Review

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Uncovering Methodological Gaps in NHMRC Systematic Reviews on Water Fluoridation: A Comparative Evaluation

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Uncovering Methodological Gaps in NHMRC Systematic Reviews on Water Fluoridation: A Comparative Evaluation

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Abstract: Objectives: This review evaluates the methodologies and search strategies in NHMRC systematic reviews on the effects of water fluoridation on dental and broader health outcomes, comparing them with Cochrane's internationally recognised standards. **Study Design:** A critical review of the search strategies, inclusion criteria, and methodologies used to assess water fluoridation's health impacts. **Methods:** The review analyses the search strategies for dental caries and broader health effects, comparing search dates, syntax, and comprehensiveness. It also evaluates methodological standards, including protocols, reporting transparency, and the inclusion of certain health outcomes. **Results:** Significant inconsistencies were found, including outdated search dates, varying search syntax, and a lack of differentiation between fluoridation agents. Exclusion of health outcomes like dental fluorosis raises concerns about objectivity and completeness. **Conclusions:** The review highlights the need for standardised protocols, transparent reporting, and updated search strategies to ensure comprehensive, unbiased findings. Addressing these gaps will improve the quality of future reviews and inform more equitable public health decisions.

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In 2017, the National Health and Medical Research Council (NHMRC) released its Public Statement on Water Fluoridation and Human Health in Australia, offering an evidence-based recommendation on community water fluoridation. This was based on an updated review of the NHMRC's 2007 report, responding to ethical and health concerns about fluoride. A research team from NHMRC Clinical Trials Centre (CTC), guided by the Fluoride Reference Group, conducted systematic reviews from 2014 to address the controversy around the dental benefits and health effects of fluoridated water. The CTC systematic review (or evidence integration) team consists of Cochrane review specialists (CTC, 2024). Cochrane is an internationally recognised leader in the production of systematic reviews that inform health decision-making.

Merilyn Haines, a representative of the Fluoride Action Network Australia, called for a Royal Commission to investigate the NHMRC's methodology, alleging the review was unscientific, biased, and flawed. Haines (2017) outlined 23 specific manipulations by the NHMRC, such as stacking review committees with advocates for fluoridation, excluding key studies, and misrepresenting evidence on fluoride's effects on health, including potential neurotoxicity. She criticised the NHMRC's reliance on outdated studies and claims that their reviews prioritise pro-fluoridation narratives over rigorous scientific inquiry.

In this critical review, I aim to contribute to the growing body of evidence regarding research bias and data manipulation in NHMRC reviews, further supporting Haines's call for a Royal Commission to investigate these issues. I will critically examine the methodologies employed by the NHMRC Clinical Trials Centre (CTC), alongside recommendations from the Cochrane Systematic Review Handbook. In particular, I will focus on the search strategies in NHMRC CTC's Technical Report (Jack et al., 2016), which may highlight limitations that could influence public health policy and shape interpretations of fluoride's effects on human health.

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Review Aims and Methodological Concerns

A systematic review is a rigorous research method that summarises existing studies on a specific topic through structured and standardised processes (McKenzie et al., 2019). It includes comprehensive literature searches, quality appraisals, and often a meta-analysis. The aim of systematic reviews is to provide transparent, objective assessments of evidence for decision-making in healthcare, policy, and education, following guidelines such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

The NHMRC review comprised systematic reviews assessing the dental effects of water fluoridation through an overview of existing reviews and recent primary studies, along with a systematic review evaluating other possible health effects. While the review sought evidence for dental caries reduction, it applied less rigorous criteria to the extensive list of other health outcomes, including developmental disorders and cancers. This inconsistency raises questions about the review's objectivity and comprehensiveness.

According to the Cochrane handbook, systematic reviews should pre-specify inclusion and exclusion criteria (Cochrane, 2024) often using PICOS criteria (population, intervention, comparator, outcomes) (Thomas et al., 2019). Although the NHMRC's *Technical Report* mentions a protocol, it does not appear to be publicly available. The PICOS criteria addressed two main questions:

1. What is the effect of community water fluoridation (0.4-1.5 ppm) compared to a non-fluoridated supply (<0.4 ppm) on dental caries?
2. What are the non-dental health effects of fluoridated water compared to a non-fluoridated supply or different fluoridation levels?

While these questions are useful, they raise several issues. Cochrane outlines the advantages and disadvantages of broad versus narrow reviews (Thomas et al., 2019); thus, addressing these two separate questions with different approaches (broad vs narrow) is questionable. First, limiting the dental caries question to 0.4-1.5 ppm excludes data from studies on lower or higher fluoridation levels. Moreover, the second question on non-dental health effects is vague, with undefined terms of "different levels," potentially leading to inconsistent interpretations of the evidence. Both questions also overlook individuals exposed to fluoride from multiple sources (e.g., toothpaste, foods), limiting the generalisability of the findings.

Focusing solely on dental caries neglects other relevant conditions, such as dental erosion (Noble & Faller, 2018) and periodontal disease (Vandana, 2014). Additionally, excluding dental caries and fluorosis from the health effects question disregards two critical outcomes of fluoride exposure. For example, a recent systematic review reported strong evidence linking elevated dental fluorosis to reduced intelligence in children, as well as moderate evidence for thyroid dysfunction (Taher et al., 2024).

Lastly, the review does not differentiate between health effects stemming from community fluoridation and naturally occurring fluoride, despite their distinct properties. Fluoride exists in various compounds, with sodium fluoride (NaF) and stannous fluoride (SnF2) being two common forms used primarily in dental products (Kowalska et al., 2024). Fluorosilicic acid is widely used as a fluoridation agent in water treatment and is mentioned in the NHMRC's Q&A report on water fluoridation and human health in Australia (NHMRC, 2023). This compound is primarily produced as a by-product in the manufacture of phosphoric acid from phosphate rock for the fertilisation industry. When phosphate rock is treated with sulfuric acid, fluorine-containing compounds are released (Yang et al., 2024).

Naturally occurring fluoride refers to fluoride ions found in nature, primarily as minerals like fluorite (CaF^2) or in groundwater, often as sodium fluoride or other fluoride salts (Khattak et al., 2022). Both fluorosilicic acid and naturally occurring fluoride can dissociate in water to release fluoride ions (Crosby, 1969), which are believed to be the active components responsible for dental health benefits. However, Crosby argued that chemical forms of fluoride may differ in how they interact with other substances in water. For instance, compounds like SiF6 2 may not dissociate completely when reacting with aluminum hydroxide Al(OH)3 and silico-fluoride residues could reassociate either in the stomach or during food preparation.

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A PhD dissertation by German chemist Westendorf (1975) supported this observation, finding that silico-fluorides do not fully dissociate, and the remaining complexes may act as more effective inhibitors of cholinesterase, an enzyme crucial for proper central nervous system function. Further research has indicated that silico-fluorides interact with other chemical compounds. For example, studies have reported associations between water treated with fluorosilicic acid and elevated lead levels in children's blood (Coplan et al., 2007; Macek et al., 2006; Masters & Coplan, 1999; Masters et al., 2000).

Additionally, fluorosilicic acid obtained from phosphate industry scrubbers may contain a variety of impurities, particularly arsenic and possibly radionuclides (Ahmad et al., 2023). The United States Environmental Protection Agency's maximum contaminant level goal for arsenic, a known human carcinogen, is set at 10 parts per billion (ppb). However, the addition of silico-fluorides to the water supply has been reported to increase arsenic levels by an average of 0.1 to 0.43 ppb, and possibly as much as 1.6 ppb (Deal, 2015). This relationship has been supported by other research comparing fluoridated treated water samples compared to non-fluoridated water (Peterson et al., 2016).

Hirzy et al. (2013) examined the economic and health implications of using fluorosilicic acid versus pharmaceutical-grade sodium fluoride (NaF) for water fluoridation. In terms of cost, fluorosilicic acid is typically less expensive than sodium fluoride, making it the more commonly used compound in community water fluoridation programs. However, the authors note that fluorosilicic acid may carry potential health risks due to the presence of contaminants, as industrial-grade fluorosilicic acid may contain impurities that are not present in pharmaceutical-grade sodium fluoride. Rice et al. (2014) further emphasised that different fluoridation agents can exhibit varying levels of toxicity, with fluorosilicic acid generally posing more adverse effects than sodium fluoride.

The differences outlined between fluorosilicic acid and naturally occurring fluoride emphasises that the two may have distinct health effects due to their chemical properties. The lack of differentiation in fluoride chemical compounds the methodologies used by the National Health and Medical Research Council (NHMRC) could obscure these significant health risks and lead to misinterpretations of the data. A more nuanced and comprehensive approach is needed in future reviews to ensure that all relevant factors such as the potential for contamination and the differing toxicological profiles of fluoridation agents are thoroughly considered in assessments of water fluoridation practices.

Age Subgroups

The Cochrane Handbook specifies that age can act as an effect modifier, where the impact of an intervention may vary at different stages of the lifespan (Chaimani et al., 2019). It also highlights that imbalanced distributions of age groups can undermine the plausibility of the transitivity assumption, thereby compromising the validity of indirect comparisons. In the NHMRC review, age groups were categorised as infants, children, adolescents, adults, and later adulthood. However, the broad age range for the adult subgroup (18–64 years) risks diluting the analysis of long-term exposure effects. Narrower age divisions (e.g., 35–45 vs. 25–35) could provide more granular insights into age-related health variations, particularly in relation to cumulative fluoride exposure over a lifetime. A more detailed analysis of age-specific health outcomes, especially in mid-life and older adults, is critical for understanding long-term health risks.

Reference Management Software

The Technical Report mentions that citations were organised using "Reference Manager Software" but does not specify the software. This omission impacts transparency, as knowledge of the specific tool used is necessary for replication. If software like Cochrane recommended Covidence (2024) was used, it would add credibility due to its robust screening and tracking features, ensuring systematic review rigor. Reference management software typically enables independent verification of reviewers' contributions, a key aspect for maintaining unbiased results. Detailing how duplicates

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were managed and including relevant screening statistics would strengthen the review's reliability and transparency.

Search Strategy Differences

A key concern lies in the differing search strategies employed for dental caries and health effects. Databases such as Embase, PsychINFO, and Global Health were utilised, but the search strategy for health outcomes was notably less robust, lacking the same rigor and breadth as that for dental caries. Additionally, certain Cochrane recommended databases were excluded such as MEDLINE and PubMed (Lefebvre et al., 2019). Furthermore, the health effects review relied on outdated search dates (October 2014), while the caries search was conducted nearly 12 months later in 2015. This disparity raises concerns about the inclusion of the most current evidence and reflects a lack of methodological consistency, increasing the risk of bias in the evidence base that informs public health recommendations.

As shown in the Supplementary Material, the use of specific search symbols and operators was inconsistent across searches, potentially limiting the retrieval of relevant studies. Embase is case-sensitive, meaning that search terms must be formatted consistently to ensure accurate results. For example, in Table 10 (dental caries), a capital "F" for fluoridation contrasts with Table 17's lowercase "f." Similarly, the inconsistent use of "af" across both searches could lead to varying retrieval results, affecting the comprehensiveness of the search. The inconsistency in using capital "OR" versus lowercase "or" across tables can also lead to variations in how Embase interprets these logical operators; uniformity in the use of "OR" is essential to prevent unintended restrictions or expansions of search results.

Additionally, the differing use of parentheses in Table 10 and the absence of them in Table 17 creates uncertainty in the grouping of terms. Proper use of parentheses is critical for clarifying the logical structure of search queries, influencing which terms are considered together. The varied application of quotations around search terms can significantly impact the search outcome. As highlighted in the Embase syntax guidelines, using quotes is necessary to ensure that keyword phrases are treated as single units. The inconsistent application of this practice raises questions about the reliability of the search results.

The differing approaches in using the "explode" function in Table 10 versus Table 17 could also result in substantial differences in the breadth of the search results. Not utilising the explode function when relevant may restrict the discovery of related terms and subheadings, particularly in the context of health effects. Overall, these inconsistencies in syntax and usage appear to enhance the search results for dental caries while potentially restricting the search for health effects. This discrepancy could lead to a skewed understanding of the evidence base, undermining the integrity of the review.

In the PsychINFO searches, both tables featured identical search terms; however, being conducted a year apart raises critical questions regarding the differing number of citations retrieved. This suggests the potential emergence of additional research on health effects during that period. If relevant studies were excluded from the health effects review due to criteria aligned with the dental caries search, it could result in an incomplete assessment of the evidence base.

The decision to conduct two separate searches in the 'All EBM' for dental caries while limiting the health effects to a single search appears inconsistent. Given the growing body of research surrounding health effects, especially in the context of water fluoridation, it is questionable why a second search was not warranted for health effects. This inconsistency suggests a potential oversight in capturing all relevant literature.

Additionally, the use of PreMEDLINE instead of MEDLINE in the searches raises concerns. The Cochrane handbook specifies that MEDLINE should be searched for all Cochrane Reviews[28]. PreMEDLINE contains records of biomedical literature that are pending full indexing in the MEDLINE database, serving as an early access point for recent research findings. While PreMEDLINE may provide access to cutting-edge studies, it may also lack the comprehensive indexing and quality control present in MEDLINE. Relying solely on PreMEDLINE could result in incomplete searches; thus, it should be complemented with MEDLINE, which offers a broader and more thoroughly vetted collection of literature.

The use of "af" in Table 14 compared to "mp" in Table 20 in the PreMEDLINE searches raises questions about consistency in terminology across the dental caries and health outcomes searches. According to the MEDLINE Database Guide, "AF" stands for "All Searchable Fields," and "MP" refers to "Default Fields for Unqualified Searches" and results from searching a term without specifying a field in Advanced search, or specifying "mp", defaults to 'multi-purpose'. This lack of clarity can lead to confusion and misinterpretation of the search strategy. If "MP" represents a specific search field, it should be explicitly defined to enhance understanding. Moreover, in Table 15, line 2, the term "af" (all searchable fields) is used, whereas in Table 21, lines 2 and 3, the terms "ti" (title) and "ab" (abstract) are employed. This inconsistency raises questions about the search strategy's coherence and the rationale behind selecting different search fields for different tables.

In Table 21, line 9, the term "man.od." is utilised, which appears to reference Organism Descriptors (OD). However, its application alongside "od" is not clearly justified. The term "man.od." should be explicitly defined in the context of the search strategy. If it refers to a specific subset of data related to human organisms, that clarification is essential for enhancing understanding.

Inclusion and Exclusion Criteria

The NHMRC report's application of inclusion and exclusion criteria reveals several inconsistencies that may impact the reliability of the findings. As shown in the 'Summary of Review Citations' (Supplementary Material), 69 studies on health effects were excluded due to language barriers, compared to only 9 studies for dental caries. The Cochrane handbook suggests that searches should not be restricted by language to reduce the risk of bias (Lefebvre et al., 2019). Further, it highlights that there is a risk of eligible studies being missed from countries with viable data. Given the significant influence of health effects on national policy, translating key studies could enrich the evidence base and support more informed public health decisions.

Twelve studies were excluded from the health effects review under "Wrong Publication Type," although the report's inclusion criteria specified a publication date threshold (post-October 1, 2006). These studies might have been better categorised under "Wrong Publication Date," a criterion used for dental caries studies. Additionally, twenty studies on health effects were excluded for "wrong outcomes," but the report lacks specific details on these outcomes, which would enhance transparency.

For dental caries, 21 studies were excluded for lacking multivariate analysis, though PICOS criteria only specified a "comparative study design." This may have led to the omission of valuable studies that met the comparative design criterion but did not perform multivariate analysis. Similarly, excluding seven studies that evaluated fluoride exposure beyond water fluoride, without clear protocol specifications, suggests potential oversight. Such studies might still provide relevant insights.

The exclusion of studies using the Community Periodontal Index (CPI) and those that didn't specify skeletal fluorosis grades was not part of the specified PICOS criteria. This oversight may have excluded relevant findings which have been found in recent studies related to periodontal health (Adam & Achmad, 2018) and skeletal effects (Srivastava & Flora, 2020). Moreover, twelve studies comparing populations with and without dental fluorosis in different areas were excluded, deemed "flawed" without detailed justification, necessitating further scrutiny of their methodologies.

Lastly, dental fluorosis was not evaluated in this review due to reliance on an existing Cochrane Review (Iheozor-Ejiofor, 2015), a choice that limited the scope of this assessment. Overall, these exclusions, especially those lacking clear rationale, may constrain the comprehensiveness and balance of the evidence base on fluoridation's health impacts.

Evidence Quality Assessment

Cochrane released the revised Risk-of-Bias (RoB) tool in 2011, designed to critically appraise studies included in systematic reviews (Boutron et al., 2019). Interestingly, the CTC research team,

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which identifies as Cochrane authors and reviewers, did not use the RoB tool when assessing the quality of evidence in the included studies. Instead, the review process for evaluating the health effects of water fluoridation lacked a specified quality assessment tool for cross-sectional and ecological studies. As a result, the NHMRC opted to use a generic instrument developed by the National Institute for Health and Care Excellence (NICE) for studies focused on correlations and associations. Additionally, the review employed an NHMRC-specific evidence hierarchy that prioritized observational studies for assessing harm but placed ecological studies at the lowest level (Level IV). These studies analyse data from groups rather than individuals, such as comparing health outcomes in different regions or populations which would seem appropriate for comparing water fluoridated areas to different levels and non-fluoridated areas. This decision, influenced by an aetiology-based hierarchy designed for causation, may underestimate the importance of ecological studies, which often highlight population-level correlations rather than individual causal links.

An alternative "Prognosis" question hierarchy, as recommended by the NHMRC (2009), might have been more suitable, as it considers ecological studies on par with cohort and case-control studies. This approach could have led to higher quality ratings for these studies, providing a more balanced perspective on fluoride exposure's health impacts. The NHMRC's choice not to adopt this hierarchy may inadvertently downplay valuable observational findings related to fluoride's potential adverse effects.

Ethical Considerations

The ethical dimensions of water fluoridation were acknowledged in the NHMRC's public-facing 'Information Paper'(2017), which claims fluoride's benefit in reducing tooth decay across demographics justifies fluoridation. However, the 'Technical Report' that underpinned this paper did not directly consider ethical issues, as stated by the authors. These ethical concerns were left to the NHMRC Australian Health Ethics Committee, which only reviewed them after the University of Sydney's team completed the systematic review. This separation of ethical review from the systematic analysis process may raise questions about the thoroughness of ethical considerations in public health policy recommendations.

Implications of the Review Findings

The NHMRC's approach, characterised by selective evidence inclusion and methodological inconsistencies, raises critical questions about the validity and comprehensiveness of its findings. By narrowing the focus to dental caries while relegating other health outcomes to the periphery, the NHMRC may inadvertently obscure important evidence relevant to public health policy, especially given growing concerns about the potential adverse effects of fluoride exposure.

The restrictive nature of the public submission process such as limiting evidence to studies available in full text, further compounds these issues, potentially introducing bias based on the accessibility of research publications. The exclusion of a significant number of public submissions and the reliance on a limited pool of citations undermine the democratic principles of evidence-based policymaking.

Conclusions

The NHMRC's 2017 *Public Statement on Water Fluoridation and Human Health* is a pivotal document that shapes public health policy in Australia. However, the methodological shortcomings outlined in this review, when compared to the recommendations in the *Cochrane Systematic Review Handbook*, underscore the need for a more rigorous, transparent, and inclusive approach to evaluating the health effects of water fluoridation. Addressing these gaps is essential to ensure that future research provides a more comprehensive and reliable basis for public health decisions.

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Recommendations

To improve the methodological rigor of future research, it is recommended to implement a unified research protocol by adopting standardised guidelines such as PRISMA and Cochrane. These widely recognised frameworks enhance consistency, transparency, and accessibility in the research process. Additionally, broadening evidence inclusion criteria would be beneficial. This involves considering studies from diverse sources, including non-English publications, and avoiding exclusions based on arbitrary criteria, thereby reducing biases and capturing a more comprehensive evidence base.

Furthermore, it is crucial to ensure that search strategies are both comprehensive and consistent across different topics. Thorough search protocols for dental caries and health effects should leverage major databases like PubMed/MEDLINE and apply uniform search techniques to maximise evidence retrieval while minimising the risk of overlooking relevant studies. Additionally, using appropriate evaluation tools tailored to the types of studies included in the review would provide a more accurate assessment of evidence quality. For example, tools specifically designed for evaluating observational studies should be employed when relevant, ensuring a balanced and nuanced understanding of the evidence.

Transparency in public submissions is also essential for building trust and inclusivity in the research process. Revising submission processes to clarify how public concerns and evidence are reviewed and incorporated can lead to more inclusive outcomes and strengthen public engagement. Moreover, future reviews should systematically evaluate all potential health effects of fluoride, including dental fluorosis, to ensure a complete assessment of fluoride's impact on health.

To further enhance the rigor and comprehensiveness of research in this area, a Royal Commission is suggested to investigate the long-term health effects of fluoridation compounds. Such an independent body could systematically evaluate existing studies, assess public concerns, and provide a thorough analysis of the risks and benefits associated with water fluoridation. By implementing these recommendations, future research can strengthen the robustness of its findings and contribute to a more informed and equitable public health discourse surrounding water fluoridation in Australia.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Statement: The author declares that there are no conflicts of interest related to this critical review. Furthermore, this work received no funding from any external sources or organisations. All aspects of this review were conducted independently, ensuring the integrity and impartiality of the research findings. Ethics approval was not required for the purposes of this review.

The editing process for this critical review involved the use of artificial intelligence tools to enhance clarity, coherence, and overall quality. AI was employed to assist with grammar, style, and formatting, ensuring that the document meets academic standards. The final content, however, reflects the author's original insights and interpretations, with AI serving as a supportive resource rather than a decision-maker in the research and writing processes. The author reviewed and approved the final manuscript.

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