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Association of indoor air pollution on cognitive dysfunction among elderly

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Abstract. – OBJECTIVE: Cognitive dysfunction among the elderly is a devastating condition preceded by accumulation of neuropathology leading to accelerated cognitive decline. Many epidemiologic studies have reported the relation between indoor air pollution exposure and cognitive impairment. To clarify the nature of the association, a comprehensive systematic review and meta-analysis were performed.

MATERIALS AND METHODS: The analysis included all observational studies, including cross-sectional studies, prospective and retrospective cohort studies. Experimental studies, randomized controlled trials (RCTs), and controlled clinical trials were excluded. Studies on the relationships of indoor air pollution and cognition published before 30 April 2021 which are peer-reviewed scientific publications available in English were included after performing a structured literature search through electronic databases, including PubMed, Embase, Cochrane Library, and clinical trial.gov. A total of 146 articles were collected, and after screening thoroughly only, 9 studies were selected. Meta-analysis for the final set of selected studies was performed using the R software.

RESULTS: The quality of all the studies was adequate as almost all reported an association between at least one pollutant and cognitive dysfunction. However, relatively few studies considered outcomes that provide the most substantial evidence for a causal effect. In total, 5 studies have reported on cognitive function. The pooled mean of cognitive function was 12.16 (95% CI: 10.73 to 13.58). However, the heterogeneity was very high (I^2=100%; chi-square test for heterogeneity = p<0.001). We used a modified JBI structured risk of the bias assessment tool, and it was minimal among the included studies as most of the studies have followed a random sampling method and explicitly mention it in their methods.

CONCLUSIONS: Exposure to indoor air pollution through fuels used for cooking and heating was significantly associated with cognitive dysfunction among elderly women. Given the limitations, a more extensive meta-analysis and longitudinal studies are recommended to investigate the biological mechanism behind the impact of indoor air pollution on cognitive health.

Key Words:
Air pollution, Cognitive dysfunction, Aged, Environmental pollutants, Biomass.

Introduction

In developing countries, air pollution has become a universal problem. Indoor air pollution (IAP) is the worsening of air quality by dangerous chemicals and materials. Outdoor air pollution is 10 times better than IAP. Indoor air has more potential pollutants due to compact areas compared to open spaces[1]. In developing countries, the effects of IAP on health are far more than outdoor air pollution. In 2010, 35,00,000 death due to 16% particulate matter pollution and 4.5% global daily-adjusted life year (DALY) were reported due to solid fuels. Even after a significant decline in household air pollution from solid fuels in Southeast Asia, the

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Global Burden of Disease ranked Southeast Asia in the third position for IAP[2]. The information on health effects of IAP is less documented in the literature.

The main sources for IAP include bioaerosols, building material, combustion radon, pesticides, heavy metals, volatile organic matter, and smoke from tobacco, asbestos[3]. In developing countries, biomass fuel combustion is a major contribution of IAP. Among 0.2 billion Indians, 49% use firewood; 8.9% cow dung cake; 1.5% coal, lignite, or charcoal; 2.9% kerosene; 28.6% liquefied petroleum gas (LPG); 0.1% electricity; 0.4% biogas; and 0.5% any other means for cooking[4]. Particulate matter (PM) from aldehydes, volatile organic compounds from resins, waxes, polishing materials, cosmetics, binders, and biological pollutants like dust mites, molds, pollen, and infectious agents produced in stagnant water, mattresses, carpets, and humidifiers are some of the agents causing IAP[5]. According to a report from World Health Organisation, an estimated 3 billion population, depend on combustible biomass for domestic energy. Nearly 40 lakhs of early deaths per year were recorded from stroke, ischemic heart diseases, chronic obstructive pulmonary disease, lung cancer, and pneumonia, all accredited to IAP[6]. Recent studies have evidenced an association of IAP with impaired cognitive function causing dementia, neurogenerative disorders, Alzheimer's, and Parkinson's disease.

Air pollutant exposure is one of the environmental factors that significantly impact cognitive function, and very little is known about the same. Significant studies in the literature have reported outdoor air pollution's impact on adults' cognitive functioning[7,8]. Several theories have been proposed to explain the association between IAP and cognitive dysfunction. The neurological and cardiovascular concept explains that brain inflammation due to stimulus from particulate matter causes cognitive dysfunction. However, these concepts are yet to be established[9,10].

Previous data regarding the association between air pollution and cognitive dysfunction suggested that learning verbally, consciousness, thinking logically, function execution, and short-term memory are the most common domains affected when exposed to pollutants. Though, acute effects were also reported on long-term exposure to air pollutants[7,8,11].

There are numerous tools used in assessing cognitive function in various populations. These include Six-Item Screener (SIS); Mini-Mental State Examination (MMSE); Persian Test of Elderly for Assessment of Cognition and Executive function (PEACE); General Practitioner assessment of Cognition (GPCOG); Functional Assessment Staging (FAST); Wechsler Memory scale (WMS); Memory Alteration Test (MAT); Rey-Auditory Verbal Learning Test (RAVLT); Trail Making Test (TMT); Boston Naming Test (BNT); Rey-Osterrieth Complex Figure (ROCF); Wisconsin Card Sorting Test (WCST); Digit Span (DS); Wechsler Adult Intelligence Scale-Revised (WAIS); Montreal Cognitive Assessment {MoCA; MoCA B, MoCA Basic}; Dokuz Eylül Kognitif Degerlendirme/Dokuz Eylul Cognitive Assessment (DEKOD); Stroop Color-Word Interference Test (SCWIT); Auditory Verbal Learning Test (AVLT); Symbol Digit Modalities Test(SDMT)[12].

In the elderly, cognitive dysfunction has become a significant health problem. Nearly 42% of the elderly across the globe were diagnosed with mild cognitive impairment[13] and are vulnerable to develop Alzheimer's and other neurological disorders[14]. Many previous studies[7,8,11] have explained the association of outdoor air pollution and cognition among the elderly due to pollutants from road traffic and industries. Literature on the association of IAP from biomass combustion and other solid fuels affecting cognitive dysfunction of the elderly is scarce[15].

Materials and Methods

The current systematic review aimed to summarize the existing evidence on the association between IAP and cognitive dysfunction.

Design and Registration

A systematic review and meta-analysis were conducted as per the MOOSE guidelines, considering the functional studies documenting the association between IAP and cognitive dysfunction. This study was registered in Prospero (International prospective register of Systematic review) with ID. 265931.

Eligibility Criteria

This review included all types of observational studies, including cross-sectional studies, prospective and retrospective cohort studies. Experimental studies randomized controlled trials (RCTs), and controlled clinical trials, single

groups before and after trials were excluded. Case studies or case reports were also excluded.

Type of Participants

We have included studies conducted across the globe, involving people of any age group and belonging to any gender.

Type of Intervention

The research question is not aimed at assessing the impact of any particular intervention.

Type of Outcome

Neuro-cognitive dysfunction was the primary and only outcome considered in the present review. Neuro-cognitive dysfunction as diagnosed by one of the standard international guidelines, including the fifth version of the diagnostic and statistical manual (DSM-V) (reference) or the Tenth version of the International Classification of Disease (ICD-10) (contact) was considered. We have realized multiply structured and validated tools are used by researchers across the globe during the initial scoping review. We have included studies assessing Neuro-cognitive dysfunction using any of the following structured assessment tools (List of tools with references from the introduction paragraph).

Search Strategy

We have included peer-reviewed scientific publications available in English. We have performed in-structured literature search through electronic databases including PubMed, Embase, Cochrane Library, and clinical trial.gov and selected studies on the relationships of indoor air pollution and cognition published before 30 April 2021. A literature search was conducted initially by a free text search for keywords and synonyms. We have also used database-specific critical concepts like "MeSH" and "Emtree" to make the search comprehensive. A detailed search strategy was constructed using appropriate Boolean operators between different search terms/concepts. Screening of references of the relevant articles was complemented by selecting those articles that did not appear in the search databases. Additional references were obtained from a simple Google search.

Study Selection Process

The search output from all the databases was imported to a reference management tool. We have followed a three-stage process of primary screening, secondary screening, and final study selection. Two independent reviewers, blinded to each other in the preliminary screening, screened all the studies' titles, abstracts, and keywords. We have removed the duplicates by automatic functionality available in the reference management tool and manual matching the author, tear, title, and DOI of the article. In the secondary screening, the full-text of the final filtered list of articles was screened by the same team of reviewers for compliance with the review's eligibility criteria. The articles shortlisted for inclusion were exported to the "Ryan" platform, and another round of detailed reading of full-text articles was done independently by both reviewers for final selection. All the disagreements were sorted out, and the team was arrived at a consensus on the final list of articles to be included by a detailed consultative process. The screening and selection process was presented in the "PRISMA flow chart" (**Supplementary Figure 1** and **Supplementary Table I**). Studies not satisfying the eligibility criteria were excluded, and reasons for exclusion have been noted. The list of excluded studies and the reasons were summarized in the "characteristics of excluded studies" table.

Data Collection Process and Management

Data extraction from the included studies was done using a structured data extraction form that was pilot tested and developed using the "Cochrane Consumers and Communication Review Group" Data Extraction Template. The following data was extracted using the form: general information about the study such as author, year of publication, title, information related to methods section such as study design, sample size, study participants, inclusion and exclusion criteria, outcome assessment method, country name, and information about outcome such as the proportion of survival rate, the incidence of adverse events. Data were entered by the primary investigator, and the entry was double-checked by secondary investigators for the correct entry.

Risk of Bias Assessment

We relied primarily on MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines for reporting the current study. Each study was evaluated independently by two investigators, and any inconsistency was ruled out

through discussion. The quality of each study selected for inclusion was ensured, including details of the cognitive assessment tool(s) used. The methods used to assess the risk of bias in the included studies were also examined. For the "other sources of bias" domain, we regularly looked for baseline imbalances like age group differences in the study population that could have biased the results. The time required for completing the screening of each study was documented independently by the investigators. Moreover, for few studies, the reviewers searched for supplemental information to get an insight view on the tools and outcome to ensure the quality of the study.

Statistical Analysis

We performed the meta-analysis with the final set of selected studies using the R software (R Foundation for Statistical Computing, Vienna, Austria). The random-effects model was applied because of the anticipated heterogeneity, and final data was reported as the pooled proportion of success rate of the TVM procedure with a 95% confidence interval (CI). Visual representation of these pooled estimates was done by forest plot.

Heterogeneity was evaluated by chi-square of heterogeneity and I^2 statistic. *p*-value less than 0.10 in chi-square test indicate significant heterogeneity, while I^2 value was used to quantify the heterogeneity using the following criteria: less than 25% = mild heterogeneity, 25-75% = moderate heterogeneity, and >75% = substantial heterogeneity.

Results

A total of nine studies were selected for inclusion in the analysis. The remaining studies need to be excluded because they did not satisfy the inclusion criteria and few studies had irrelevant data for analysis.

Characteristics of Studies and Participants

Table I shows the features of the prospective observational and cross-sectional studies, participant's age. The 9 studies included were conducted involving elderly from China (n = 6), USA (n = 1), India (n = 1), Mexico (n = 1). The sample size was in the range of 59 to 37,870 (a total of 73,876 participants). The mean age of study participants from all the studies ranged from 57.6 to 82.0 years. The majority of the studies comprised higher women participants, ranging from 57.2% to 100% compared to men.

Particulate Matter

One study considered PM2.5 exposure association with cognitive dysfunction. Other studies considered PM10, NO_2, CO, SO_2, and O_3, polycyclic aromatic hydrocarbons, benzene, and other toxic organic compounds, propane exposure association with cognitive impairment. The majority of the studies supported a positive association between IAP and cognitive dysfunction measured in dementia, Alzheimer's disease, general ability test performance, learning verbally, function execution, logical thinking, processing information, and episodic memory visually. Conversely, one study supported an adverse association with visual-spatial ability, and yet another supported a negative association with reasoning or fluency.

Exposure Measurement

A significant variation among studies in measuring the source of exposed air pollutants was observed. A wide range of methods and tools were used to measure the exposure. The methods included were subjective reporting of the type of fuel used, and the variety of burners was considered a proxy for indoor air pollution. Efforts also were made to quantify indoor air pollution by the ears of use. One study used the proximity of the house to major roadways was as a proxy for IAP. Structured assessment tools like the ETS exposure questionnaire were used by two studies, and only one study used a GIS-based spatial-temporal model to assess monthly exposure to the particulate matter level of 2.5.

Outcome Assessment

Outcome measurement was also quite heterogeneous across the studies. A study in the USA used SPMSQ (Short Portable Mental Status Questionnaire). The study in Mexico was assessed through Cross-Cultural Cognitive Examination (CCCE) and study in INDIA used Mini-Mental Scale Examination (MMSE). The remaining 6 studies in China were evaluated through Scottish MONICA surveys. Mini-Mental Scale Examination (MMSE), Telephone Interview of Cognitive Status and figure drawing/word recall tests, Montreal Cognitive Assessment (Hong Kong version; MoCA), and using a structured questionnaire (containing three dimensions: orientation and attention, episodic memory, and visuo-construction).

Table I. Characteristic of inclusion table.

SN	Author	Country	Study design	Exposure measure	Outcome measure	Sample size	Outcome measure
1	Ajmani, 2016	USA	Cross-sectional study	GIS-based Spatio-temporal models predicting monthly PM 2.5 concentrations	(Cognition) SPMSQ Global cognitive function -	2221	9.2 ± 1.2
2	Yanan, 2020	China	Retrospective study	Respondent used solid fuel for cooking	mental status and episodic memory	37,870	8.72 ± 4.11
3	Adrian, 2020	China	A 3-year Case-control study that was Prospective and longitudinal.	Over the past 5 years self-reported incense burnt at home ≥ weekly basis	Cognitive performance at year 3-Mo CA Total score	156	20.8 ± 4.5
4	Xurui, 2020	China	A prospective cohort study	Residential proximity to nearest major roadways	MMSE score	11,187	5.0 ± 6.9
5	Chen, 2012	China	A multicenter cross-sectional study of dementia	ETS exposure questionnaire	GMS-AGECAT depression Dementia Alzheimer's disease	810 810 810	28 (3.5%) 21 (2.6%) 14 (1.75)
6	Ruoling Chen, 2012	China	Cross-sectional study	ETS exposure questionnaire	Depressive syndrome (level 3-5) Dementia syndrome (level 3-5)	2153 2153	127 (5.9%) 292 (3.6%)
7	Krishnam-oorthy, Yuvaraj, 2019	South India	Cross-sectional study	Biomass and kerosene used as fuel for cooking in the house	Cognitive impairment-Mini-Mental State Examination	59	16 (27.1%)
8	Limin Cao, 2020	China	Cross-sectional and follow-up analyses	A structured questionnaire used to evaluate the household energy sources, including cooking and heating fuel	Clean fuel used for both cooking and heating Pure fuel used for cooking solid fuel used for heating Charcoal and coal used for cooking and pure fuel used for heating Charcoal, coal used for both cooking and heating	1,256 2,038 349 4,754	14.28 ± 4.73 13.74 ± 4.75 13.48 ± 4.78 12.31 ± 4.75
9	Saenz, Joseph, 2017	Mexico	Cross-sectional study	Most frequently used fuel for cooking by the respondent	Verbal learning (Gas/Wood) Verbal recall Attention Verbal fluency Orientation	Gas 11515 Wood 1508	4.95 ± 1.2/ 4.28 ± 1.2 4.69 ± 2.0/ 4.04 ± 2.1 32.0 ± 15.4/ 20.2 ± 12. 15.8 ± 5.3/ 12.9 ± 4.4 2.55 ± 0.8/ 2.18 ± 1.0

Cognitive impairment was measured in terms of olfaction in one study, alzheimer's disease and dementia in two studies, mental status and episodic memory, orientation and attention in two studies, episodic memory, and visuo-construction, learning and recalling verbally, attention, orientation, and verbal fluency in remaining studies.

Meta-Analysis Pooled Results

In total, only 5 studies have reported relationship between indoor-air pollution and cognitive function. The pooled mean of cognitive function was 12.16 (95% CI: 10.73 to 13.58) (Figure 1). However, the heterogeneity was very high (I^2=100%; chi-square test for heterogeneity = p<0.001).

Risk of Bias Assessment

We have used a modified JBI structured risk of the bias assessment tool. As per the summary, the risk selection bias was minimal among the included studies as most of the studies have followed a random sampling method and explicitly mention it in their methods. Comparability of the cohorts also was good among all the included studies minimizing the possibility of confounding bias. However, the risk of bias due to poor ascertainment of exposure and resulting misclassification of subjects was very high among the studies. Except for two studies, most of the studies relied on self-reported information elicited in an unstructured manner for exposure assessment. Thus, though the risk of ascertainment bias in outcome ascertainment is minimal, the tools used were quite heterogeneous (Table II).

Discussion

We assessed the global association of IAP and cognitive dysfunction among the elderly by summarising the literature's available evidence and investigating whether variables like age, exposure tools, and outcome assessment tools could explain this association. According to the literature reviewed, IAP showed a positive association with cognitive dysfunction, and hence we conclude, age category, gender as strong predictors of cognitive dysfunction.

Characteristics of Participants

In the present analysis, participants' mean age from all the studies ranged between 57.6 to 82.0 years. In all the studies included, 57.2% to 100% of the participants were women compared to men. The findings were consistent with a Nationwide Irish Longitudinal Study on Ageing (TILDA) by Maher et al[16] in Ireland. The sample comprises older people aged 50-74 years and more aged than 74 years significantly associated with impaired cognitive function when compared to men. However, the study did not show any association between the use of open fire and cognitive impairment. Almost every study considered for present analysis showed some association between IAP and cognitive outcome supporting the already existing epidemiologic evidence on effects of IAP and elderly. Compared to outdoor air pollution (OAP), the impact of IAP is 100 times higher, as the efficiency of potential pollutants is much higher in compact space compared to open space. The major source of IAP is from the

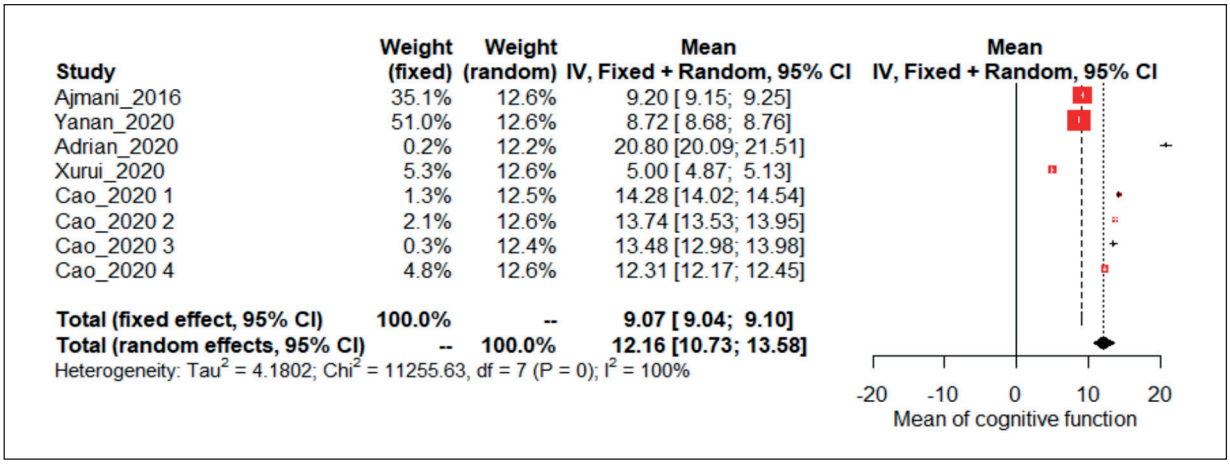

Figure 1. Forest plot depicting the mean cognitive scores among people exposed to indoor air pollution.

Table II. Risk of bias among the included studies.

Study	Selection	Ascertainment of exposure	Comparability of cohorts	Assessment of outcome
Ajmani, 2016	Good	Good	Good	Good
Yanan, 2020	Good	Fair	Good	Good
Xurui, 2020	Good	Good	Good	Good
Chen, 2012	Good	Fair	Good	Good
Chen, 2013	Good	Fair	Good	Good
Krishnamoorthy,2 019	Good	Fair	Good	Good
Limin Cao, 2020	Good	Fair	Good	Good
Saenz, Joseph, 2017	Good	Fair	Good	Good

type of fuel used, and more than half of the global population depend on solid fuels, such as charcoal, biomass, and coal for their day-to-day cooking and heating needs. As most women account for work in a domestic environment, the effect of IAP is more on women than men. The consequences of IAP are just not restricted to rural areas but are also a complex issue in urban areas due to modern housing arrangements. Many internal sources like the materials used for building, heating, systems used for ventilation and air conditioning, products with higher chemical contents, and other human activities help in increasing the concentration of pollutants in urban areas[17].

Exposure Assessment

Different epidemiological studies have reported the association between exposure to particulate matter (PM) and cognitive decline at various stages of life. The risk of IAP is assessed by spatial variability of the air pollutant, geographical area, and the assessment tools to measure exposure like Global cognitive function – mental status and episodic memory questionnaire, (exposure to environmental tobacco smoke) ETS questionnaire, type of fuel used, the proximity of the house to major roadways. The type of fuel and proximity of the house to major roads was considered a proxy for IAP in the present analysis as most of the studies reported them as a source of exposure to IAP. In the literature reviewed in the current analysis, there was a vast difference in exposure variability across studies. The standardization of the tools used for exposure assessment in the studies was not mentioned. Most of the studies in the present analysis were dependent on fuels like kerosene, coal for their daily cooking and warming/steaming needs. Indoor air quality parameters were measured using PM 2.5 concentrations in one study and PM10, NO_2, CO, SO_2, and O_3, polycyclic aromatic hydrocarbons, benzene, and other toxic organic compounds, propane, etc. These findings are similar to an analysis by Roth et al[18] in the UK, where he considered PM10 (μg/m^3) levels above the WHO guideline as having statistically and economically significant association with cognitive health. There were differences in the sources of IAP exposure in the studies included in the present analysis. The exposure to IAP in studies by Krishnamoorthy et al (2018)[19] and Saenz et al (2018)[15] derived from cooking and, in the case of Qiu et al (2019)[20], from either cooking or heating. The exposure to IAP due to cooking is more than heating as by standing near a cooker, the risks exposure to pollutants increases significantly than an open fire. The evidence regarding the relevance of the type of pollutant responsible for IAP is inadequate and uncertain from the studies reviewed in the present analysis.

Outcome Measurement

Most studies reported dementia, Alzheimer's disease, Olfaction, mental status and episodic memory, orientation and attention, episodic memory, visual-construction, learning verbally, remembering, consciousness, adaptation, and verbal fluency as notable changes of cognitive impairment. These findings are similar to an analysis by Lai et al[21] developed in China, where older respondents (aged 55 and above) in counties with higher frequencies of fire points have scores that are 0.267 standard deviations lower in the test of mental intactness and recall objects that are 0.201 standard deviations lower in the delayed memory tests. The analysis showed a negative association between fire and cognitive health. In epidemiological studies,

cognitive function assessment tools are informational and comparatively easy to use. The test scores from these tools are less sensitive in measuring normal to impaired cognitive function. The estimated associations of cognitive level, as assessed by outcome assessment tools like SPMSQ (Short Portable Mental Status Questionnaire), Cross-Cultural Cognitive Examination (CCCE), Mini-Mental Scale Examination (MMSE), Scottish MONICA surveys, Telephone Interview of Cognitive Status and figure drawing/word recall tests, Montreal Cognitive Assessment (Hong Kong version; MoCA) and using structured questionnaire are susceptible to confounding. Potentially moderate to strong confounders, like socio-demographic data, comorbidities, past history on tobacco, occupational exposure was not reported in several studies, and the conclusions made by most of the studies were made by crude adjustments. Nonetheless, a formal mediation analysis with attention to measuring the detailed confounders in evaluating the actual impact of IAP on cognitive health is warranted.

Pathophysiology of Cognitive Dysfunction

The exact mechanism behind the association of IAP and cognitive dysfunction is not fully understood. A systematic review by Dimakakou et al[22] reported that exposure to PM causes irritation and oxidative stress that are the main contributors to the pathogenesis of neurological disorders. Another systematic review by Cipriani et al[23] concluded that poor age-related cognitive Performance is linked with inflammatory markers of neuropathology associated with neurodegenerative conditions of the brain. Animal models[24]. reported that PM reaches the brain either through blood-brain-barrier (BBB) or by directly invading through the olfactory bulb. These PMs can cause cognitive dysfunction even without invading the brain parenchyma. However, the data supporting all these mechanisms stand volatile due to the complex nature of air pollution and the synergistic interaction of multiple pathways that explain the complex stimulus-response relationship.

Considering the current pandemic scenario, the findings of the present analysis are compatible in supporting future researchers, skilled industrialists, public health policymakers, and government bodies to decrease the risk factors causing exposure to IAP. Furthermore, as heating and cooking are fundamental prerequisites of human beings, lawmakers need to provide subsidies to the poor and elderly on utilizing pure forms of energy, which are less dangerous to their own health and the health of others.

Strengths

Our findings add to the evidence that globally, there is wide heterogeneity in the effect of IAP on cognitive dysfunction among the elderly. The analysis was reported as per the MOOSE guidelines and is the first to study the association of IAP and cognitive dysfunction among the elderly.

Limitations

Our analysis has few limitations. Our findings mainly relied on observational data that might affect exposure-effect estimates resulting in bias. Further longitudinal studies and randomized control trials are suggested to check the association between IAP and cognitive dysfunction to establish a temporal relationship. Second, the quantity of fuel exposure and fuel smoke exposure were not studied as most of the studies used self-reported questionnaires. The available pooled data from the studies included were closely linked to age and women using fuel for cooking and cannot be generalized to the overall population. Third, confounders like occupational exposure, history of tobacco smoking, and other comorbidities were not observed in the present analysis. Finally, for this analysis, the type of fuel and type of burners were considered as a proxy for IAP, which again may result in bias as it was not adjusted adequately.

Conclusions

Our findings suggested a highly significant association regarding the effect of IAP on cognitive dysfunction, especially among elderly women. Poor quality of housing, less awareness of the effects of indoor second-hand smoke, residing near busy roads, and more people living per unit area of space resulting in higher suspended particles are a few of the related causes of IAP. In addition, there is a significant impact on health, resulting in a financial burden on developing countries due to IAP. Hence, a holistic approach should be adopted that focuses mainly on improving indoor air quality, modifying present building designs, making them more ventilated and sustainable, using clean household fuels, and reducing the dependency

on vehicles. Our analysis had focused mainly on the adult population, but further research should investigate the possible effects of IAP on the cognitive development of infants and children across the globe.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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