BMJ Open

Urinary cotinine cut-off concentrations in children under 5 years for assessing environmental tobacco smoke exposure: a systematic review and meta-analysis protocol

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To cite: Sayed Mohamed Zain SM, Abdul Shukor IH, Mohamad N, *et al* . Urinary cotinine cut-off concentrations in children under 5 years for assessing environmental tobacco smoke exposure: a systematic review and meta-analysis protocol. *BMJ Open* 2025;**15**:e094077. doi:10.1136/bmjopen-2024-094077

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-094077).

Received 23 September 2024
Accepted 24 April 2025

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ABSTRACT

Introduction Environmental tobacco smoke (ETS) is generally known as secondhand smoke. Assessing the magnitude of children's exposure to ETS from early infancy is essential for public health and research endeavours. Urinary cotinine is now widely recognised as the primary indicator for assessing exposure to ETS across all age groups. This systematic review and meta-analysis aim to synthesise all the published evidence on the urinary cotinine cut-off concentrations used to categorise children under 5 years as being exposed to ETS.

Methods and analysis We will conduct a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A comprehensive search will be conducted from various databases including PubMed, EMBASE, Scopus and Cochrane Library. This search will be performed from the earliest published articles up to the latest available studies until February 2025. We will include all the experimental and observational studies, such as cohort, case–control and cross-sectional, that measure urinary cotinine concentrations in children under 5 years old. Data extraction will be conducted using a standardised data extraction form, and the study quality will be evaluated according to the guidelines specified by the Newcastle-Ottawa Scale. The extracted data will be pooled and combined for meta-analysis. Two reviewers will independently screen, select and assess the quality of the included study. The result will be tabulated in a table of characteristics of the included study, which consists of the cut-off cotinine concentrations, analytical technique, method referred, study design, study area and respondents' characteristics.

Ethics and dissemination Ethics approval is not required as this is a review of collected published data. Findings will be disseminated in peer-reviewed publications and conference presentations, as well as with key stakeholders, health policymakers and healthcare professionals.

PROSPERO registration number CRD42024556969.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, ensuring consistency and uniformity in reporting the review.
⇒ This review will be the first to include a meta-analysis to provide evidence and quantitative estimates of urinary cotinine cut-off concentrations in children under 5 years to assess exposure to environmental tobacco smoke.
⇒ This assessment will retrieve data from English-language databases only and will not include grey literature, thereby limiting the inclusion of possible related studies.

INTRODUCTION

Environmental tobacco smoke (ETS), otherwise known as secondhand smoke, comprises approximately 4800 compounds, such as nicotine, polycyclic aromatic hydrocarbons, aromatic amines and carbon monoxide, among which more than 250 are toxic[1] with at least 70 carcinogenic.[2] Worldwide, tobacco smoke exposure results in 8 million annual deaths of individuals, with approximately 1.2 million of these deaths attributed to passive smoking among non-smokers.[3] Globally, 33% of adult non-smokers and around 40% of children have been exposed to ETS at home. This exposure leads to various health problems such as respiratory tract infections, asthma, wheezing, low birth weight, orofacial clefts, childhood cancer, attention-deficit/hyperactivity disorder and cognitive and language impairments, which can cause significant illness and death.[4–7] Children are vulnerable to the harmful effects of ETS because of their narrower bronchi, faster respiratory rate and immature immune system. Studies have also found that infants

born to mothers who were exposed to ETS during pregnancy had a risk of being small for gestational age, which is between one and five times higher than those who were not exposed to tobacco smoke.[8 9]

Cotinine is a derivative of nicotine, the addictive compound found in tobacco smoke. On inhalation, nicotine undergoes metabolism in the human body, resulting in the formation of cotinine. Contrary to nicotine, which is rapidly eliminated from the body within an average of two to 3 hours,[10] cotinine has a longer half-life of approximately 19–20 hours.[11] This characteristic makes cotinine a more precise measure of the accumulative exposure to ETS over some time. It has been widely used as a biomarker for validating smokers and passive smokers.[12 13] In addition, using cotinine as a biomarker of ETS exposure is advantageous since 72% of nicotine is converted to cotinine, which is the most abundant nicotine metabolite compared with other metabolites.[14] Cotinine can be identified in many biological samples, including urine, blood, hair and saliva.[15–18] Studies have shown that the level of cotinine in different biological fluids, such as serum, saliva or urine, strongly correlates with the degree of nicotine exposure.[19–21]

Serum or plasma samples were traditionally chosen as biomarkers as they showed a more cotinine level stability and were not confounded by the analytical time.[22] However, there is a lack of standardisation among studies in the selection of cotinine cut-off values for distinguishing smokers from non-smokers, and the values differ between gender and age.[12 23–25] Salimetrics in the USA provides a guideline for serum cotinine cut-offs, ranging from 1 to 5 ng/mL, as the level differs between ethnicity and gender.[24] On a separate note, a study by Kim reported that serum cotinine cut-off ranges between 3.0 and 20 ng/mL.[12] The South African Cohort Study and the Hokkaido Cohort Study reported cut-off values for serum or plasma cotinine, with non-smokers ranging between 10 and 15 ng/mL and smokers at 11.48 ng/mL.[23–25] Additionally, a review by Avila-Tang *et al* indicated that the commonly used cut-off value in England decreased from 14 to 12 ng/mL.[26]

Conversely, urine is a common sample used for cotinine biomarkers as it is easy to collect, non-invasive and can be obtained in large volumes.[27] Additionally, urinary cotinine has greater average concentrations than blood or saliva cotinine, making it a more sensitive matrix for detecting low-level exposures.[28 29] Urinary cotinine concentration is influenced by urine dilution. To account for this variation, urinary creatinine is used to standardise cotinine levels, ensuring consistency in measurement across different dilution levels. Several studies have reported the cut-off value for urinary cotinine for smokers/exposed and non-smokers/unexposed. For example, European human biomonitoring found that urinary cotinine cut-off differs between countries with a range for mother (4.45–254.15 mg/L, 6.07–165.8 mg/g creatinine) and children urinary cotinine (1.45–4.80 mg/L, 2.15–3.18 mg/g creatinine).[30] While a review by Avila-Tang *et al* found that urinary cotinine cut-off points were 50 ng/mL for secondhand smoke exposure.[26] Another study from the New Hampshire birth cohort study found a lower cut-off value among pregnant mothers, with 1.8 ng/mL for active smokers and 1.2 ng/mL for secondhand smoke.[31]

Rationale of review

Evidence from previous literature concludes that cotinine cut-off value varied between biological samples used, gender, age, ethnicity and geographical location. Determining a cotinine cut-off value among young children is limited. Several researchers have suggested that the frequency of ETS exposure reported by mothers is lower than the exposure levels detected in children using urinary cotinine measurement.[32–34] However, the lack of agreement might be related to a limited selection of urinary cotinine cut-off values. There has been no previous review on the urinary cotinine thresholds to assess exposure to ETS in children under the age of 5 years old. Therefore, it is imperative to determine the cut-off value among infants and children, as these groups are more vulnerable to the health effects of ETS exposure. Vanker *et al* found that 56% of newborns at birth and 53% of infants between 6 and 10 weeks old had urinary cotinine levels that indicated exposure to ETS.[35] In addition, early life and preschool-aged children are generally unable to control their environment and avoid exposure to their surroundings.[36] Furthermore, their ability to eliminate carcinogenic substances is low, resulting from exposure to ETS.[37 38] Another review by Mourino *et al* assessed serum cotinine cut-off value for children under 5 years. The review found that only three studies specifically examined postnatal exposure in children under the age of 5 years, and none of the 51 studies included in the review provided age-specific criteria for this age group.[39] This could be attributed to the difficulties in obtaining serum samples from children, as the process is invasive compared with collecting other biological fluids such as urine. However, a systematic review is absent for a more sensitive and non-invasive method, which causes the difference in the urinary cotinine cut-off values across the populations. Therefore, this proposed review is vital for gaining a conclusive understanding of ETS exposure among young children from birth up to 5 years old through urinary cotinine assessment exposure.

Objectives for systematic review and meta-analysis

1. To synthesise all published evidence on the urinary cotinine cut-off concentrations used to assess ETS exposure in children under 5 years of age.
2. To assess the changes in the urinary cotinine cut-off values across different methods used and over time.

Review questions

1. How accurate is urinary cotinine as a biomarker for assessing exposure to ETS in children under 5 years old?

2. How to define specific age cut-offs for urinary cotinine cut-off concentrations to assess exposure to ETS in children under 5 years?
3. Which specific cut-off urinary cotinine concentrations have been used to categorise exposure to ETS in children from birth to 5 years old?
4. Have the urinary cotinine cut-off concentrations evolved from earlier studies to those conducted in more recent years?
5. Do the urinary cotinine cut-point values vary across different countries?
6. Did the selected studies consider age-related differences in cotinine metabolism?
7. Which analytical method was used to quantify the urinary cotinine concentrations in the selected studies?
8. What approaches were used to establish the particular urinary cotinine cut-offs in the selected studies?

METHODS

This review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.[40] This protocol was developed following the PRISMA checklist protocol (see online supplemental file 1)[41] and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024556969.

Inclusion criteria

All original articles published in English, whether peer-reviewed, preprint or expedited, will be included. These articles will consist of observational (cohort, case–control and cross-sectional) and experimental study designs to measure the concentration of cotinine in urine among children under the age of 5 years. We will include studies that recruit all children from birth to 5 years old, with information on urinary cotinine cut-off concentrations, parental self-report to ETS and mother–child pairs study. We will also include studies that address indoor or outdoor (ambient air) exposure to ETS, such as exposure at the parent's or caregivers' workplace, school or kindergarten, home and public areas. Only secondhand smoke due to cigarettes is included. Personal sampling and specific study areas defined by authors will also be included (eg, industrial or waste incinerator areas). This review will consist of studies conducted when ETS exposure was determined and the measurement of urinary cotinine in urine samples. We will also compare urinary cotinine levels of unexposed subjects (described by the author) to ETS. The outcome will be the urinary cut-off concentrations with exposure to ETS based on primary study findings.

Exclusion criteria

We will exclude studies that report urinary cotinine without cut-off values. Studies reporting urinary cotinine obtained from parents or caregivers will also be excluded. Studies measuring cotinine from other biological samples such as serum, amniotic fluid, blood, plasma, saliva, hair, meconium or breast milk will be excluded. Animal studies will also be excluded. Studies that rely on secondary sources for urinary cotinine cut-off concentrations will be excluded to prevent redundancy from multiple publications referencing the same cut-off values. Studies that are not published in English and non-peer-reviewed sources such as reports, communications, theses, proceedings, books, editorials, letters, conference abstracts, conference papers, notes and guidelines will also be excluded. Grey literature is excluded due to concerns about reliability, accessibility and methodological inconsistencies. It is challenging to guarantee the quality and comparability of grey literature findings due to a lack of peer review, possible bias, inconsistent reporting, indexing issues and resource limitations, which could jeopardise the review's validity. Table 1 summarises the population, interventions/exposure, comparison and outcomes (PICO) search approaches for this review.

Electronic search

To identify relevant studies, we will conduct a systematic search across four databases such as PubMed, EMBASE, Scopus and the Cochrane Library. A manual search will be undertaken in the references of the selected articles and relevant review articles to identify any relevant further research. Only papers written in English will be included. The search will cover articles published in electronic databases from the earliest available articles until February 2025.

Search strategy

Two authors will independently perform the search from each database using the specific based on the PICO: (1) study population (child* OR newborn OR infant* OR infancy OR preschool* OR toddler*); (2) intervention/exposure (environmental tobacco smoke OR tobacco smoke OR secondhand smoke OR passive smoker OR cigarette* OR tobacco OR nicotine); and (3) outcome (urin* cotinine) (table 2). The Boolean operator 'AND'

Table 1 PICO(s) search strategies and sources of review

Population	Intervention/exposure	Comparison	Outcome
Children from birth to 5 years old	Exposure to (ETS) or secondhand smoke from indoor or ambient air	Children that are unexposed to ETS	Urinary cotinine cut-off concentrations

ETS, environmental tobacco smoke; PICO, population, interventions/exposure, comparison and outcomes.

Table 2 Proposed search terms

Components	Search terms (search each term; then combine using OR)
Population Children under 6 years	child* newborn infant* infancy preschool* toddler*
Exposure Environmental tobacco smoke exposure	"environmental tobacco smoke" "tobacco smoke" "secondhand smoke" "passive smoker" cigarette* tobacco nicotine
Outcome Urinary cotinine cut-off	urin* cotinine

note: * = retrieves all word variations starting with that root word

will combine all three search components. Search results will be imported into EndNote X9 reference manager software, which we will screen and manually remove the duplicates independently. The full search syntax for all databases is presented in online supplemental file 2.

Record screening and selection

All articles gathered for this review will be saved, organised and managed using the EndNote X9 Reference Manager Software. Identified studies will then be extracted to Microsoft Excel Spreadsheet Software and independently reviewed for eligibility by two authors in a two-step process. A first screen will be performed based on the title and abstract, while full texts will be retrieved for the second screen. Two reviewers will individually evaluate the titles and abstracts by applying the predetermined eligibility criteria to assess the eligibility of the potential studies for inclusion. We will classify the articles from the abstract and title screening as 'include', 'exclude' or 'not sure'. We will retrieve the full-text study reports from the identified relevant articles. Then, two additional review authors will independently screen the full text to identify studies that are eligible for inclusion. We will code them as 'eligible' (eligible or potentially eligible), 'not eligible' or 'not sure'. We will exclude all the ineligible studies and record the reasons for the exclusion. We will discuss disagreements or consult a third review author if necessary. We will ensure that the selection process is thoroughly recorded to enable the completion of the PRISMA flow diagram and a table outlining the aspects of the excluded studies.

Data extraction and management

This evaluation will use a standardised data extraction form generated by the Microsoft Excel Spreadsheet Software to collect information on study characteristics and outcome data. Two reviewers will independently extract outcome data from the study that has been included. We will note in the 'characteristics of included studies' table if outcome data is not reported in a usable way. If any disagreement arises, we will address it by engaging in discussion or, if necessary, acquiring the opinions of a third reviewer. We will verify the accuracy of the data by cross-referencing the information in the review with the study reports. The included studies will be independently extracted according to general information (title, authors, year of publication, country and region); study characteristics (study design, source of data, study period, sample size and age groups); methods (sample type, personal sampling, ambient sampling, type of environment and analytical technique); and at last the outcomes (cotinine cut-off values and method reference for urine cut-off). For missing data, authors of the primary studies will be contacted. In the event that the included studies have missing data, the risk of bias due to missing evidence will be used to evaluate the impact of missing studies on the overall conclusions of a meta-analysis. This will aid in enhancing the transparency and reliability of systematic reviews.

Data analysis and synthesis

A narrative synthesis will be presented to describe general information and outcome details. We will present individual study results. We will then collectively compare and contrast cotinine cut-off values with similar purposes for their quality rigour and results. The results will be pooled in a random-effects meta-analysis, and a separate analysis will be conducted if there are different cut-off units. Robust variance estimation will be considered to account for dependencies. Meta-regressions may be considered to address moderators. If there are at least 10 included studies, the meta-analysis will be scrutinised by funnel plot and Egger's test to identify any publication bias. Sensitivity analyses will be used to identify outliers that may affect the analysis by leave-one-out method. Heterogeneity will be assessed using the I^2 or H^2 statistics if the number of included studies is less than 10. Subgroup analyses will be conducted according to predefined categories. The meta-analysis will be presented using a Forest Plot generated by STATA software V.18 (StataCorp, 2023).[42]

Quality assessment

Two reviewers will independently assess the quality of the included studies. The selected studies will be assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS is a commonly employed scale for evaluating the reliability of non-randomised studies, such as cohort and case–control studies, in systematic review and meta-analysis.[43] NOS implemented a 'star system' to evaluate studies, considering three main categories: (1) the 'selection' of study groups (four items); (2) the 'comparability' of these groups (one item); and (3) the assessment

of 'exposure/outcome' (three items). A study will be awarded a maximum of one star for each item within the 'selection' and 'exposure/outcome' categories, and a maximum of two stars can be given for 'comparability'. The highest achievable score is nine stars, and the quality of studies can be categorised as good, fair or poor based on specific threshold scores:

1. Good: 'selection' domain (3 or 4 stars); and 'comparability' domain (1 or 2 stars); and 'exposure/outcome' domain (2 or 3 stars).
2. Fair: 'selection' domain (2 stars); and 'comparability' domain (1 or 2 stars); and 'exposure/outcome' domain (2 or 3 stars).
3. Poor: 'selection' domain (0 or 1 star); or 'comparability' domain (0 star); or 'exposure/outcome' domain (0 or 1 star).

We will use the Cochrane risk-of-bias tool for experimental studies, and methodological quality will be assessed using the Joanna Briggs Institute. It has two parts: internal validity and statistical conclusion validity. The internal validity is further divided into four bias assessments: bias related to selection and allocation, bias related to administration of intervention or exposure, bias related to evaluation, detection and measurement of the outcome and bias related to participant retention. Each bias assessment question has four choices: yes, no, unclear or not available, with a justification column to explain the choices made for each question.[44] The overall appraisal decision will be decided at the end of the appraisal tool. By subjecting every study included in a systematic review to a rigorous critical appraisal, we will delicately consider how the conduct of individual studies may impact the pooled result and be interpreted appropriately.

Patient and public involvement

As this will be a review of published data, patients will not be primarily involved in any stage of the study. Data will be collected from published studies available in the underlined electronic databases.

REACHING CONCLUSIONS

The protocol has been registered in PROSPERO and we will initiate the review in October 2024, and results should be expected by 1 May 2025. This review shall contribute an update to the existing literature on urinary cotinine cut-off concentrations that are used to categorise children under 5 years who are being exposed to ETS. We will base our conclusions on findings from the quantitative or narrative synthesis of included studies for this review. The conclusions can be used as guidelines for other related studies and stakeholders in controlling ETS exposure. Our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

ETHICS AND DISSEMINATION

By the guidelines, our review protocol had been registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 22 June 2024 (registration number CRD42024556969) and the National Medical Research Register (NMRR), Ministry of Health Malaysia on 25 June 2024 (ID NMRR ID-24-02027-YGI). We will present the findings of this review as a manuscript to be published in a peer-reviewed journal. Furthermore, the results will be disseminated through scientific venues, conferences and among relevant healthcare stakeholders at national and international conferences.

Acknowledgements We thank the Director General of Health, Ministry of Health Malaysia for his permission to publish this protocol. We thank Dr Nor Asiah Muhamad, Dr Nur Hasnah Ma'amor and the team for their guidance in preparing this protocol

Contributors SMSMZ is the guarantor. SMSMZ initiated and designed the study, devised search strategies, drafted the inclusion selection form and drafted the protocol. All authors contributed to developing the selection criteria and critically revised the study design and initial draft for important intellectual content. ZFA, NM and WNFWA performed the introductory section. IHAS revised the manuscript for data analysis and synthesis content. All authors read and approved the final protocol.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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