vessels.[20] These growth factors are used by lens protein to proliferate, cramped, and forming a cloudy layer. In addition, 75% retinopathy occur after the fifth year of diabetes, thus acute diabetes cause much less impact on cataract compared to chronic diabetes.[21]

Alcohol and smoking

Consumption of alcohol and cigarette smoking are found to be associated with an increased risk of cataract. In studies conducted by Miglior, Phillips, Neale, Rafnsson, Williams, and Leske, smoking was found to be associated with an increased risk of cataract by 5.44, 1.11, 1.28, 1.92, 1.74, and 1.68 folds respectively. In addition, the studies by Miglior and Phillips also revealed an increased risk of cataract by 1.06 and 1.18 times respectively with the consumption of alcohol.

Alcohol is found to facilitate the production of reactive oxygen species (ROS), as it stimulates the activity of enzyme cytochrome P450s which is believed to be involved in ROS production. Furthermore, the product of its metabolism may eventually lead to ROS generation in the cell.[22] As a result, such conditions contribute to the development of oxidative stress in the body. Similarly, cigarette smoking is also linked to such an increase in oxidative stress. Cigarette smoke components, especially cigarette tar, are found to

contain high levels of both stable and unstable free radicals and ROS.[23] Moreover, smokers are found to have an increased level of cadmium in their blood, and cadmium could subsequently replace metals associated with the enzyme superoxide dismutase (SOD), such as copper, zinc, and manganese, thereby inactivating the enzyme.[24] SOD is an enzymatic antioxidant the function of which is to remove free radicals by converting them to harmless products.[25] Reduction in SOD enzymatic activity therefore significantly weakens the antioxidant defense mechanism, increasing ocular lens susceptibility to ROS. The double effect of both increased oxidative burden and decreased protection by antioxidants in smokers therefore significantly contributes to early onset of cataractogenesis.

Nutrition

Research and various studies have also indicated the relationship between nutrition and cataract, in which diet and nutrition are shown to have an important role in helping to reduce the risk of cataract. A study conducted by Leske discovered that adequate nutritional intake of vitamin A, C, E, as well as riboflavin, niacin, thiamine, and iron is linked with the reduction of NSC risk by 0.45, 0.48, 0.66, 0.72, 0.57, 0.60, and 0.59 folds respectively. This shows consistency with the study by Ghanavati which concluded that a healthy diet has the chance of reducing the risk of cataract by 0.19 folds, considering fruits and vegetables are actually main sources of these vitamins. Tomatoes, papaya, and oranges, for examples, are proven to have a high content of vitamin C.[26] On the other hand, Miglior found in his study that consumption of high levels of uric acid, creatinine, and triglycerides in the diet multiply the risk of cataract by 1.72, 2.16, and 2.32 folds respectively.

The findings above are consistent with the fact that several vitamins, such as vitamin C and E, can act as antioxidants. Moreover, several green leafy vegetables are also found to contain lutein and zeaxanthin, which also have important antioxidant properties.[26] Damage to the ocular lens can be caused by the photochemical generation of reactive oxygen species, commonly known as oxygen radicals, eventually leading to oxidative stress and consequently, cataract. Antioxidants, however, are able to react with these free radicals, stopping the free radicals chain reaction, thereby preventing further damage done.[25] A healthy diet which includes adequate amounts of

vitamins and antioxidants, especially those consisting of fruits and vegetables, is therefore an important protective factor to fight against the risk of cataract.

Strengths and limitations of the study

This study is a primary review to give readers a broad image about nuclear sclerotic cataract conditions worldwide and factors which may precipitate or easen it. This study is expected to give information on prevention of nuclear sclerotic cataract occurrence. However, the exclusion of inaccessible and unpublished papers limited our review. In addition, heterogeneity of the subjects included in studies and places studies were held could lead to limitation on generalizability of data.

Conclusion:

This systematic review of large case-control studies is conducted to analyze preventable risk and applicable protective factors related to cataract, focusing primarily on NSC as the most common cataract in Indonesia. Based on the above review, we conclude that excessive sunlight exposure, diabetes, alcohol and smoking are important preventable risk factors contributing to incidence of NSC. A healthy diet and good nutrition, on the other hand, may help to reduce the risk of cataract with its protective traits. Those factors are expected to help primary health-care workers and others in educating the community in-order to reduce the incidence and prevalence of NSC in the world, especially Indonesia, thus eradicating preventable blindness, hence, make possible WHO's aim: "VISION 2020: The Right to Sight."

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Not applicable.

Conflict of interests

Writers declared that this research has no conflict of interest.

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Authors' contributions

Jeremy Rafael Tandaju (Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization,

supervision, project administration), and Jessica Audrey (Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization, supervision, project administration).

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